# Gender Differences In Post-MI Remodeling

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## Abstract

**Background:** Gender and sex-specific differences have been described in the process of post-MI remodeling leading to congestive heart failure. The cause for this differences still remain unknown. The aim of this study was to elucidate the sex-specific differences in post-MI gene-expression profile and to correlate them with morphology, hemodynamics and endothelial function.

**Methods:** MI was induced in male and female Sprague-Dawley rats using coronary ligation. Seven, 21 and 42 days post-MI animals were sacrificed and examined morphologically. Hemodynamic measurements were made 21 and 42 days post-MI prior to sacrification. Gene-expression profiling was conducted 7 and 42 days post-MI together with assessment of endothelial function.

**Results:** Females showed faster development of hypertrophy and hemodynamic dysfunction compared to males. Endothelial function analysis revealed no endothelial dysfunction for both sexes 7 and 42 days post-MI. EDHF induced vasodilation was upregulated in both sexes at 7 days and remained upregulated in females 42 days post-MI. Gene-expression profiling showed similar patterns at 7 days for both sexes although sex-specific targets were activated. At 42 days post-MI sex-specific differences were observed in the pattern of gene-expression.

**Conculsion:** Gender-specific differences were observed in all parameters evaluated. These differences are highly time-dependend. The main difference observed was a difference in velocity rather than quantity or quality of the response.

## Zusammenfassung

**Hintergrund:** Sowohl klinische als auch experimentelle Studien haben geschlechtsspezifische Unterschiede im Prozess des post-MI remodelings beschrieben. Die Ursachen für diese Unterschiede sind weitgehend unbekannt. Das Ziel dieser Studie war es geschlechts-spezifische Unterschiede im Gen-Expressions-Profil nach Myokardinfarkt zu beschreiben und diese mit hämodynamischen, morphologischen Parametern und der Endothelialen Funktion zu korrelieren.

**Methoden:** Mittels koronarer Ligatur wurde in männlichen und weiblichen Sprague-Dawley Ratten ein Myokardinfarkt erzeugt. Nach 7, 21 und 42 Tagen wurden die Tiere sakrifiziert und morphologisch untersucht. Hämodynamische parameter wurden nach 21 und 42 Tagen vor der sakrifizierung bestimmt. Sieben und 42 Tagen post-MI wurde das Gen-Expressions-Profil mittels GeneChips erhoben sowie die Endothel-Funktion untersucht.

**Ergebnisse:** In Weibchen war eine schnellere Entwicklung der Hypertrophie sowie der Reduktion der hämodynamischen Parameter zu beobachten. Die Analyse der Endothel-Funktion zeigte keine endotheliale Dysfunktion an beiden Zeitpunkten. Die EDHF abhängige vasodilatation war nach 7 Tagen in beiden Geschlechtern hochreguliert und blieb in Weibchen hochreguliert 42 Tage nach dem Myokardinfarkt. Das Gen-Expressions-Profil zeigte ein ähnliches Muster in beiden Geschlechtern 7 Tage post-MI, jedoch wurden in beiden Geschlechtern spezifische Targets aktiviert. Nach 42 Tagen zeigten sich Unterschiede im Muster der Gen-Expression.

**Schlussfolgerung:** Es wurden in sämtlichen erhobenen Parametern geschlechtsspezifische Unterschiede beobachted. Diese waren stark vom Zeitpunkt abhängig. Der grösste Unterschied war nicht im Ausmass der Reaktion auf den Myokardinfarkt zu sehen, sondern in der Geschwindigkeit der Entwicklung der Herzinsuffizienz.

# Contents

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# Chapter 1

# Introduction

## 1.1 Gender in Medicine

### 1.1.1 History of Gender in Medicine

Until the end of the 1980s the gender or sex of patients was not regarded an important factor in general medical diagnostics and therapy. Most medical studies included male patients only or didn't focus on differences between the genders[2, 3]. Certain doctors even postulated it to be not good scientific practice to focus on these differences[2]. The turning point of interest towards gender specific medicine is clearly revealed when doing statistics on the medline database. With the help of the online tool medline trend[4] a quick research on the number of articles indexed by the medline database was made. As can be seen in figure 1.1 an increase in the number of published articles matching the keyword 'gender differences' around the year 1990 happened. In fact in three years from 1988 to 1991 the number of articles about gender specific medicine doubled. And the number of articles is still rising. However, the important point is not only the absolute number of published articles. Figure 1.2 shows the percentage of entries matching the keyword 'gender differences'. The same increase around the year 1990 is seen but due to an increase in articles, the percentage of matching articles stayed at a stable level around 0.35%. The World Health Organization acknowledged the thematic by founding a "Gender Working Group" in 1996[5]. This working group defined the differences between gender and sex as follows: Sex is determined by biological and physiological characteristics of an individual, whereas gender refers to the socially constructed role an individual lives in. Gender differences do exist in medicine in all possible fields. Differences have been described in management of patients, presentation of symptoms, epidemiology, etiology and risk factors, pathophysiology and finally in the clinical outcome of

Figure 1.1: Absolute number of matching articles

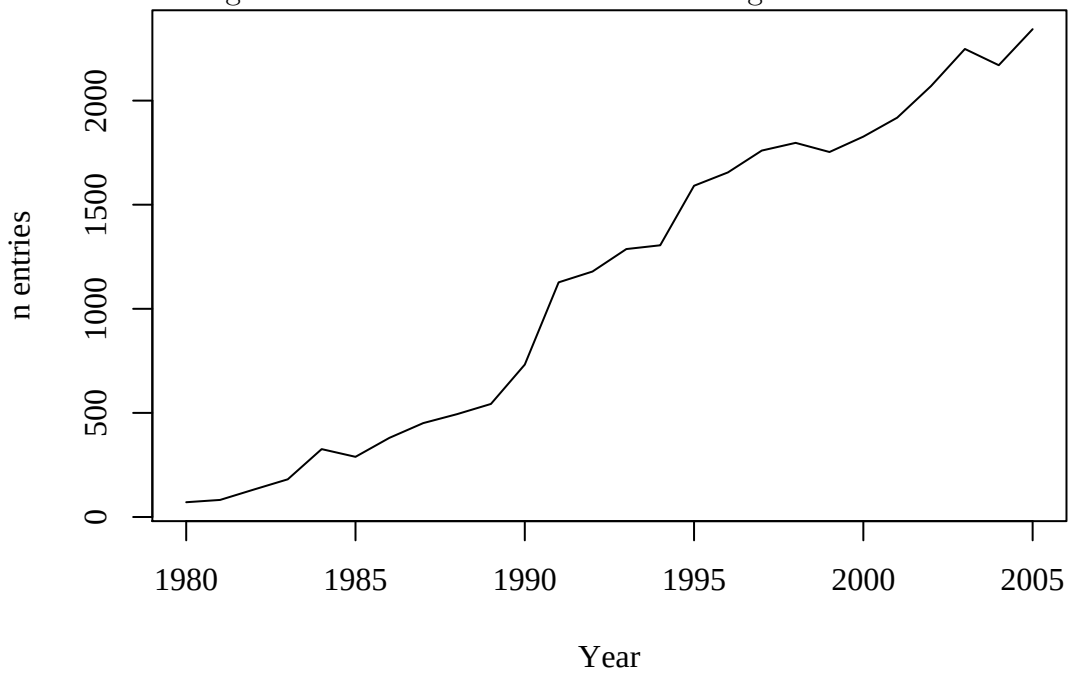
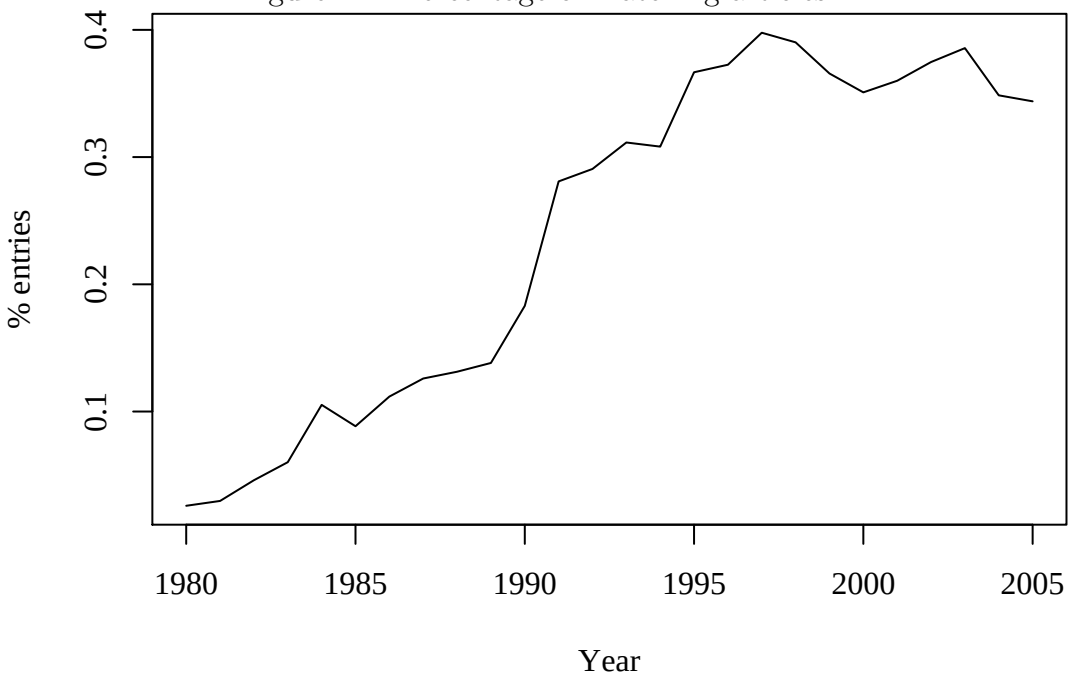



Figure 1.2: Percentage of matching articles



different diseases[2]. This diverse factors provide an additional challenge to the examination of gender differences. In clinical studies it often is not clear whether the described differences is caused by the gender or by other factors, like different management of women compared with men. And finally doctors themselves when treating a patient subconsciously differentiate between women and men.

### 1.1.2 Gender Differences in Cardiovascular Diseases

Despite the common misconception that cardiovascular diseases (CVD) are no major health problems in women[6] they are the major causes of death in both genders. CVDs were the cause of death in 45% of males and 58% of females in Europe in the year 2002. Ischaemic heart disease accounted for 53% of males and 44% of females who died from cardiovascular diseases. Whereas more woman than men died from cerebrovascular diseases (32% vs. 26%). The incidence of cardiovascular diseases increases with age[7, 8]. Mortality from cardiovascular events decreased overall in Europe, but when the decrease was analyzed by gender men showed greater decrease than women[9]. The onset of cardiovascular diseases in women is usually around 10 years later as it is in men[10]. However when it comes to stroke this difference in age shrinks to only 4 years[11, 12]. Despite their older age women suffering from stroke tend to have a better survival rate at 1 year than men, this is even more pronounced the older the patients get[12]. Interestingly studies described a worse neurologic outcome for women who suffered from stroke compared to men.[13]

There are not only differences in the epidemiology of CVDs between the genders but there are also differences in the response to therapy. In 2005 Ridker et al. showed that low dose aspirin showed no significant reduction of the risk of myocardial infarction in females while it showed a significant reduction of risk in males. Furthermore when it came to stroke, low dose aspirin showed a significant reduction of risk in females, while it showed a non significant increase of risk in men.[14]. And a subgroup analysis of the Digitalis Investigation Group trial revealed a higher mortality for women receiving digitalis compared to placebo, whereas there was no difference in men[15]. However gender-specific differences in therapy of CVDs are not well established yet and need further research.

## 1.2 Congestive Heart Failure

### 1.2.1 Definition

Congestive heart failure used to be defined as a clinical syndrome which involves failure of the heart as a pump and leads to congestion of blood in the venous system. This furthermore leads to orthopnea and edema. As the heart is not only mechanically impaired recent definitions include molecular changes as the one by Katz used in this thesis, which describes heart failure as *a clinical syndrome in which heart disease reduces cardiac output, increases venous pressures, and is accompanied by molecular abnormalities that cause progressive deterioration of the failing heart and premature myocardial cell death*[16]. This definition unites the two different failures seen in the clinical syndrome of heart failure. Forward failure, the failure to maintain cardiac output, and backward failure, the failure to remove the blood of the venous system. The two failures are equivalent with the two cardiac dysfunctions seen in clinical life. Systolic dysfunction equals forward failure, where the ejection fraction of the heart is lower than 60% and leads to the clinical symptoms of general weakness and fatigue. Diastolic dysfunction is the impairment of ventricular filling in the diastole and equals backward failure which leads to edema and dyspnea. Finally it describes the progressive nature of this disease leading to a high mortality.

### 1.2.2 Epidemiology

In the USA around 5 Million people suffer from congestive heart failure[17]. In Europe a similar prevalence rate can be observed[18]. Due to the better survival of patients with heart diseases the overall prevalence of heart failure is still rising. This makes congestive heart failure a major health burden. In Europe heart failure is a diagnosis for 24% of patients admitted to a hospital. Survival rates after the onset of congestive heart failure are comparable to malignomas with 5 year survival rates of 25-38%[19].

### 1.2.3 Etiology

Heart failure is the endpoint of several cardiovascular diseases. The most common etiologies can be seen in table 1.1. To understand the mechanisms which lead to heart failure it is important to conceive the work done by the heart. Basically, two different kinds of work are performed by the heart: external and internal heartwork. External heartwork is determined by the work done on expelling the blood, this is to push and accelerate a certain amount of blood against the

Table 1.1: etiologies by importance

| Etiology | Percentage |
|---|---|
| Coronary heart disease | 36 |
| Unknown / idiopatic | 34 |
| Hypertension | 14 |
| Valve disease | 7 |
| Atrial fibrillation or flutter | 5 |
| Pulmonary Hypertension | 2 |
| Alcohol | 2 |

derived from Cowie et al.[20]

periphery resistance. This can be described by the following formula.

$$W = w \times R + \frac{w \times v^2}{2} \tag{1.1}$$

Where $W$ is the work done, $w$ is the weight of the expelled blood, $R$ is the total systemic resistance and $v$ is the velocity of the expelled blood. The second part of this equation ($\frac{w \times v^2}{2}$) is a lot smaller than the first part, therefore it is often ignored and as systemic resistance can be measured using mean arterial pressure and the weight of expelled blood is dependent on the volume expelled, the formula for external heart work breaks down to[21]:

$$W \approx V \times P \tag{1.2}$$

.

Internal heartwork is the work done by the heart in isovolumetric contraction: raising the pressure inside the ventricle to a level above diastolic blood pressure so blood can be expelled. The formula for this work can be deduced from Laplace's law[22, 23]:

$$P = T \times (\frac{1}{R_1} + \frac{1}{R_2}) \tag{1.3}$$

Where $P$ is the pressure inside an hollow object, $T$ is the wall tension and $R_1$ and $R_2$ are the main radii of this object. The work done in isovolumetric contraction is raising the pressure without raising the volume. Furthermore the radii are determined by the volume of blood inside the ventricle. Assuming the heart is a sphere the formula for internal heart work can be simplified to:

$$W \approx \frac{dP \times \sqrt[3]{V}}{dt \times 2\pi} \tag{1.4}$$

There is a third kind of work done by the heart described in 1957 by Burton[23] it is keeping the wall tension. This is often abbreviated as the tension×time index. Here again tension, deduced from Laplace's law (equation 1.3) is determined by pressure and volume. This illustrates the following fact: The work done by the heart, be it internal, external heartwork or tension × time, is determined by volume and pressure.

This leads to three possible mechanisms heart failure can evolve: Volume overload, pressure overload or mixed volume and pressure overload. Volume overload as induced by insufficiency of cardiac valves leads to a higher blood volume transported. Pressure overload as pulmonary or aortic stenosis and systemic or pulmonary hypertension leads to a higher afterload where the heart needs to perform more work in order to eject the same volume of blood. And finally there is the mixed volume and pressure overload as in myocardial infarction[24]. All three result in a higher workload the heart and as a consequence to adverse remodeling and the failure to eject the required amount of blood.

## 1.3 Post MI Remodeling

### 1.3.1 Definition

The event of a myocardial infarction (MI) has tremendous impact on the cardiovascular system. Due mechanical overload, inflammatory and neurohumoral response the heart enters a process of adaptation to the loss of contractile myocardium. This process is commonly called Post-MI remodeling. It involves both the transition of the infarcted area into a solid scar as well as changes to the non-infarcted myocardium. At first the understanding of Post-MI remodeling was limited to the mechanic processes and to the morphometric changes following the increased load of the remaining myocardium. It was suggested that decreasing the load on the heart by decreasing the afterload would attenuate post-MI remodeling and therefore reduce hypertrophy and heart failure[25]. Studies using pharmacologic drugs only reducing afterload showed that this is not a sufficient strategy. A more complex view of post-MI remodeling evolved and the importance of the cardiac fibroblasts and the extracellular collagen matrix was recognized[26].

Today post-MI remodeling is seen as a process involving both mechanical, inflammatory and neurohumoral response to the stimulus of myocardial infarction.

### 1.3.2 Epidemiology of MI

The incidence of myocardial infarction is higher in men than in women. The Rotterdam Study calculated an incidence of 12.6 per 1000 person years for men while it is only at 6.7 per 1000 person years for women aged 55 or older. This includes both recognized as well as not recognized myocardial infarction. Women tend to be older when the first MI occurs than men and they tend to have more unrecognized myocardial infarctions than men (54% in women vs. 33% in men)[27]. Mortality in the first 30 days post-MI ranges between 7.4% to 11.1%[28]. One year mortality post-MI is significantly higher in woman than men[29, 8]. Of patients surviving MI more women than men develop congestive heart failure [8].

### 1.3.3 Etilolgy of MI

The most common cause of MI is coronary heart disease (CHD). Common risk factors for CHD include: Smoking, hypertension, dyslipidaemia and diabetes mellitus. Therefore they are common risk factors for myocardial infarction. Other risk factors include prior MI, family history of MI and recent angina pectoris. Women tend to have more hypertension and more often congestive heart failure at the onset of MI whereas men tend to have a higher percentage of smokers and patients with prior MI[29, 30].

### 1.3.4 Inflammatory Response

The stimulus of ischemia leads to an activation of the inflammatory system in the myocardium finally resulting in the immigration of leukocytes into the exposed territory. A first description of inflammation following ischemia and myocardial infarction in an animal model was made in 1899 by Baumgarten[31]. Since then progress has been made to understand this complex process. The benefit of inflammation in myocardial healing has been questioned leading to studies trying to improve the prognosis of myocardial infarction by inhibiting inflammatory reaction. The failure of these studies showed the importance of inflammation on scar formation and remodeling in the injured area[32].

#### Cytokine Cascade Activation

The trigger activating the cytokine cascade after an ischemic event is not yet known. However there is evidence for the involvement of cardiac mast-cell degranulation in the early phase of this cascade[33]. Mast-cells have the ability to degranulate as a reaction to different stimuli. The ones involved in this process

probably are the complement system and the formation of reactive oxygen species. The postulated mechanism of complement activation in the early phase of ischemia prior to myocardial necrosis is direct activation of complement factor C3[34]. Furthermore when myocyte necrosis occurs phospholipids of mitochondrial membranes of cardiomyocytes like cardiolipin are able to activate the complement system via cleavage of C1[35]. Another mechanism to trigger cardiac mast-cell degranulation are reactive oxygen species formed by the endothelium in ischemia and to a larger extent in reperfusion[36, 37], as well as by neutrophils immigrating into the area at risk[38].

### Cytokines

The above factors lead to a degranulation of mast-cells located in cardiac tissues primarily along vessels[33]. This mast-cells express TNF-$\alpha$ constitutively and release it among other mediators when they degranulate. TNF-$\alpha$ is a central cytokine in inflammatory response in myocardial ischemia and reperfusion[39, 40]. It is not only formed by macrophages but also by cardiac myocytes[41]. Its central role in post-MI inflammation and remodeling is shown by the variety of effects this cytokine has: Transgenic mice overexpressing TNF-$\alpha$ develop dilated cardiac myopathy[42] as well as hypertrophy[43], it induces apoptosis in cardiac myocytes[44], it is negative inotrope[45, 46], it leads to an inflammatory activation of cardiac myocytes[47, 48] as well as endothelial cells[39] leading to an expression of adhesion molecules. The latter leads to an immigration of neutrophils and monocytes into cardiac tissue.
In the process of post-MI remodeling inflammatory activation of both cardiac myocytes and fibroblasts spreads over the whole organ cytokines as TNF-$\alpha$ and IL-1$\beta$ are expressed in non-infarcted myocardium[41, 49, 50, 51]

### Immigration of Inflammatory Cells

Activated and attracted by numerous cytokines produced in inflammatory response neutrophils and monocytes immigrate into myocardial tissue. If reperfusion was established immigration spreads over the whole area at risk, whereas when the nurturing vessel remains closed immigration starts at the borderzone advancing towards the middle of the ischemic area[31]. Neutrophils and monocytes are attracted by several chemotactic factors produced during ischemia, as the ones produced in complement activation[34, 52]. Furthermore cardiac mast-cells and myocytes release MCP-1 a factor with chemotactic effects on monocytes[39, 48]. Both neutrophils and monocytes help to establish a

surrounding for fibroblast proliferation and extracellular matrix remodeling in order to facilitate the formation of a solid scar[39, 53].

### 1.3.5 Neurohumoral Response

#### Catecholamines

The activation of the sympathetic nervous system occurring as a reaction to decreased output and systemic blood pressure after myocardial infarction and the consequent release of norepinephrine and epinephrine was the first neurohumoral activation described. Several studies describe an significant increase in plasma norepinephrine and epinephrine levels post-MI although using only small sample sizes[54, 55, 56, 57, 58, 59, 60, 61]. There seems to be a strong correlation of norepinephrine levels with left ventricular dysfunction.[58, 60, 61] as well as with infarction size[57]. The increase in both epinephrine and norepinephrine is most pronounced in the hours immediately after myocardial infarction and returns to normal levels in the subsequent days[58]. However a correlation of catecholamine excess and prognosis could be observed[55, 57] leading to a better understanding of remodeling towards heart failure and the inclusion of $\beta$-blockers in standard therapy of patients suffering from myocardial infarction[62].

#### Renin-Angiotensin-Aldosterone System

Another neurohumoral system activated in myocardial infarction is the renin-angiotensin-aldosterone system. Both low renal blood perfusion as well as sympathetic activity lead to a release of renin, which activates angiotensinogen to angiotensin I. The latter is further converted by angiotensin converting enzyme (ACE) into angiotensin II, the biologically most effective metabolite. Besides raising periphery vascular resistance it causes excretion of aldosterone of the adrenal glands. Several studies showed elevated serum renin activity in patients with acute MI[57, 58, 60, 61, 63]. As a consequence of elevated renin activity angiotensin II and aldosterone levels increase[58, 63]. Although there is a positive correlation of norepinephrine and renin plasma levels in acute myocardial infarction[63], plasma levels of renin remain high and even increase in patients showing left ventricular dysfunction after myocardial infarction whereas norepinephrine levels tend to decrease to normal levels[58, 60]. Similar to norepinephrine renin plasma levels correlate with infarct size[57] and patients with complicated course show higher renin plasma levels than those without complicated course[57, 63]. Furthermore there is evidence for a autocrine secretion of angiotensin II by cardiac myocytes as a reaction to stretch[64]. This findings

lead to the inclusion of ACE-inhibitors as well as angiotensin II and aldosterone blockers into standard therapy of post-MI heart failure[62].

#### Vasoactive Peptides

Vasoactive Peptides are another class of components reacting in post-MI remodeling. One of the first discovered was vasopressin. Its plasma levels are markedly increased following myocardial infarction[58, 60, 61, 65, 66, 67] and show significant correlation with both norepinephrine and renine levels[65]. It returns to normal 10 days post MI[58, 60]. However since there are no good non peptide antagonists for its receptors yet, vasopressin antagonism didn't make its way into the therapy of post-MI heart failure[67].

Another prominent pair of vasoactive peptides is atrial natriuretic peptide and brain natriuretic peptide. Plasma levels of both are elevated post-MI as well as in heart failure[61, 68]. Lacking both the understanding of pathophysiology as well as selective blockers, these peptides are only used for prognosis[69] and diagnosis[70].

The third group of vasoactive peptides responding to myocardial injury is the group of the endothelins. Vasoconstrictive peptides produced mainly by endothelial cells. The isoform predominantly active in cardiovascular system is endothelin-1[71]. Myocardial infarction leads to elevated plasma levels of endothelin-1 as well as its precursor big-endothelin-1[68, 71, 72, 73]. Its plasma levels return to normal about one week after myocardial infarction[72]. Endothelin-1 levels are increased in patients with congestive heart failure[74] and seem to have prognostic value[75]. However clinical trials with endothelin-1 receptor antagonists (both unselective and selective endothelin A receptor blockers) showed dissapointing results. This might be caused by too late onset of therapy[76].

### 1.3.6 Morphological Changes

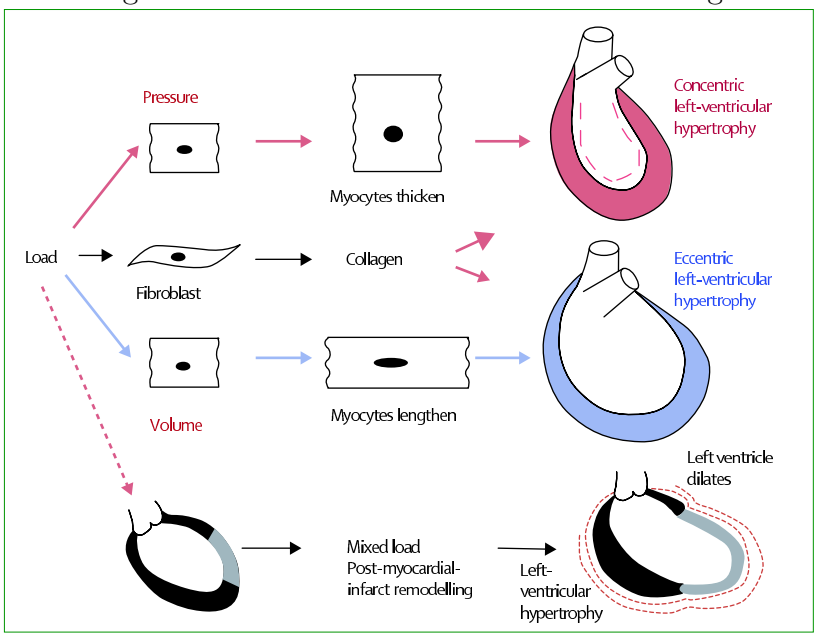
The changes to the shape of the heart following myocardial infarction can be explained by it's pathophysiology. If oxygen and substrates are cut cardiac myocytes become unable to do their work. One of the works done by cardiac myocytes is to maintain wall tension (see subsection 1.2.3). If cardiomyocytes cease to maintain this tension, it is determined by the whole tissue, which has higher elasticity than active cardiomyocytes. As a consequence dilation and thinning of the ischemic myocardium occurs. This has been described as myocardial infarct expansion[77, 78]. Subsequently the volume increases, resulting in increased wall stress and higher workload on the rest of the myocardium

according to Laplace's law (equation 1.3). The latter can be transformed into[22]:

$$P = k \times n \times (\frac{1}{R_1} + \frac{1}{R_2}) \tag{1.5}$$

Where $k$ is the tension per unit and $n$ is the number of units. As the tension per unit can only vary in a certain range the only adaption possible is the increase of units[23]. This increase is observed as hypertrophy of the ventricular walls. The major morphological changes observed post-MI are infarct expansion, ventricular dilation and hypertrophy of the non-infarcted myocardium[24].

Figure 1.3: Patterns of ventricular remodeling

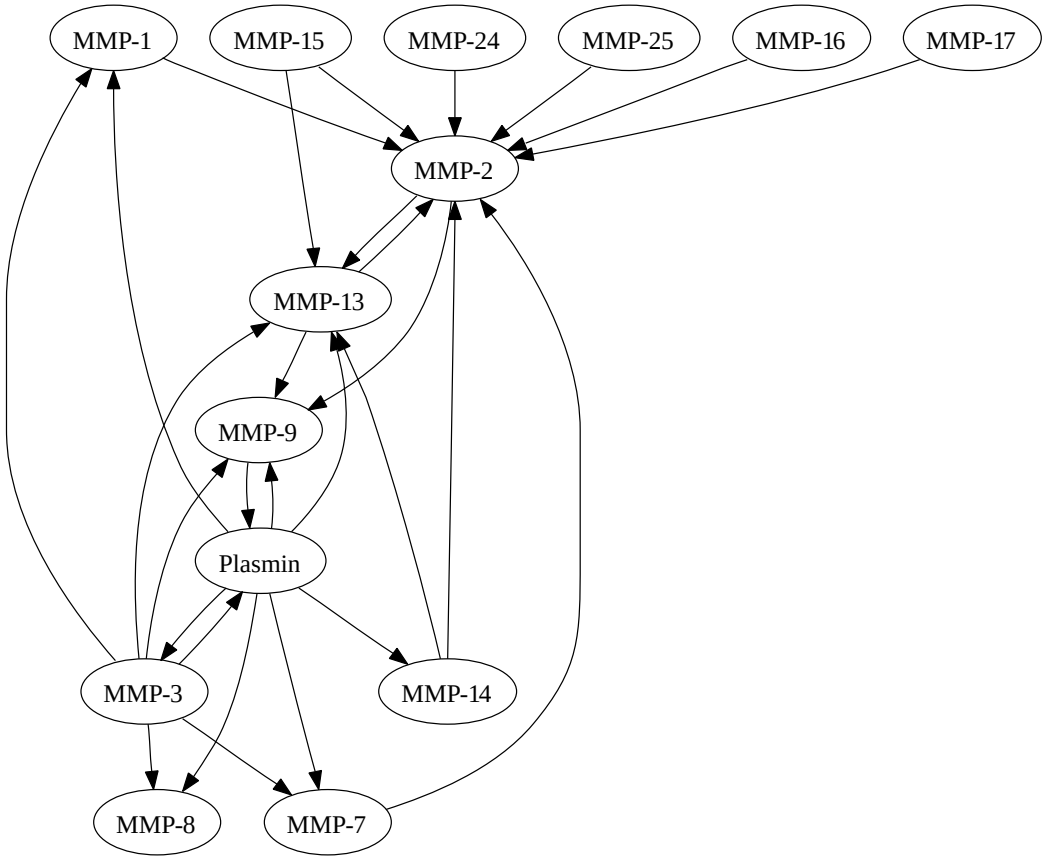



derived from Opie et al. 2006[24]

### 1.3.7 Extracellular Matrix Remodeling

The concept of the heart as a muscle often masked the fact that the heart not only consists of cardiac myocytes. In the recent years focus shifted onto the extracellular matrix. The main proteins in the hearts extracellular matrix are collagens and the importance of these collagen fibers arranged around cardiomyocytes has been acknowledged. Collagen has several functions: It acts as a lateral connection between cells and muscle bundles and coordinate the delivery of force generated by those. And their tensile strength is an important factor in keeping the shape of the heart and wall thickness[79]. Collagen I is the primary collagen and accounts for 85% of the collagens in healthy myocardium, whereas collagen III the second most frequent collagen accounts for only 11%[79]. After a

Figure 1.4: Mutual MMP activation




MMPs and their mutual activation. Derived from [83]

myocardial infarction a process of collagen remodeling starts in both the infarcted as well as the non-infarcted tissue[80, 81]. This process of accelerated collagen generation and degradation is an important factor in myocardial infarct expansion and ventricular dilation[79, 80, 81] and as a consequence myocardial pump-failure[82]. Degradation of collagen accomplished by a set of Zinc containing proteases the matrix metallo-proteases (MMPs). An overview about MMPs known today and their substrates can be found in table 1.2. Most MMPs are secreted as proenzymes and activated as well as degraded via proteolysis by MMPs, plasmin or other proteases[83]. An overview of the mutual activation of MMPs can be found in figure 1.4. The regulation of proMMP synthesis is influenced by numerous factors present in myocardial infarction[84]. ProMMP synthesis is increased by inflammatory mediators such as TNF-$\alpha$[84, 85] and IL-1$\beta$[84]. Interestingly precursors of both factors are substrates to MMPs and therefore cleaved when MMP activation occurs[86, 87]. Furthermore collagen turnover is accelerated by factors of the neurohumoral response such as angiotensin-II[88, 89, 90], aldosterone[88], norepinephrine[91, 92] and endothelin-1[84, 93].

Table 1.2: MMPs and their substrates

| Enzyme | MMP Classification | Substrate | Activated by |
|---|---|---|---|
| **Collagenases** | | | |
| Collagenase-1 | MMP-1 | Collagens (I,II,III,VII,X), gelatin, tenascin, enactin | MMP-3, -10, plasmin, kallikrein, chymase |
| Collagenase-2 | MMP-8 | Collagens (I,II,III,VII,X), gelatin | MMP-3, -10, plasmin |
| Collagenase-3 | MMP-13 | Collagens (I,II,III,IV,IX,X,XIV), gelatin, tensascin-c, fibronectin | MMP-2, -3, -10, -14, -15, plasmin |
| Collagenase-4 | MMP-18 | Not Known | Not Known |
| **Gelatinases** | | | |
| Gelatinase A | MMP-2 | Collagens (I,IV,V,VII,X,XI,XIV), gelatin, elastin, fibronectin, laminin, tenascin-C | MMP-1, -7, -13, -14, -15, -16, -17, 24, -25 |
| Gelatinase B | MMP-9 | Collagens (IV,V,VII,X,XIV), gelatin, elastin, fibronectin | MMP-2, -3, -13, plasmin |
| **Stromelysins** | | | |
| Stromelysin 1 | MMP-3 | Collagens (III,IV,V,IX), gelatin,fibronectin,laminin,tenascin-C | Plasmin, kallikrein, chymase, tryptase |
| Stromelysin 2 | MMP-10 | Collagens (III,IV,V), gelatin, elastin | Elastase, cathepsin G |
| Stromelysin-3 | MMP-11 | laminin, fibronectin, gelatin, collagen IV | Furin |
| **Membran type MMPs** | | | |
| MT1-MMP | MMP-14 | Collagens (I,II,III), elastin, fibronectin, gelatin, laminin, large tenascin-C | Plasmin, furin |
| MT2-MMP | MMP-15 | Large tenascin-C, fibronectin, laminin | Not Known |
| MT3-MMP | MMP-16 | Collagen III, gelatin, fibronectin | Not Known |

Derived from Chakraborti et al.[83] and Creemers et al.[94].

MMP activity is antagonized by a set of proteins called tissue inhibitors of matrix metallo-proteinases (TIMPs). There are several TIMPs with different affinity to different MMPs[94]. As expected TIMP synthesis is altered by the stimulus of myocardial infarction[81, 95]. Furthermore TIMP-1 deficiency leads to an excerebration of post-MI extracellular matrix remodeling[96, 97]. This lead to the hypothesis that attenuating extracellular matrix remodeling via inhibition of MMPs is beneficial. This has been proved by inhibiting nuclear factor $\kappa$b (NF-$\kappa$b) a transcription factor mediating both collagen and MMP transcription[98, 99, 100]. Furthermore direct MMP inhibition showed the same results[101, 102, 103]. However extracellular matrix remodeling is not only detrimental. It is even needed in order to form a solid scar. Thus starting MMP inhibition immediately after myocardial infarction leads to a higher incidence of cardiac rupture[104]. Thus extracellular matrix remodeling is seen as beneficial in the early stage of post-MI remodeling and turns out to be detrimental later on. This accentuates the importance of timepoint in pharmacologic therapy post-MI.

### 1.3.8 Endothelial Dysfunction

Endothelial dysfunction is not only etiology of myocardial infarction, as in arteriosclerosis, but also a consequence, in the form of secondary endothelial dysfunction. The interest in this secondary endothelial dysfunction rose as it was reported in patients with congestive heart failure[105, 106]. Experimental heart failure seems to be a good model to study this secondary endothelial dysfunction isolated from any other influences. However these experiments show diverging results. This inconsistency can partly be explained by differences in examined vessel[107, 108, 109]. Another source of divergence is the different strains used for experiments. Experiments using Sprague-Dawley rats reported no significant endothelial dysfunction post-MI [109, 110] whereas many others using thoracic aortal rings of Wistar rats reported a significant reduction of endothelial dependent relaxation[111, 112, 113, 114]. As secondary endothelial dysfunction is thought to evolve secondary to heart failure, the timepoint of experimentation is also crucial[111].

The pathophysiology of secondary endothelial dysfunction is not yet clear. One of the suggested mechanisms is superoxide formation. Two studies of the group lead by Bauersachs showed increased superoxide formation in thoracic aortal rings 8 and 10 weeks post-MI[113, 114]. The addition of superoxide dysmuthase partly restored endothelial dysfunction[113]. Furthermore they reported an increased expression of eNOS and iNOS post-MI[113, 114]. Interestingly this finding is contradicted by Smith et al. using a rapid pacing model of heart failure in

dogs[115]. Teerlink et al. tried to link post-MI endothelial dysfunction to renin-angiotensin-aldosterone system activation. However they only fond weak correlation of RAAS-activity and endothelial dysfunction[111]. Nevertheless studies using ACE inhibitors showed improved post-MI endothelial function especially when combined with aldosterone antagonists[108, 114, 116]. This is of specific interest as there is one report showing that aldosterone induces acute endothelial dysfunction in vivo[117].

Another focus of interest are the different pathways involved in endothelium dependent vasodilation. As usual the results here are contradicting. There was no study reporting differences in prostacyclin dependent endothelial function. Interestingly there seem to be differences in endothelium derived hyperpolarization factor dependent vasodilation. Malmsjö et al. reported an up-regulation of EDHF dependent vasodilation post-MI[118]. This finding was contradicted by Gschwend et al. showing a decrease in EDHF while NO dependent vasodilation remained the same concluding that post-MI endothelial dysfunction is due to diminished production of EDHF[112]. However due to the limited availability of reports on secondary endothelial dysfunction the underlying mechanisms and pathophysiologic consequences are not yet clear.

### 1.3.9 Molecular Remodeling

Post-MI remodeling not only involves cellular hypertrophy and stimulation of extracellular matrix remodeling. In the recent years the focus has switched to distinct regulation of myocyte protein regulation. This changes are frequently summarized as molecular remodeling. It involves the transcription of fetal proteins, isoform switches and regulation in proteins important for electromechanic coupling.

The stimuli of diverse neurohumoral and growth factors seem to stimulate fetal protein expression in cardiac myocytes. Yue et al. reported c-myc, an oncogene usually expressed during the proliferative phase of fetal heart development, which is induced by a variety of growth factors and mechanical stress, to be up-regulated 1 and 7 days post-MI in a rat model of coronary ligation[119]. In the same work they reported c-fos another oncogene to be unchanged at all points measured[119]. This finding was contradicted by Gidh-Jain et al. using the same model of experimental ischemic heart failure who reported c-fos to be up-regulated 3 and 21 days post-MI[120]. Furthermore tenascin-C, an extracellular matrix protein important in fetal development and wound-healing, is expressed post-MI[121].

Another interesting process is the switch towards the expression of fetal isoforms of certain proteins. Gidh-Jain et al. found a switch from the $\alpha_2$- towards the $\alpha_3$-Isoform of $Na^+$-$K^+$ ATPase, the fetal form of murine $Na^+$-$K^+$ ATPase[120].

Furthermore they reported a switch towards $\beta$-myosin-heavy-chain, representing the fetal isoform of myosin-heavy-chain in rats[120]. According to that this switch in MHC isoforms has been reported in human failing hearts. It is to note that $\beta$-MHC are already the predominant isoform in non-failing adult human myocardium. However a change in ratio between $\alpha$- and $\beta$-MHC is to be seen comparing non-failing and failing human myocytes[122, 123, 124].

The observation of frequent arrythmias in post-MI failing hearts lead to the hypothesis of changes in electromechanic coupling and electrophysiology in post-MI remodeling. The changes in electrophysiology can be linked to changes in the expression of ion channels[125]. This include changes in $K^+$-Channels[126] and $Na^+$-Channels[127]. Furthermore $Ca^{++}$ handling seems to be disturbed. This was frequently linked to SERCA2a malfunction and subsequent $Na^+$-$Ca^{++}$-Exchanger up-regulation[128, 129, 130, 131]. This up-regulation seems to have a role in diastolic function[130].

The development of GeneChip® technology lead to the possibility of genome-wide transcription analysis and the comparison of gene-expression profiles of failing and non-failing hearts[132, 133]. Using this approach it is possible to achieve a systematic overview of gene-expression patterns in certain diseases as well as identification of interesting and critical targets.

## 1.4 Gender Differences in Heart Failure

Although there seems to be no gender-specific difference in incidence[20], there are differences in many other factors determining congestive heart failure.

Gender-specific differences have been reported in: Etiology, morphology, ventricular function, neurohumoral factors, management and finally prognosis[134].

### 1.4.1 Epidemiology

As described above there is no difference in incidence and prevalence of CHF. However women tend to be older at the onset of congestive heart failure than men[135, 136, 137, 138]. Thus the prevalence of heart failure in women older than 75 years is higher than in men of the same age[134, 18]. Studies evaluating gender differences in risk factors showed quite clearly that more men than women had the history of smoking or were current smokers[136, 137, 138, 139]. Hypertension as mentioned above was more common in women. When it comes to diabetes mellitus the situation remains unclear. Some studies report no difference in the prevalence of diabetes mellitus[135, 136, 138, 140] while others report a higher prevalence of

diabetes in women with congestive heart failure[137, 139]. The same applies to adipositas where a higher incidence either in women[137], in men[139] or no significant difference in BMI between men and women[138, 140] has been reported.

### 1.4.2 Etiology

Table 1.1 shows the rate of etiologies described by Cowie et al. Although they differentiated between men and women in incidence they didn't examine if there are gender specific differences in etiologies[20]. However these have been described by numerous other studies[135, 136, 137, 138, 139, 140, 141]. Ischaemic heart disease as in coronary heart disease and MI is the most common etiology for heart failure only in men. Several studies showed independently that a higher percentage of men suffering form heart failure has a history of ischaemic heart disease compared to women[135, 136, 137, 138, 139, 140, 141]. If ischaemic heart disease is split up into patients with a history of MI and such with coronary heart disease without the record of MI both of the groups still show a higher prevalence in men[135, 137]. Interestingly it seems like, although MI has a higher prevalence in male patients with heart failure, more women than men develop heart failure post MI[8]. However this is not yet well examined. When it comes to systemic hypertension the situation looks opposite. More women than men suffering from congestive heart failure have a history of hypertension. It is the most common etiology for HF in women in several studies[136, 137, 139, 140] while others only reported a significantly higher systemic blood pressure in women[138] or it is not the most common etiology although it is more frequent in women than men[135]. Idiopatic heart failure and heart failure secondary to valvular diseases seems to be more common in women than men[140].

### 1.4.3 Morphology

Morphological differences in failing hearts have been subject of both experimental as well as clinical research. Hypertrophy as an index parameter for failing hearts showed no difference in most clinical studies[142, 143, 144] while others reported more hypertrophy in male hearts[145, 146]. Experimental studies showed similar results, most experimental studies reported no difference in hypertrophy markers between male and female animals[147, 148, 149, 150] while others reported a more pronounced hypertrophy in females[151]. The most striking difference however is not seen in the magnitude of hypertrophy but in the geometry of hypertrophe ventricles. In general women showed more concentric hypertrophy with smaller end-diastolic and end-systolic diameters whereas men tend to have highly dilated

ventricles[142, 144, 146]. Garavaglia et al. compared pre and post-menopausal women and found the mentioned difference only in pre-menopausal women[142] which suggest involvement of female sex hormones in the process of remodeling. Experimental studies support these findings[147, 148, 149, 150].

### 1.4.4 Haemodynamics

The differences in morphology between the genders finally result in a difference in ventricular function. Studies evaluating left ventricular function in both men and women showed coherent results. Besides the smaller end-systolic and end-diastolic diameters female patients also showed a preserved ejection fraction in most studies[135, 136, 137, 142, 146, 152, 153]. However some studies showed no difference in ejection fraction between the genders[138, 139, 141]. In studies separating patients with preserved and reduced left ventricular systolic function a significantly higher percentage of women was observed in the preserved function group[145, 154, 155]. The latter suggests a higher incidence of diastolic dysfunction in women. However studies describing the gender differences in patients with diastolic dysfunctions are missing.

### 1.4.5 Neurohumoral Factors

Luchner et al. examined ANP and BNP serum levels in male and female patients with preserved and reduced left ventricular systolic function and described gender specific differences. Men with preserved left ventricular systolic function showed significantly lower ANP and BNP serum levels compared to women. In patients with reduced left ventricular systolic function men showed higher ANP and BNP levels than women. There was a significant difference in ANP and BNP levels in male when comparing preserved with reduced left ventricular systolic function. In women when comparing the same groups there was no significant increase in ANP and BNP levels.[145]. Another study by Smith et al. examined endothelin-1 serum levels post-MI on ovariectomized rats. They observed a significant increase in endothelin-1 serum levels in rats receiving estrogens, while in those receiving placebo there was no significant increase. This suggests gender differences in neurohumoral response in congestive heart failure.

### 1.4.6 Management

Some of the studies mentioned above recorded medication of their patients and described differences in medication between the genders. There seemed to be no

difference in the prescription of $\beta$-blockers between men and women[135, 137, 156, 157, 158]. Interestingly there were gender differences in the prescription for ACE-Inhibitors. Some studies reported a higher rate of prescription among male patients[135, 138, 139, 158] while others reported no significant difference in prescription rates for ACE-Inhibitors[136, 137, 140, 156, 157, 159]. Acetylsalicylic acid (ASA) or other platelet inhibiting drugs were more frequently prescribed in males[135, 137, 138, 139, 140, 158] probably due to a higher prevalence of coronary heart disease in male patients. Only one study so far reported no difference in the prescription rate for ASA[156]. A less coherent situation is to be found in the prescription rates of diuretics, studies reported no difference[140, 138, 156, 158, 157] higher[137, 139] or lower[135, 159] prescription rate in women. No difference has been described in the prescription of digitalis as positive inotropic drug in several studies[135, 136, 140, 138, 139, 157, 158] while some studies showed a higher prescription rate in women[135, 159] or in men[156]. There seem to be differences in the prescription rates in genders but the results are too incoherent to allow a general statement.

There are not only differences in the prescription of drugs but there seem to be differences in the efficacy of certain drugs. Pharmacologic studies showed differences in the pharmacodynamics of ACE-Inhibitors[160] and $\beta$-blockers[161]. A clinical trial showed no survival benefit for women receiving ACE-Inhibitors[162]. This might be accounted to the low number of women included in the trial. However several other studies showed little or no gender-specific difference in survival[163, 164, 165] and finally, a meta analysis of several ACE-Inhibitor trials showed no survival difference between men and women[166] receiving ACE-Inhibitors. Although there seem to be gender specific differences in pharmacodynamics, clinical trials using $\beta$-blockers showed no significant difference in survival between men and women[139, 167] receiving therapy. Rathore et al. published a subgroup analysis of the Digitalis Investigation Group trial in 2002 showing a significant increase in mortality of women receiving digitalis compared to men, where no significant differences in mortality between placebo and treatment were observed[15]. Further clinical trials providing reasonable subgroup analysis and including a reasonable number of female patients would be necessary to elucidate the impact of gender onto the efficacy of certain medical therapies. Furthermore there is difference in the diagnostic procedures used: The only studies recording data if echocardiography was performed in patients reported that echocardiography is less frequently performed in women compared with men[137, 157].

### 1.4.7 Prognosis

As described above congestive heart failure has a mortality comparable to several malignomas. The Framingham heart study reported a mean survival after onset of congestive heart failure of 1.66 years for men and 3.17 years for women[19]. This shows another striking difference between genders. Women seem to have a better prognosis showing less mortality after onset of heart failure[135, 136, 137, 139, 140, 141] . However when an analysis was performed concerning the different etiologies, this difference vanishes in the group with ischemic etiology[135, 136, 140, 141]. Furthermore the CIBIS II trial where there was no significant difference in the percentage of patients with a previous MI showed no significant difference in survival between men and women receiving placebo[138]. Only one study reported no significant influence of etiology on gender specific survival differences in heart failure[139]. Thus it seems like the benefit in survival is due to the lower percentage of women with a history of MI. As women present with better left ventricular systolic function the question arrised if systolic function has the same value as a predictor of mortality in men and women. Martínez-Sellés et al. reported no difference in mortality in women with preserved compared with women with reduced left ventricular systolic function whereas men showed a significant lower mortality with preserved left ventricular function[137]. In contrary Ghali et al. reported left ventricular ejection fraction to be a stronger predictor of mortality in women compared to men[136]. Thus the influence of the interaction between gender and left ventricular systolic function on prognosis remains unclear.

### 1.4.8 The Role of Sex-Hormones

Ever since the discovery of estrogen receptors in the heart[168] sex hormones were accounted for the sex specific differences in heart failure. Subsequently their effects on the cardiovascular system was a major focus of experimental research. This is supported by the later onset of cardiovascular diseases in women in a post-menopausal age[10]. As a logical consequence hormone replacement therapy was said to be beneficial to the prognosis of cardiovascular events. In 1998 the HERS research group published the results of the first multicentric double blind placebo controlled study showing no significant effect of estrogen replacement on the primary outcome if administered after the onset of coronary artery disease[169]. Numerous experimental studies evaluated the effect of estrogen on both volume[170, 171, 172] and pressure[173, 174, 175] overload heart failure. While studies with pressure overload models reported a beneficial effect of estrogen on

hypertrophy[173, 174, 175] studies using myocardial infarction models reported increased hypertrophic response with estrogen replacement[171, 172]. Pelzer et al. evaluated the effect of estrogen receptor-$\beta$ on post-MI remodeling and reported a non-significantly higher mortality in ER-$\beta$ knock out mice[170], in contrast to this van Eickels et al. showed a significantly higher mortality post-MI in mice receiving estrogen replacement therapy[171]. This correlates with the clinical finding of higher mortality in younger women suffering from MI[176, 177]. Furthermore the differential effect of estrogen on different models of heart failure correlates with the findings in prognosis of heart failure reported above. The current data suggest positive influence of estrogen and thereby female gender on pressure overload heart failure and little or even negative effect of estrogen on volume overload heart failure.

### 1.4.9 Molecular Mechanisms

Not only the effect of sex hormones on heart failure and cardiac remodeling leading to heart failure are of interest, the molecular mechanisms leading to these differences are another major topic of research. Studies focusing on gender related differences in apoptosis of failing hearts report a reduced number of apoptotic cells in both human[178] as well as experimental heart failure[171, 179]. This seems to be associated to estrogens[171, 179].

Gender specific differences have been reported too in intracellular $Ca^{++}$ concentration regulation in both human[180] as well as rodent cardiac myocytes[170, 181, 182]. Myocytes of male failing hearts showed an increase in phospholamban, an inhibitor to the cardiac isoform of the sarcoplasmatic $Ca^{++}$-ATPase (SERCA2a), whereas these of female failing hearts showed no increase[180] this seems to be mediated by estrogen[170]. SERCA2a concentrations were reported to be higher in female failing hearts by one study[181]. A study examining healthy myocytes showed a significant decrease of the SERCA2a to phospholamban ratio in ovariectomized rats[182]. This results suggest an influence of estrogen on intracellular $Ca^{++}$ regulation in failing hearts.

Neurohumoral response and its effects is another field of interest to explain gender differences in failing hearts. Bridgman et al. examined the interaction of sex and genotype in ATII type 1a receptor knock-out mice on post-MI myocyte hypertrophy and found that female ATII type 1a receptor knock-out mice showed significantly reduced myocyte sizes, whereas there was no difference in male knock-out mice compared to correlating wild type mice[183]. This suggests a gender specific response to angiotensin stimulation post-MI. Smith et al. examined expression of endothelin 1 receptors post-MI on ovariectomized rats. They

described a 3-fold increase in $ET_b$ receptor mRNA in placebo treated animals while there was no increase in the group treated with estrogens comparing MI with sham operated groups[184]. Knowing the influence of neurohumoral factors on fibrocytes and extracellular matrix formation differences in neurohumoral response might show differences in extracellular matrix proteins. Cavasin et al. focused on extracellular matrix remodeling post-MI and reported a significantly higher matrixmetalloproteinase 2 activity in males 7 days post-MI[148]. If this result is confirmed by other studies in the future this could be another factor of gender differences in failing hearts.

Weinberg et al. researched gender specific differences in the genomic response to pressure overload in rats and reported that first, males tend to have a higher number of targets differentially transcribed to the stimulus of aortic banding than females, and second, the number of targets differentially transcribed in both males and females is small[147]. Thus suggests a differential regulation of transcription in male and female hearts following the same stimulus. Thus a differential regulation of gene transcription could be one of the possible mechanisms leading to gender specific differences in congestive heart failure.

### 1.4.10 Animal Models of Gender Differences in CHF

A variety of experimental models of congestive heart failure exist. Most of them are well suited to evaluate sex-specific differences. Some of them are constitutive models like spontaneous hypertensive rats developing heart failure due to pressure overload. Others are surgical models like coronary ligation or transverse aortic constriction for volume and pressure overload respectively. The third large group is transgenic models of heart failure in mice, where single genes are knocked out or overexpressed and transgenic animals develop constitutive heart failure. A nice overview can be found in a review by Vanoli et al.[185].

Two different approaches exist for the evaluation of sex-specific differences. First studying the influence of sex hormones with models of gonadectomy and consequent replacement of sex hormones and second a physiological approach where sex hormone status remains untouched. Most of the studies limit the gonadectomy to ovariectomy and subsequent estrogen replacement to study the effect of estrogens on development of congestive heart failure[174, 175, 172]. Only a few groups do evaluate both the effect of estrogen and testosteron, using gonadectomy and subsequent replacement of sex hormones[186]. A special case of sex-hormone studies are transgenic models of sex hormone receptor knock outs. Pelzer et al. used estrogen receptor-$\beta$ knock out mice to study the influence of estrogen on post-MI remodeling with a coronary ligation model[170]. Other groups

prefer models of physiologic sex-hormone function to get a general overview over sex-specific differences without focus on sex hormone effects. This has been done in models of MI[148], transverse aortic constriction[181], salt-sensitive hypertension[187] or coronary ligation[188]. Jain et al. used this way and combined myocardial infarction with salt-sensitive rats for a model of combined volume and pressure overload[149]. Furthermore a variety of transgenic models of heart failure showed sex-specific differences and have been evaluated both in physiologic state as well as with gonadectomy and sex-hormone replacement. An extensive review of gender-specific differences in transgenic mouse models has been published by Du[189].

## 1.5 Aim of this Study

The Aim of this study is to evaluate gender-specific differences in post-MI hypertrophy and cardiac function using a physiologic sex-hormone status. Furthermore to elucidate gender-specific differences in secondary endothelial dysfunction and to correlate this findings with gene-expression analysis.

# Chapter 2

# Material & Methods

## 2.1 Studypopulation

Nine week old male (300±50g) and female (250±50g) adult Sprague-Dawley rats were obtained from the Besondere Einrichtung für Biomedizinische Forschung, Abteilung für Labortierkunde und -genetik (Himberg, Austria). Animals were separated into 6 groups according to table 2.1. Each of the groups containing both male and female individuals.

### 2.1.1 Animal Care

Animals were housed in an air-conditioned room with a 12/12 hours day/night cycle given free access to water and standard rat chew. All experiments were approved by the local committee for ethics and animal trials and conducted according to the *Guide for the Care and Use of Laboratory Animals* published by the US National Institute of Health (NIH publication No. 85-23, revised 1985).

Table 2.1: Studygroups

| Followup | Infarcted | | Sham-Operated | |
|---|---|---|---|---|
| days | male | female | male | female |
| 7 | 16 (mM7) | 16 (fM7) | 12 (mS7) | 12 (fS7) |
| 21 | 10 (mM21) | 10 (fM21) | 6 (mS21) | 6 (fS21) |
| 42 | 16 (mM42) | 16 (fM42) | 12 (mS42) | 12 (fS42) |

## 2.2 Coronary Ligation

Myocardial Infarction was induced in the MI groups using the technique described by Pfeffer et al.[190]. Rats were anesthetized using xylazine (1mg/100g bodyweight) and ketamine (10mg/100g bodyweight) received intratracheal intubation with a fine polyethylene tube and were mechanically ventilated using a Bigler animal respirator(Bigler KTR-1, Bigler Gmbh, Mauerbach, Austria) using a mixture of oxygen and room air. Isoflurane (0.2%) was added to the oxygen-air mixture.

A left lateral thoracotomy was performed in the fourth intercostal space. The pericardium was opened, the left anterior descendent artery (LAD) visualized and ligated using a prolene® 6-0 suture. The area at risk was clearly visible by change in coloration of the anterior left ventricular wall. If necessary a second suture was placed to reach the desired infarct size. The chest was closed using a 3-0 Vicryl® suture after evacuation using a polyethylene cannula. Isoflurane supply was stopped and the skin sutured. The Rats were placed into a monitoring cage and as soon as they awakened they were extubated, received a subcutaneous injection of 3mg piritamid and placed in their original cage. Sham operated animals underwent the same procedure except the ligation of the LAD. The perioperative mortality in the first 48h was below 30%. No animals died during the follow up period.

## 2.3 In-Vivo Examinations

### 2.3.1 Echocardiography

To record in-vivo hemodynamic data echocardiography was performed at 21 and 42 days prior to sacrificing the animals. Rats were anesthetized with xylazine (1mg/100g BW) and ketamine (10mg/100g BW). The left half of their thorax was shaved and they were placed on their left in order to provide the best access for ultrasonograpy. Echocardiography was performed using a commercially available 7.5MHz standard pediatric transducer connected to a computer console (Sontron Vingmed CFM 800, Vingmedsound Als, Horten, Norway) by an experienced echosonographer. Phased array technology with a spatial resolution of 0.2mm was used.

Parasternal short axis view was used to measure left ventricular (LV) dimensions. As soon as good image quality of the mid-papillary level had been obtained in B-Mode, LV dimensions at end-systole (ESD) and end-diastole (EDD) were measured using M-Mode. Fractional shortening (FS) was calculated using the formula displayed in equation 2.1. Measurements of three heartbeats were

performed and the averages were used for further analysis.

$$FS = \frac{EDD - ESD}{EDD} \tag{2.1}$$

## 2.4 Ex-Vivo Examinations

### 2.4.1 Morphology

After 7,21 or 42 days animals were anesthetized with xylazine (1mg/100g BW) and ketamine (10mg/100g BW). The heart, lung, liver and tibia were extracted. The heart was weighted, the atria removed and the ventricles weighted in total. The process continued with removing the right ventricle wall, the septum and finally separating left ventricular free wall and scar. All the parts were weighted and of each part samples were snap frozen in liquid nitrogen and stored at -80°C for further analysis. Lung and liver were weighted separately and put into drying chamber for 3 days to determine dry weight. Wet to dry ratios were calculated as a parameter for left or right ventricular congestion respectively.

As markers for hypertrophy ventricular to bodyweight and left ventricular to bodyweight ratios were calculated. Infarct size was determined by weighing total left ventricular mass and putting the scar and peri-infarction into relation to this mass. To have a simple measurement of congestion lung and liver dry to wet ratios were calculated.

### 2.4.2 Endothelial Function

In order to be able to assess changes in endothelial function after MI the thoracic aorta in several animals surviving 7 or 42 days was removed after harvesting of the heart. The aorta was rinsed with ice cold Krebs-Henseleit buffer, cleaned from connective tissue and finally cut into 6 rings of 3-4mm width. The rings were mounted into an organ-bath filled with aerated Krebs-Henseleit buffer using hooks. One of these hooks was connected to a isometric force transducer (Biegastab K30 type 351; Hugo Sachs March-Fr, Germany) connected to a recorder (Graphtec WR3320, UK) for continuous recording of tension. After equilibrating for 30 minutes rings were stretched stepwise until the final tension of 4g was reached. Rings were incubated for another 30 minutes.

Viability of the vessels was documented by contracting the vessels using potassium chloride (KCl, 60mmol/l). Next phenylephrine (Phe, $5x10^{-8}$ - $10^{-7}$ M) was added to precontract the vessels to 80-90% of KCl induced contraction. Dose dependent acetylcholine (Ach, $10^{-9}$ to $10^{-5}$ M) induced vasodilation was recorded after

reaching a stable plateau phase. In order to determine basal NO activity, vessels were mildly precontracted with Phe to reach 10-20% of KCl induced vasoconstiction, reaching a stable plateau a NOS inhibitor (L-NAME, 300$\mu$mol/l ) was added and the magnitude of contraction recorded. After incubation period of 15 minutes vessels were precontracted with Phe as mentioned above and the same dosages of Ach were used to asses NO-independent component of Ach induced vasodilation. Endothelium independent vasodilation was evoked by sodium nitroprusside (NaNP, $10^{-9}$ to $10^{-5}$ M). To determine whether EDHF or prostacycline is the major player in the NO-independent vasodilation observed, $COX_1$ or $COX_2$ inhibitors (indomethacin 1 $\mu$M, rofecoxib 1 $\mu$M, respectively) were used to block Prostacycline production and $K^+$ channel blocker tetraethylammonium chloride (TEA, 10mM) or epoxygenase inhibitor miconazole (MICO, 10$\mu$M) were introduced to block EDHF dependent vasodilation.

### 2.4.3 Histology

Histology samples were collected 42 days post-MI. To preserve the preparations hearts were rinsed with formaldehyde right after they were excised and stored in formaldehyde until processing.

Atria were removed from the hearts and the latter were cut in two levels: mid-papillary and in the middle of the infarction. These cuts were embedded in paraffin and stained using elastic Van Gieson (EVG) staining.

## 2.5 Gene Expression Profiling

### 2.5.1 GeneChipAnalysis

To be able to discover gender-differences in the profile of gene expression post-MI genome wide expression analysis was performed using RAE230A GeneChip® arrays (Affymetrix, Santa Clara, CA, USA). This allows to assess and compare the expression levels of $\tilde{1}4.000$ rat genes represented by UniGene clusters. Briefly, total RNA was isolated from LV free wall, subjected to reverse transcription, in vitro transcription, cRNA labeling, microarray hybridization and data analysis.

### 2.5.2 RNA Extraction

RNA was extracted using non-infarcted areas of the LV (and similar areas in sham-operated animals). The snap frozen samples were grinded with mortar pestle and hammer, the resulting powder suspended in 2ml RLT buffer (Quiagen,

Valencia, CA) and carefully homogenized using a micropipette. Following this proteinase K digestion was performed. For this procedure the homogenized lysate was diluted with 4ml de-ionized water and incubated with 65$\mu$l proteinase solution (Quiagen) for 20 minutes at 55°C. This procedure was performed according to the guidelines provided with the RNeasy Protect Midi Kit (Quiagen).
For quality control RNA concentration was first determined photometrically (Biotek Wave 200, Bio-Tek Instruments, VT, USA) and RNA quality checked using the RNA 6000 Nano LabChip Kit on an Agilent 2100 Bioanalyzer (Agilent Technologies, Palo Alto, CA, USA). RNA samples were stored at -20°C until processing.

### 2.5.3 Expression Profiling

A pooling strategy was used to analyze gene expression profile. Two microgram of RNA were pooled from three animals per group. The pools were subjected to cDNA synthesis using Superscript reverse transcriptase (Invitrogen Life Technologies, Carlsbad, CA, USA) followed by phenol/chloroform purification. An aliquot (11$\mu$l of 12$\mu$l) of cDNA was used for in vitro transcription with the ENZO BioArray RNA transcript labeling kit (Affymetrix). This resulted in biotin labeled cRNA which was purified using the RNeasy kit (Quiagen) and put to random fragmentation in a buffer at pH 8.1 (200mM Tris-acetate, 500mM KOAc, 150mM MgOAc). The extent of RNA fragmentation (40 bp to 200bp sized fragments) was assessed on an Agilent 2100 Bioanalyzer. Of the resulting fragmented cRNA 11$\mu$g were hybridised to the RAE 230A GeneChip® arrays in 200$\mu$l hybridization buffer by incubating at 45°C for 16h with rotation of 60rpm. Finally, the arrays were processed using recommended fluidics station protocols (Affymetrix) stained using the streptavidin-phycoerythrin antibody amplification protocol and scanned in an Agilent GeneArray Scanner (Affymetrix) at a resolution of 3$\mu$. The complete protocols used can be found at the Affymetrix corporate website[191].

### 2.5.4 Data Analysis

Image scans were analyzed using the affy package contained within the open source software Bioconductor[192]. Expression measures and detection calls, present calls (P) and absent calls (A) were determined via the MAS 5.0 algorithm. All multi-array comparisons and all queries of data were performed within Microsoft® Excel 2003. Probeset annotations, biological informations on genes and gene ontology data were retrieved from the NetAffx analysis center and from the OMIM database.

## 2.6 Statistics

All data presented is expressed as mean±SD. Recorded data was stored using Microsoft Excel for Mac. Statistical analysis was performed using R 2.3.1[193]. Morphometric and Hemodynamic data was analyzed using three way anova to evaluate differences between the genders, timepoints, and infarcted versus sham treated animals. Two sided Student's t-test with Bonferroni adjustments was used as post-hoc test. P values $<0.05$ were considered significant.

# Chapter 3

# Results

## 3.1 Morphology

### 3.1.1 Animal Characteristics

Female rats of the same age are generally smaller than male rats. Bodyweight on the day of operation was 242.90±14.15g versus 356.53±51.43g ($p<0.01$). These differences were seen throughout the whole experiment in bodyweights. There was however no significant difference in bodyweight between infarcted and sham operated rats. As a second parameter for size tibia length was measured in all sacrificed animals. Females were again smaller throughout the whole experiment and there was no significant difference between animals receiving infarction and sham operated controls. There was a significant correlation of tibia length and bodyweight (figure 3.1). Table 3.1, table 3.2 and table 3.3 show the respective values for animals with a follow-up period of 7,21 or 42 days.

### 3.1.2 Infarct Size

Overall calculated infarct sizes of female animals were slightly higher than in male rats (48.50±4.99 vs. 46.51±4.96). However there was no significant difference in infarct sizes between the sexes at all timepoints.

### 3.1.3 Morphology of the Heart

Total heartweight was always higher in males compared to females due to the difference in size. However a significant influence of infarction could be seen in statistical analysis using 3-way anova. To get comparable data heartweight and ventricular weights will be normed to bodyweight.

Figure 3.1: Correlation of bodyweight and tibia length

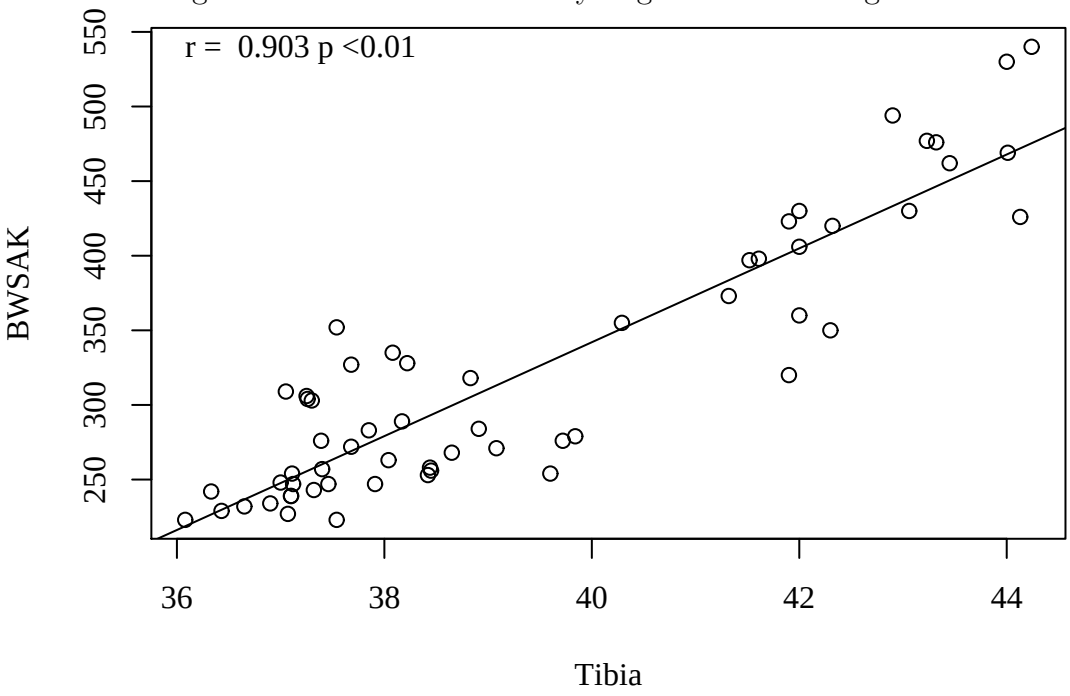



Table 3.1: Morphology 7 day group

| | fs7 (n=6) | fm7 (n=6) | ms7 (n=5) | mm7 (n=6) |
|---|---|---|---|---|
| bw.op (g) | 238.67±13.87** | 243.50±9.40** | 313.80±23.56 | 319.60±15.73 |
| bw.sak (g) | 240.17±13.93** | 239.75±8.06** | 309.40±23.09 | 322.20±19.00 |
| tl (mm) | 36.91±0.73** | 36.96±0.38** | 37.54±0.34 | 37.78±0.73 |
| infarct (%) | | 49.68±4.56 | | 47.01±2.69 |
| hw/bw | 4.28±0.50 | 5.18±0.39 | 4.32±0.66 | 4.46±0.32 |
| vw/bw | 3.14±0.18 | 3.66±0.21 | 3.31±0.31 | 3.24±0.23 |
| lvw/bw | 2.37±0.17 | 2.90±0.29 | 2.56±0.23 | 2.54±0.18 |
| rvw/bw | 0.65±0.05 | 0.74±0.05 | 0.78±0.11 | 0.85±0.11 |

bw.op: Bodyweight at time of Operation, bw.sak:bodyweight at time of sakrification, tl: tibialenght, hw/bw: heartweight to bodyweight ratio, vw/bw: ventricular weight to bodyweight ratio, lvw/bw: left ventricular weight to bodyweight ratio, rvw/bw: right ventricular weight to bodyweight ratio. **: $p<0.01$ females vs. males

Table 3.2: Morphology 21 day group

| | fs21 (n=5) | fm21 (n=7) | ms21 (n=5) | mm21 (n=7) |
|---|---|---|---|---|
| bw.op (g) | 245.80±14.10** | 236.75±12.69** | 318.80±36.71 | 357.75±21.23 |
| bw.sak (g) | 255.40±17.67** | 242.50±13.30** | 373.20±44.29 | 387.25±29.65 |
| tl (mm) | 37.84±0.67** | 37.46±0.35** | 42.04±0.15 | 41.28±0.70 |
| infarct (%) | | 50.25±6.62 | | 46.03±7.84 |
| hw/bw | 5.00±0.68## | 7.05±0.71** | 4.25±0.85 | 4.67±0.52 |
| vw/bw | 3.29±0.11## | 4.89±0.67** | 3.13±0.19 | 3.59±0.56 |
| lvw/bw | 2.65±0.22## | 3.53±0.59** | 3.37±0.20 | 3.00±0.36 |
| rvw/bw | 0.69±0.16## | 1.15±0.12** | 0.75±0.06 | 0.72±0.13 |

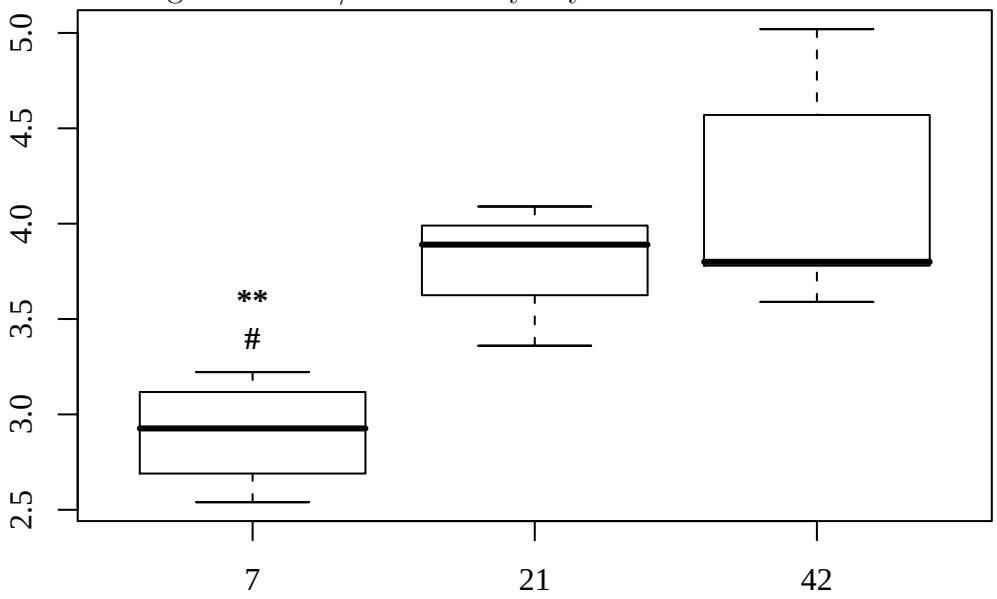
For abbreviation see table 3.1. ##: p<0.01 sham vs. infarct, **: p<0.01 females vs. males

Table 3.3: Morphology 42 day group

| | fs42 (n=6) | fm42 (n=8) | ms42 (n=7) | mm42 (n=7) |
|---|---|---|---|---|
| bw.op (g) | 245.60±11.97** | 239.20±5.81** | 414.57±37.62 | 400.50±37.62 |
| bw.sak (g) | 264.80±21.11** | 267.20±11.51** | 466.43±46.13 | 464.00±50.31 |
| tl (mm) | 37.95±0.81** | 39.34±0.57** | 43.35±0.95 | 43.18±0.69 |
| infarct (%) | | 46.16±3.85 | | 46.37±5.13 |
| hw/bw | 5.34±0.81 | 6.68±0.74 | 4.13±0.55## | 6.10±0.72 |
| vw/bw | 3.90±0.27## | 4.82±0.44 | 3.26±0.30## | 4.73±0.51 |
| lvw/bw | 3.02±0.27## | 4.15±0.61 | 2.50±0.16## | 3.48±0.21 |
| rvw/bw | 0.83±0.06## | 1.11±0.06 | 0.67±0.09## | 1.36±0.17 |

For abbreviation see table 3.1. ##: p<0.01 sham vs. infarct, **: p<0.01 females vs. males

Figure 3.2: LV/BW ratio by day for females with MI




**: p<0.01 vs. day 42, #: p<0.05 vs. day 21.

At day 7 none of the groups with infarction showed significant increase in heartweight to bodyweight, ventricular weight to bodyweight and left ventricular weight to bodyweight ratio compared to the respective sham-groups. However there was a strong tendency towards increased ratios in females with infarction compared to sham-operated females.

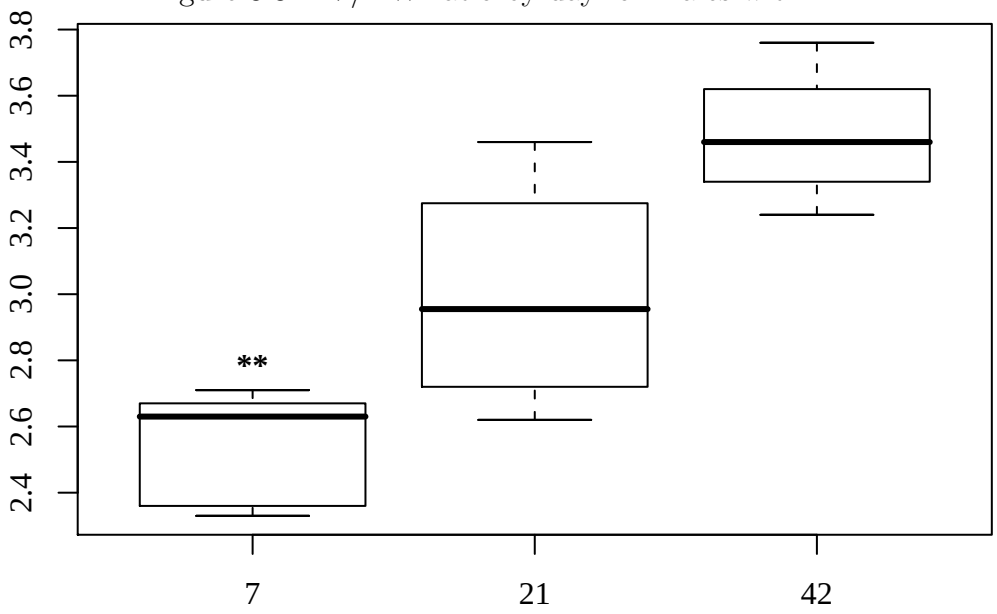
This situation changed on day 21: Females with MI showed a significant increase in heartweight to bodyweight, ventricular weight to bodyweight and left ventricular weight to bodyweight ratio compared to sham-operated females. Males with infarct showed tendencies toward higher heartweight to bodyweight and ventricular weight to bodyweight ratio compared to respective sham group. However this tendency did not turn out to be significant.

On day 42 post-MI both males and females showed significant increases in ventricular weight to bodyweight and left ventricular weight to bodyweight ratio when compared to the correlating sham-group. Heartweight to bodyweight ratio showed a significant increase only in males, while females only showed a strong trend towards an increase of the ratio.

Figure 3.2 and Figure 3.3 show the increase in left ventricular to bodyweight ratio by day for females and males respectively. Females showed an significant increase of left ventricular to bodyweight ratio comparing 7 and 21 days and 7 and 42 days, whereas males only showed a significant increase comparing 7 and 42 days.

Statistical analysis via 3-way anova for timepoint, gender and infarction showed significant influence of gender, infarction and timepoint on left ventricular to bodyweight ratio. It also showed significant interaction between gender and

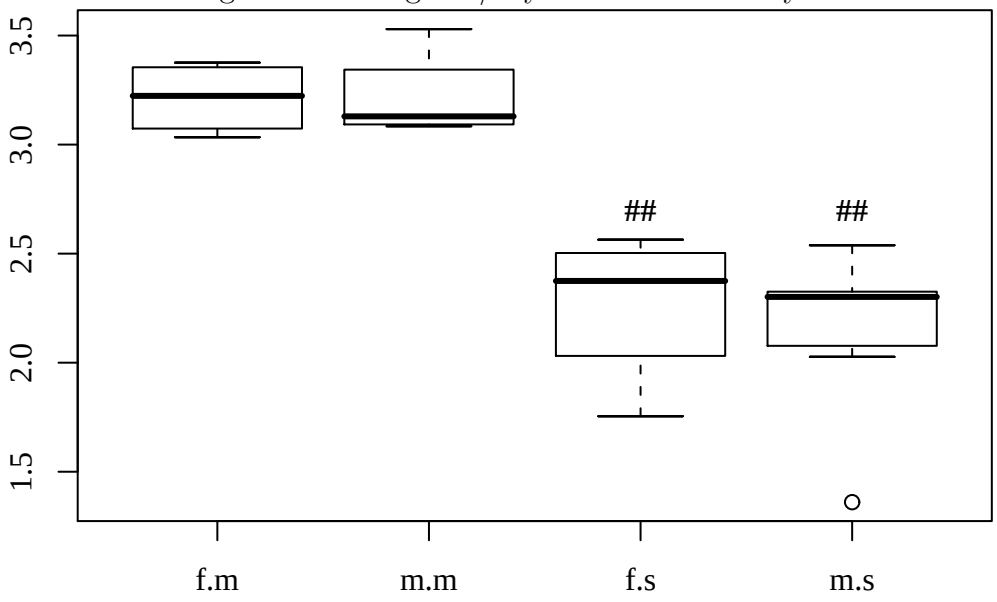
Figure 3.3: LV/BW ratio by day for males with MI




**:p<0.01 vs. day 42.

timepoint and infarction and timepoint. However the three parameters gender, timepoint and infarct together showed no significant interaction. Interestingly this interaction could be observed in both ventricular weight to bodyweight and right ventricular weight to bodyweight ratio.

Figure 3.4: Lung wet/dry Ratio after 42 days




##: p<0.01 sham vs. infarct.

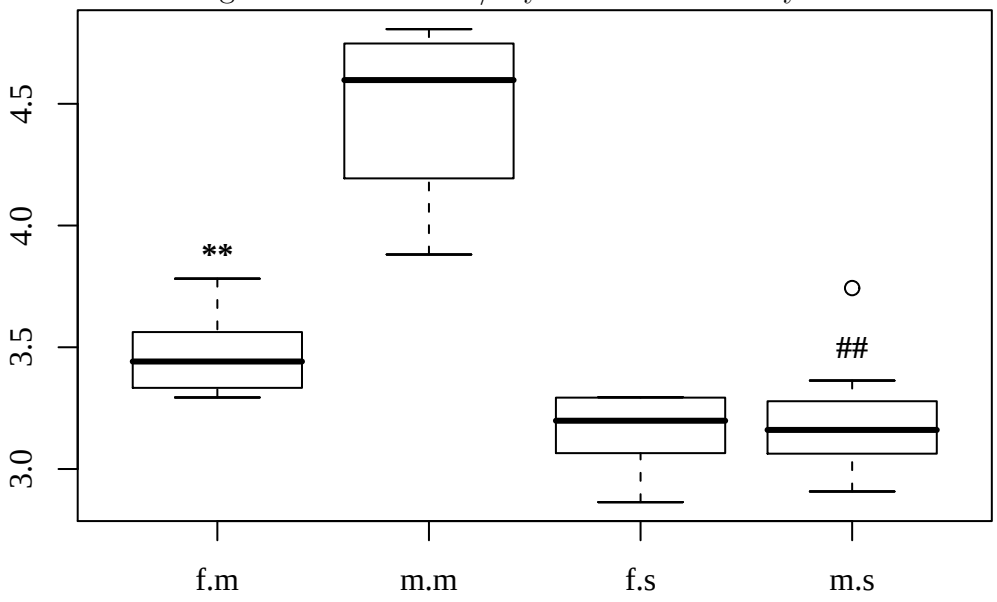
### 3.1.4 Congestion

Lung congestion as measured by lung wet to dry ratio was significantly higher in infarcted animals compared to sham as can be seen on figure 3.4. As a marker for right heart failure and congestion liver wet to dry ratio was measured. Interestingly only males showed a significant increase in liver congestion compared to sham (figure 3.5). Statistical analysis using a two-way anova for the factors gender and infarction revealed a significant influence of infarction on lung wet to dry ratio. Gender and the interaction between gender and infarction showed no significancy for this ratio. However for liver wet to dry ratio a significant influence of both gender and infarction was revealed and there was a significant interaction between gender and infarction.

## 3.2 Echocardiography

On day 21 post-MI both genders showed left ventricular dilatation compared to correlating sham-groups. As can be seen in figure 3.6 and figure 3.7 both males and females showed a significant dilatation in both end-diastolic (EDD) as well as end-systolic diameter (ESD) compared to the correlating sham-group. As males have bigger hearts their EDD and ESD are bigger than the ones of females. As a parameter for contractility fractional shortening (FS) was calculated. As can be seen in figure 3.8 both males and females showed significant impairment of fractional shortening. Interestingly there were significant differences between the

Figure 3.5: Liver wet/dry Ratio after 42 days



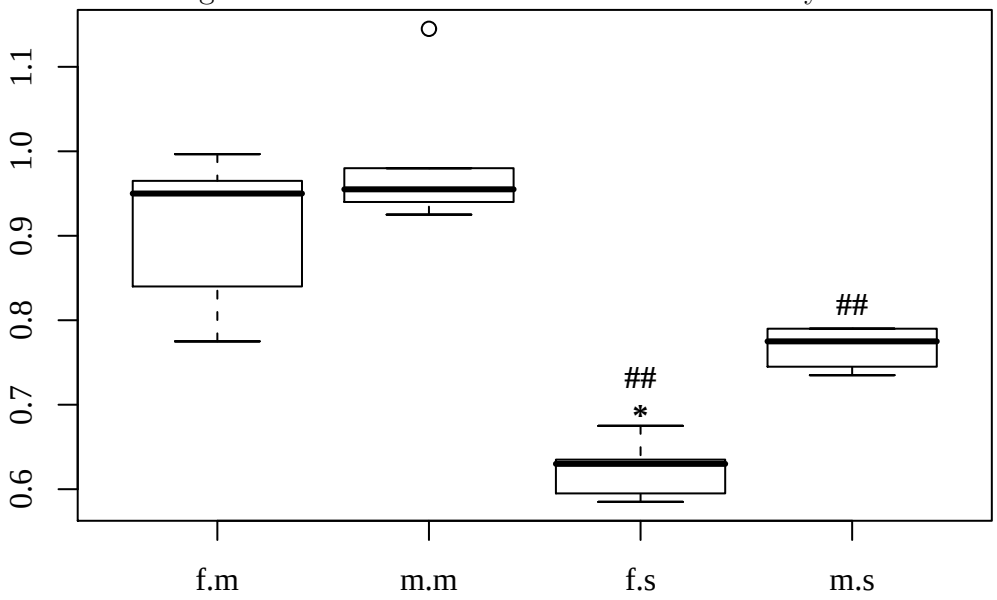

**: p<0.01 females vs. males, ##: p<0.01 sham vs. infarct.

sham operated groups. Female sham showed smaller diameters and a higher fractional shortening compared to male sham. Albeit this difference in sham-operated animals, animals with MI showed no differences in echocardiography at this timepoint.

A similar picture could be observed at day 42 post-MI. Both genders showed a significant increase of both end-systolic (figure 3.9) as well as end-systolic diameter (figure 3.10) compared with sham. As at 21 days severe reduction of contractility could be observed. This is showed in figure 3.11 for fractional shortening. Again significant differences in sham groups could be observed. Females showed smaller diameters and increased fractional shortening compared to males. There was a strong trend for males with MI to have bigger left ventricular diameters and lower fractional shortening however this only turned out to be significant for end-systolic diameter.

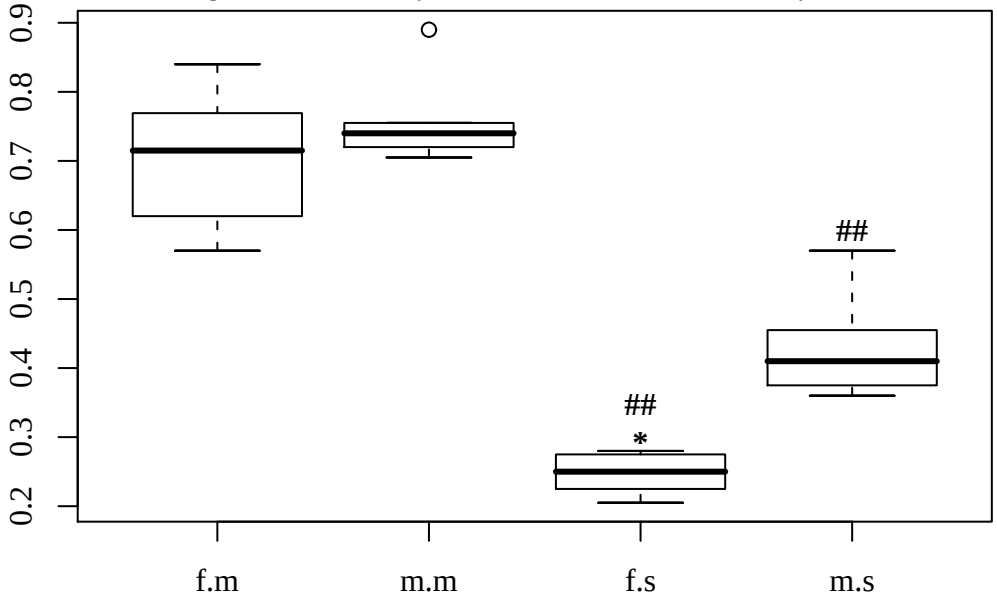
Statistical analysis revealed a significant influence of gender, infarction and timepoint on fractional shortening and end-systolic diameter, with a significant influence of the interaction between gender and infarction. Interestingly in end-diastolic diameter this interaction could not be observed. However end-diastolic diameter showed significant influence of gender, infarction and timepoint.

Figure 3.6: End-diastolic Diameter after 21 days



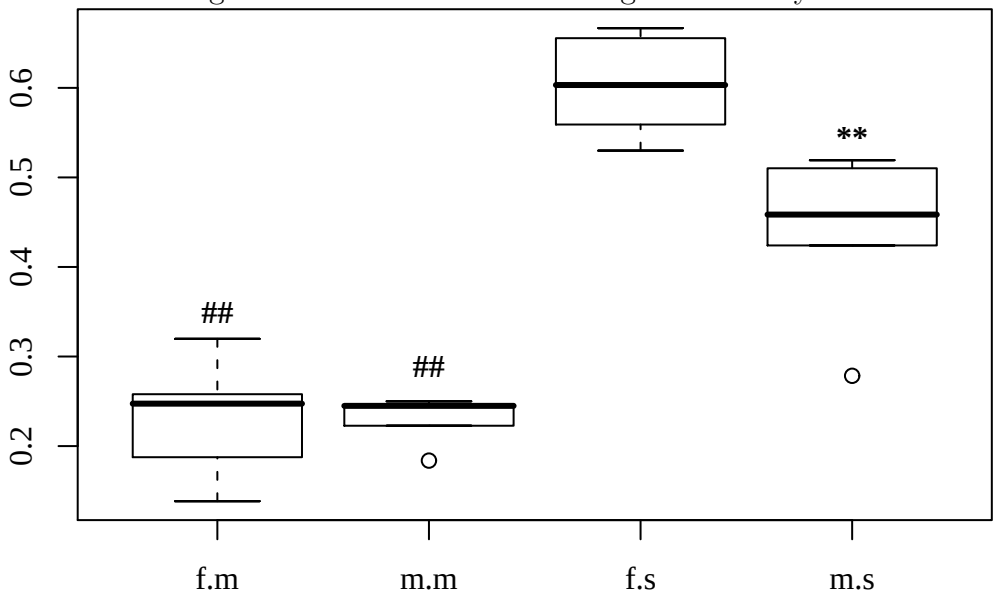

*: p<0.05 female vs. male, ##: p<0.01 sham vs. infarct.

Figure 3.7: End-systolic Diameter after 21 days



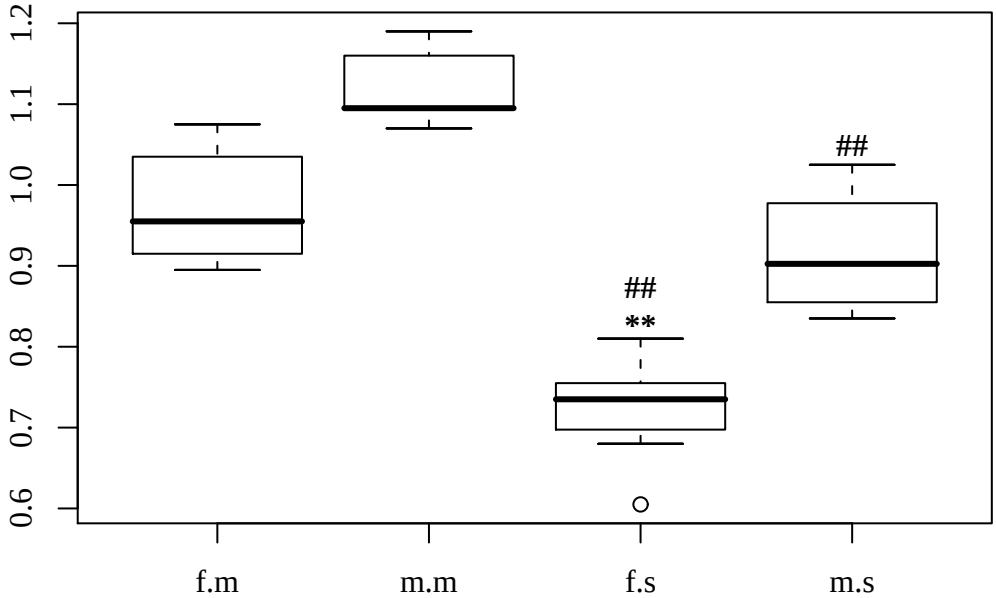

*: p<0.05 female vs. male, ##: p<0.01 sham vs. infarct.

Figure 3.8: Fractional Shortening after 21 days



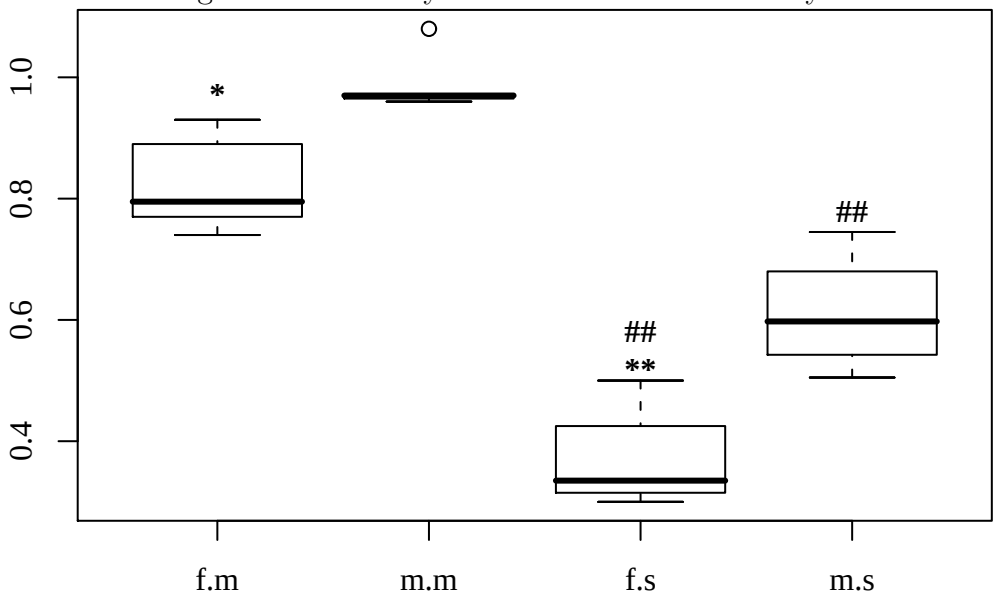

**: p<0.01 female vs. male, ##: p<0.01 sham vs. infarct.

Figure 3.9: End-diastolic Diameter after 42 days



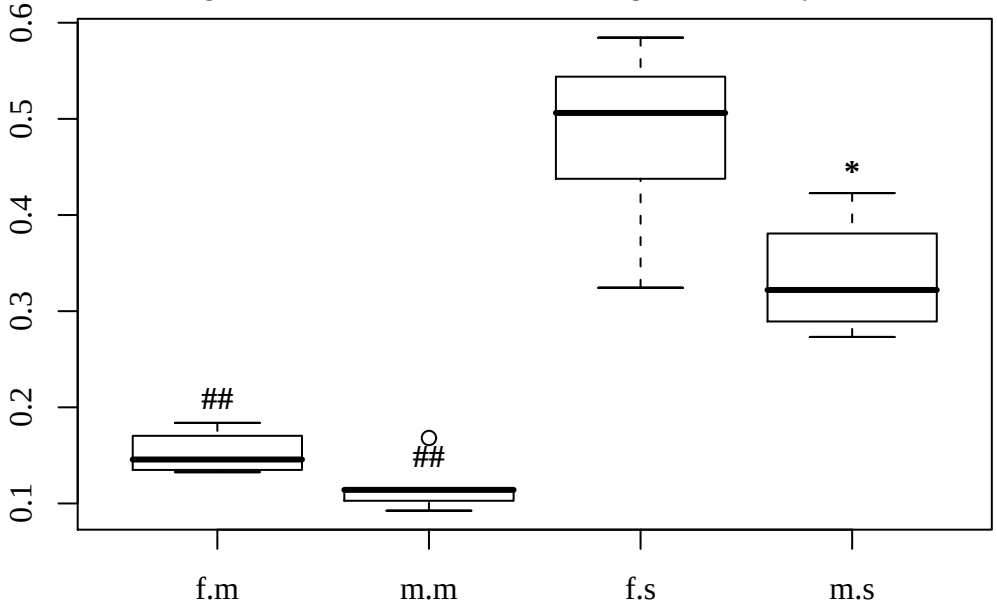

**: p<0.01 female vs. male, ##: p<0.01 sham vs. infarct.

Figure 3.10: End-systolic Diameter after 42 days




**: p<0.01 female vs. male, ##: p<0.01 sham vs. infarct.

Figure 3.11: Fractional Shortening after 42 days




*: p<0.05 female vs. male, ##: p<0.01 sham vs. infarct.

## 3.3 Endothelial Function

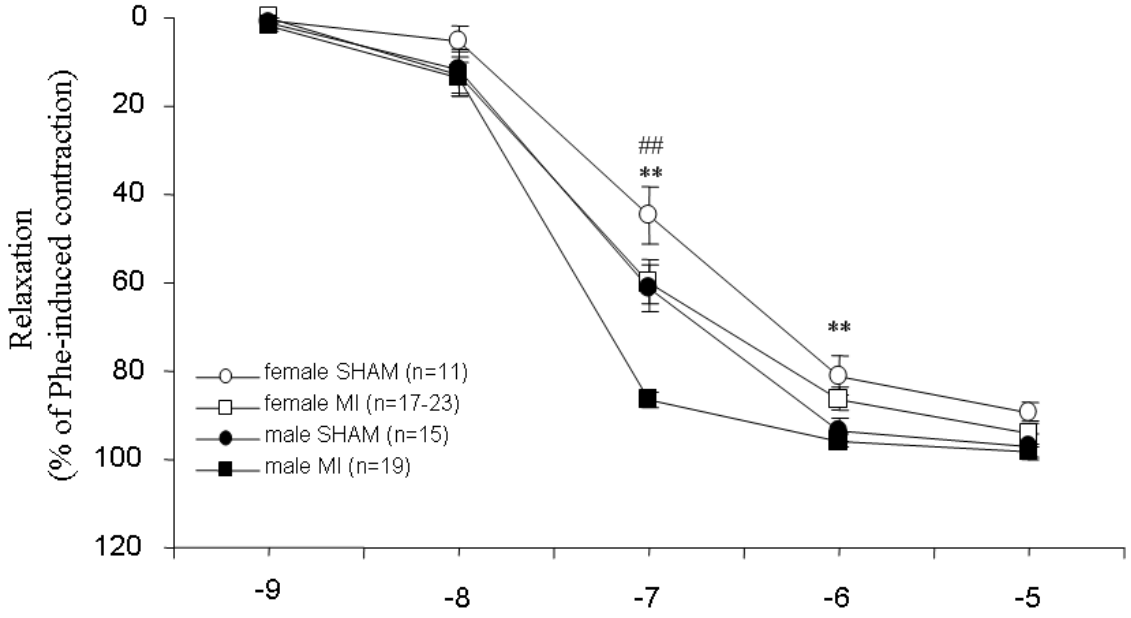
There was no impairment in Ach induced vasodilation at 7 (figure 3.12) or 42 days (figure 3.13) when infarcted groups are compared with non infarcted groups. It is however interesting to note that Ach induced vasodilation was augmented in male and female animals with infarction 7 days post-MI compared with the correlation sham groups for Ach concentrations of $10^{-7}$ and $10^{-6}$M, in males this augmentation reached statistical significance. There was no difference in endothelium independent vasodilation with NaNP after 42 days 101.55±2.71% vs. 101.44±2.87% in females and 100.97±4.46% vs. 105.1±1.80% in males comparing MI and sham groups.

Basal NO production was reduced 7 days post-MI irrespective to gender: 21.76±2.89% vs. 54.32±5.11% ($p<0.05$) for females and 37.61±4.81% vs. 51.98±5.05% ($p<0.05$) for males comparing MI and sham groups. In the late phase 42 days after MI reduced basal NO production was only present in males (21.42±2.6% vs. 33.85±4.1%, $p<0.05$) but not in females (24.49±2.78% vs. 27.01±2.56%, ns).

The most striking difference between the genders was seen in NO- and COX-independent vasodilation. There was a significant up-regulation of Ach induced vasodilation in both genders 7 days post-MI (figure 3.14). However at 42 days post-MI this up-regulation was only seen in female animals with MI but not in male animals (figure 3.15).

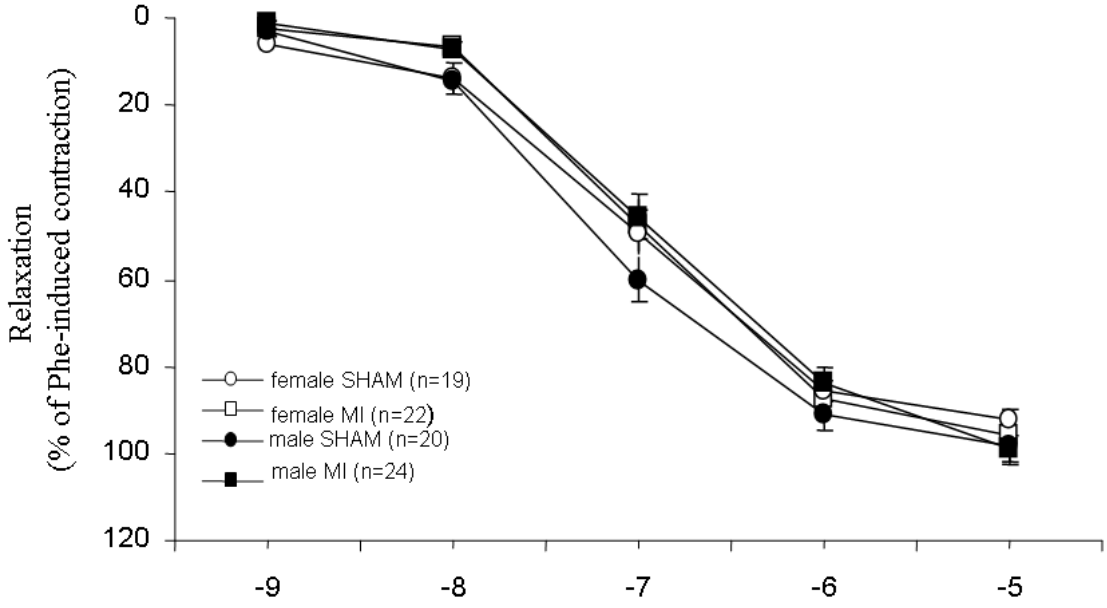
As can be seen in figure 3.16 this NO-independent vasodilation was totally blunted when either TEA or miconazole were added to the organ bath.

Figure 3.12: Ach induced vasodilation 7 days post-MI



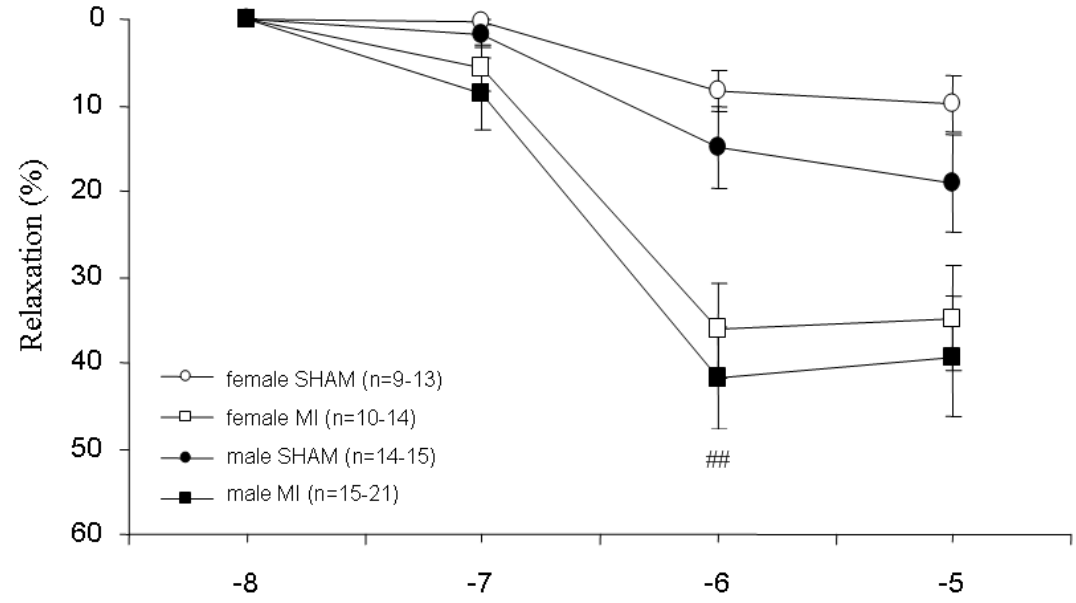

Ach log(M) 7 days post-MI. **: p<0.01 male vs. female, ##: p<0.01 MI vs. sham.

Figure 3.13: Ach induced vasodilation 42 days post-MI



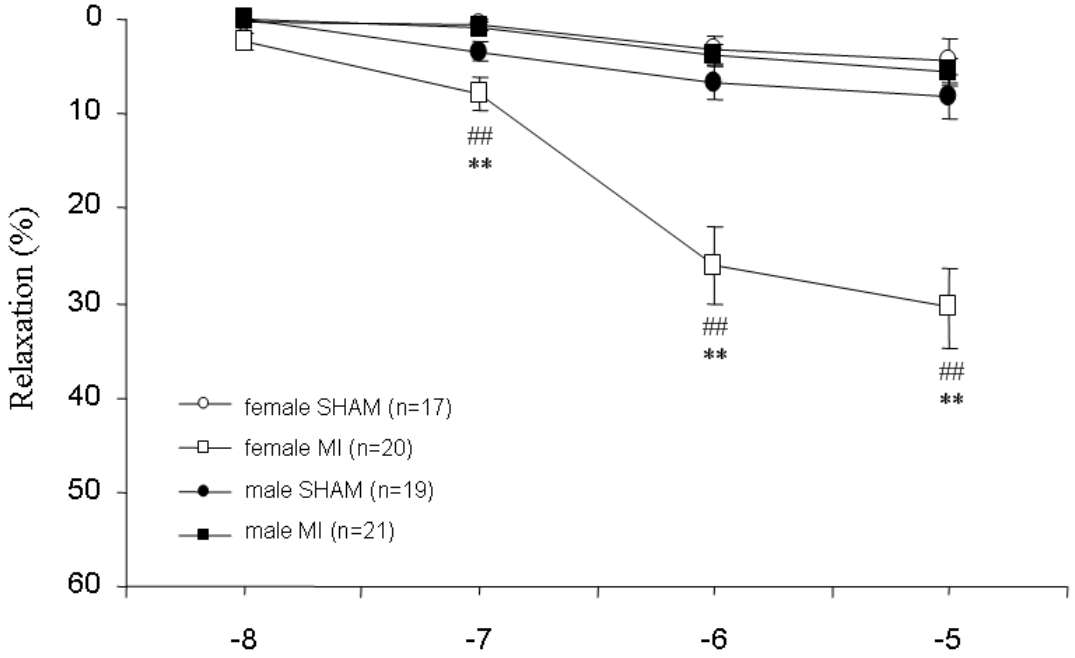

Ach log(M) 42 days post-MI.

Figure 3.14: NO-independent Ach induced vasodilation 7 days post-MI



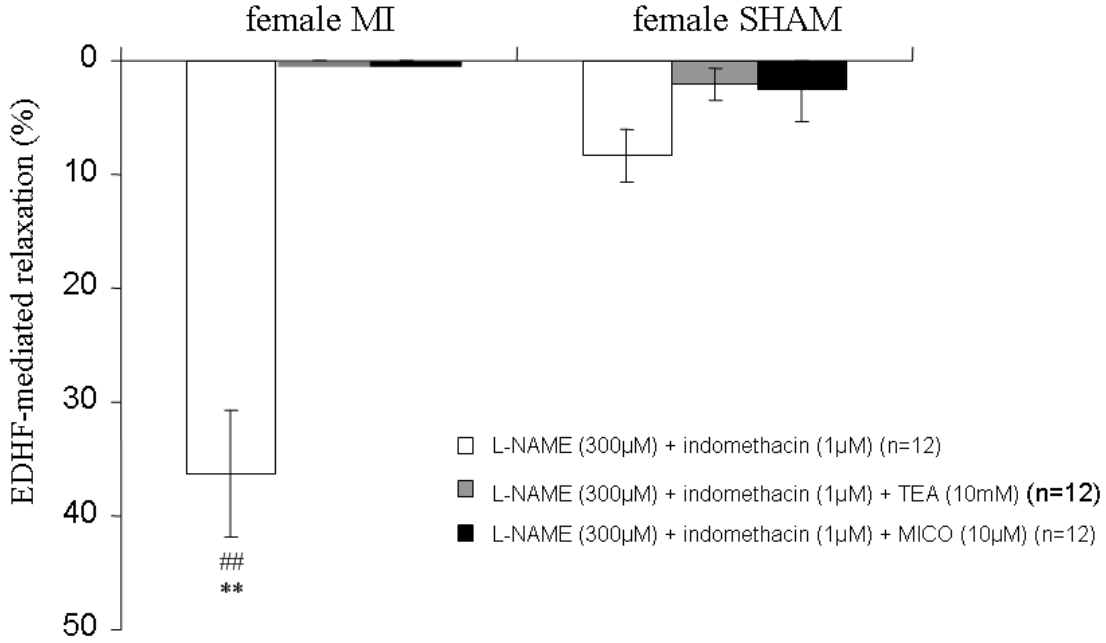

Ach log(M) in the presence of L-NAME and indometacin. ##:p<0.01 MI vs. sham.

Figure 3.15: NO-independent Ach induced vasodilation 42 days post-MI




Ach log(M) in the presence of L-NAME and indometacin. **:p<0.01 female vs. male, ##:p<0.01 MI vs. sham.

Figure 3.16: NO-independent vasodilation with addition of TEA or miconazole

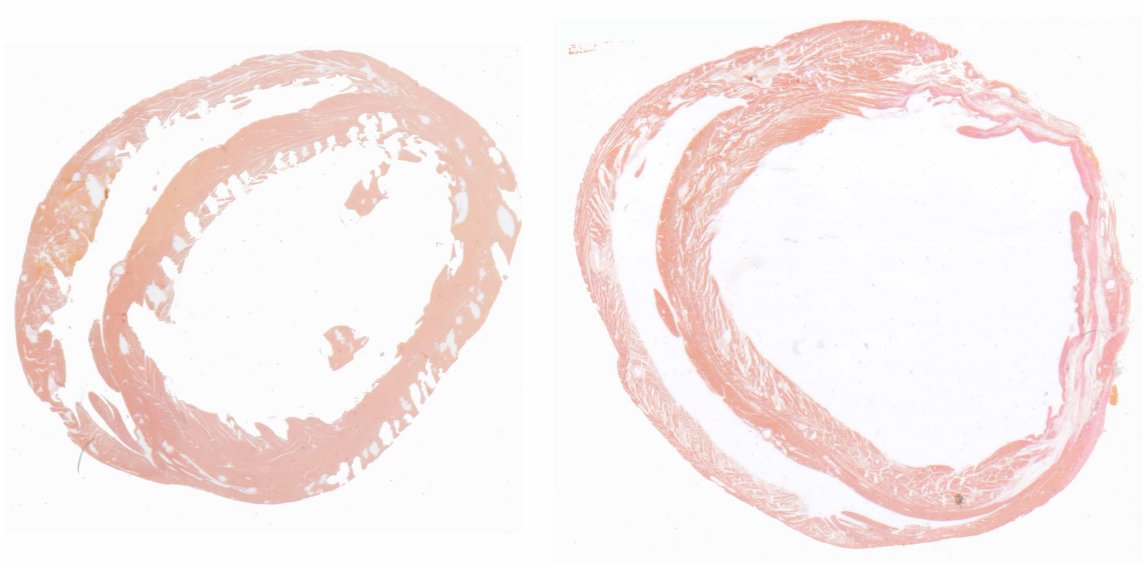



Ach -6 log(M). **: $p<0.01$ L-NAME + inodmetacin vs. L-NAME + indometacin + TEA, ##: $p<0.01$ L-NAME + inodmetacin vs. L-NAME + indometacin + miconazole.

## 3.4 Histology

Representative histological slides can be seen on figure 3.17 and figure 3.18 for males and females 42 days post-MI. Both infarcted groups show thinning and collagen deposition at the area of the scar. Furthermore infarcted hearts show an increase in ventricular diameter as clearly can be seen on the representative slides. Comparing male hearts to female hearts the male hearts seem to have thicker ventricular walls and less intraventricular diameters compared to the female hearts. However no measurements were performed.

Figure 3.17: Histology of females 42 days post-MI



Representative histological slides of both sham operated (left) and infarcted (right) females 42 days post-MI.

## 3.5 Gene Expression Profiling

### 3.5.1 Seven Days post-MI

At day seven post-MI gene expression analysis showed 681 targets significantly changed in females with MI and 479 targets in males with MI compared to the correlating sham group. The predominant response was up-regulation. 67.4% of targets in females with MI and 78.5% of targets in males with MI were up regulated ($p<0.01$). As can be seen on the Venn diagram in figure 3.19 only 193 targets were significantly changed in both genders the rest of the targets where either only changed in females (488) or in males (286) when comparing MI with sham groups. To define the functional classes the targets belong to, GO annotations were performed. The results of this annotation can be seen in

Figure 3.18: Histology of males 42 days post-MI

Representative histological slides of both sham operated (left) and infarcted (right) males 42 days post-MI.

figure 3.20 for absolute number of targets and figure 3.21 for percent of total up- or down-regulation respectively. The majority of targets belonged to the class of 'other or unknown' function. Besides that the highest changes can be seen in the groups of 'intracellular signaling and cell-cell communication', 'metabolism', 'gene and protein expression' and 'transport' in descending order. Most of the groups show no differences between the genders. Interestingly there seem to be more targets down-regulated relatively in 'gene and protein expression' in males. However this difference is not seen in the number of absolute targets.

### 3.5.2 42 Days post-MI

At 42 days post-MI gene expression analysis showed 490 targets significantly changed in females with MI and 217 targets significantly changed in males with MI compared to the correlating sham group. Like 7 days post-MI up-regulation was the predominant answer with 81.8% of targets up-regulated in females and 69.1% of targets significantly up-regulated in males with MI ($p<0.01$). The Venn diagram in figure 3.22 shows that only 53 targets are significantly changed in both genders whereas 437 and 164 are only changed in either females or males respectively. The results of the GO annotation can be seen in figure 3.23 and figure 3.24 for absolute number of targets and relative change in percent respectively. Here again the majority of genes belong to the class of 'others or unknown'. The majority of changes besides this class was seen in the classes of 'transport', 'intracellular signaling and cell-cell communication', 'gene and protein expression' and 'cell cycle and development' in descending order. Interestingly differences can be seen

between the genders in nearly all groups in relative as well as in absolute change. This is the most apparent in the classes of 'gene and protein expression', 'intracellular signaling and cell-cell communication' and 'metabolism'.

### 3.5.3 Changes in Time

Not only the differences between the genders at a certain timepoint but also the differences between the timepoints in a certain gender are of interest. Figure 3.25 and figure 3.26 show Venn diagrams comparing targets significantly changed 7 and 42 days post-MI in females and males respectively. A decrease in the number of targets was seen in both genders. Furthermore only 101 targets were the same in females at 7 and 42 days whereas 580 and 389 targets were only changed significantly at 7 and 42 days respectively comparing MI to sham groups. A similar picture can be seen in males, where only 49 targets were changed in both 7 and 42 days post-MI whereas 430 and 168 targets were only changed in 7 and 42 days respectively.

Figure 3.19: Venn diagram for males and females 7 days after MI

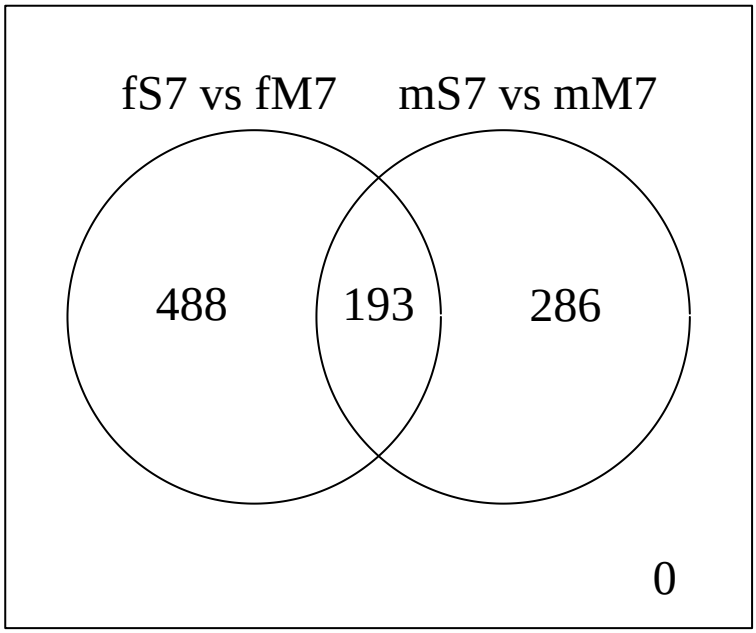



Figure 3.20: Annotated genes after 7 days total probesets

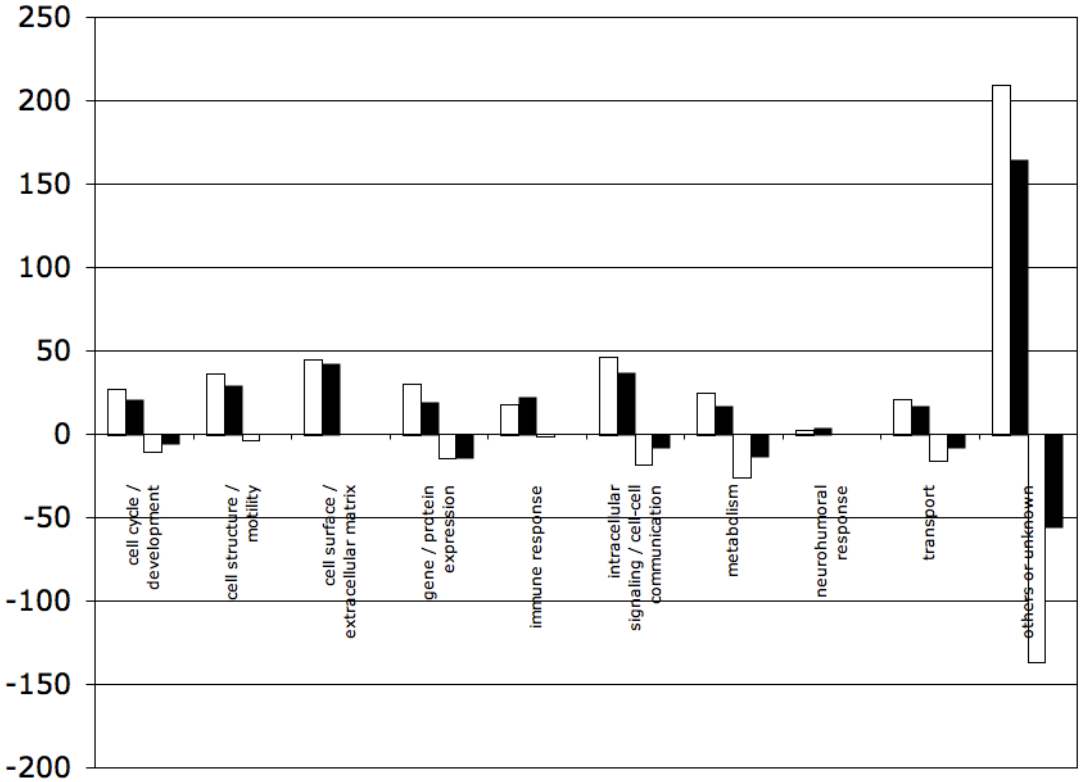


Figure 3.21: Annotated genes after 7 days in % of total change

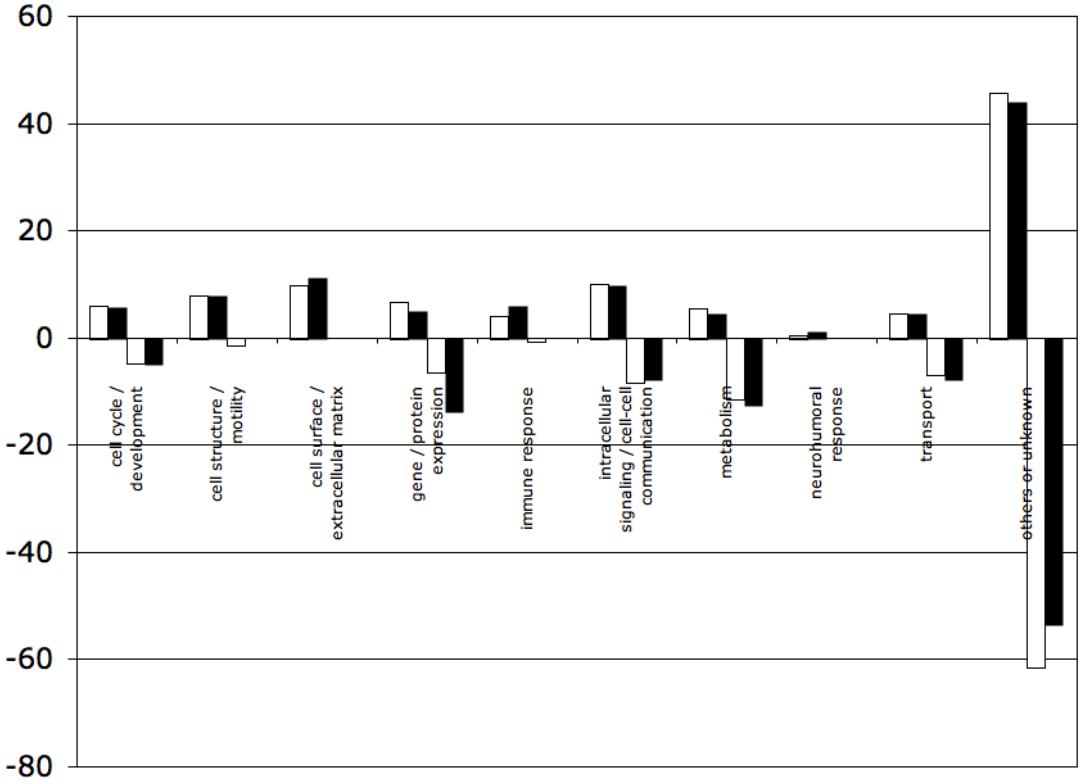



Figure 3.22: Venn diagram for males and females 42 days after MI

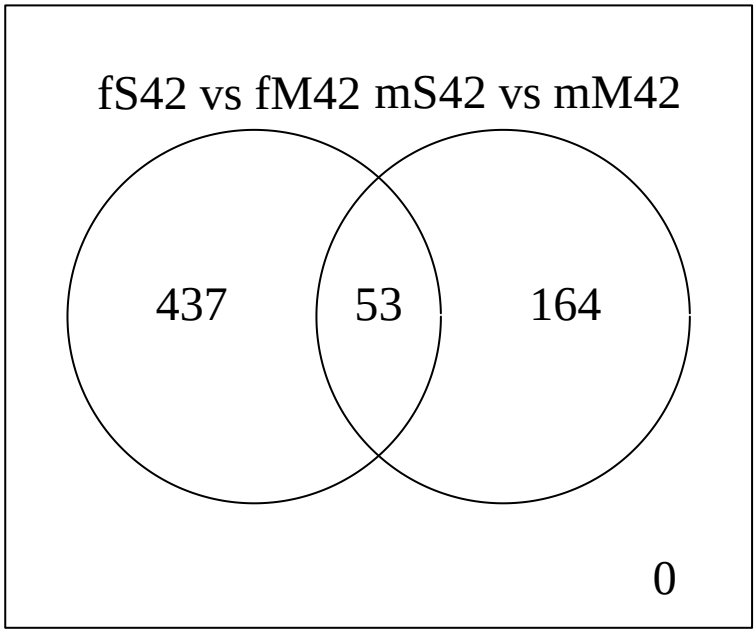


Figure 3.23: Annotated genes after 42 days total probesets

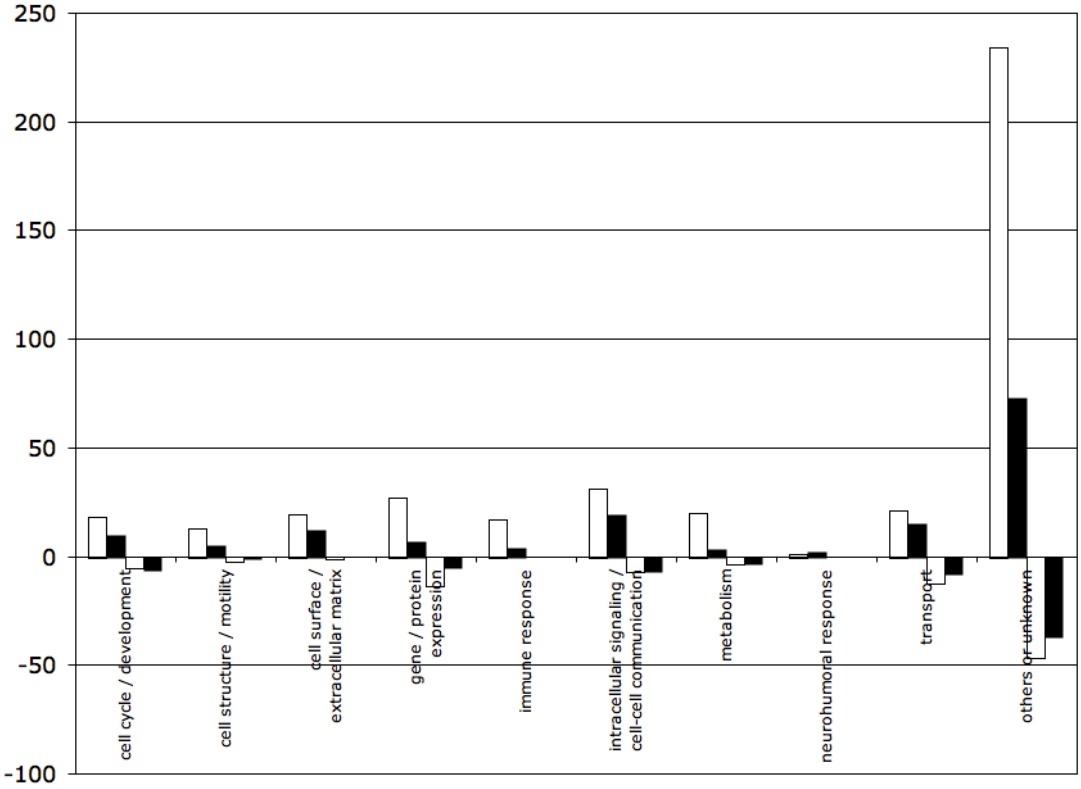



Figure 3.24: Annotated genes after 42 days in % of total change

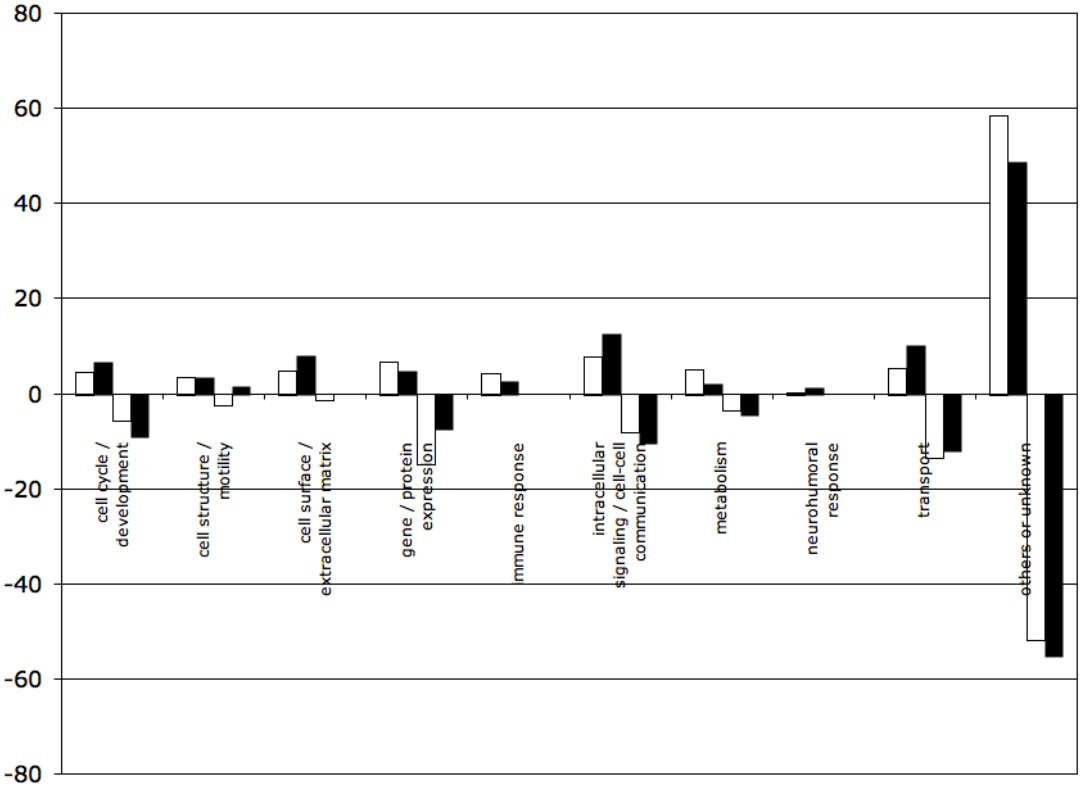


Figure 3.25: Venn diagram for females 7 and 42 days after MI

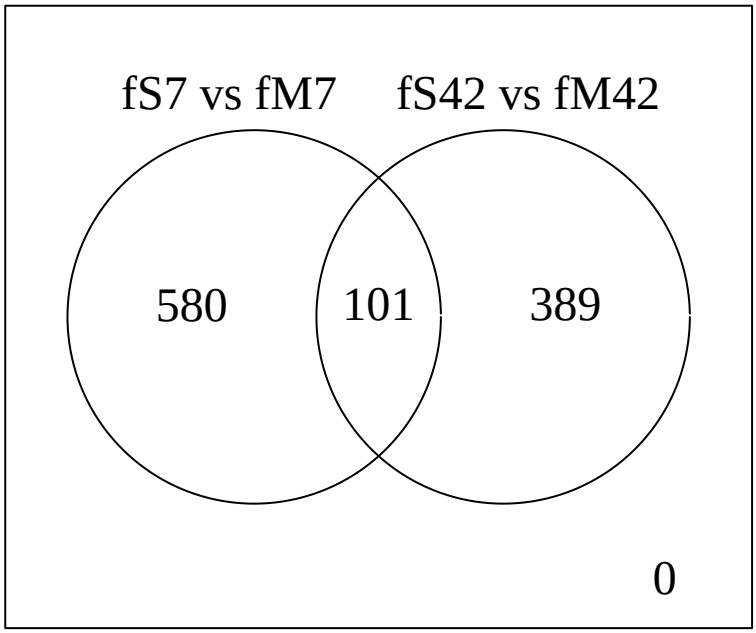
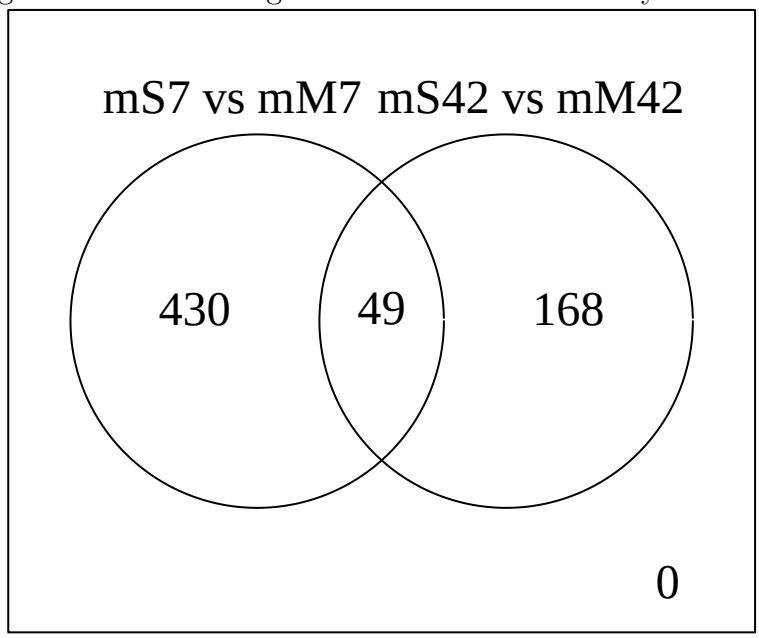



Figure 3.26: Venn diagram for males 7 and 42 days after MI



# Chapter 4

# Discussion

## 4.1 Morphology

Although the same age female rats were smaller than male rats throughout the whole study in both tibia length and bodyweight. However the bodyweight inside the genders were consistent. Consequently total heart weight and subsequent weights were smaller too. To get comparable data between the genders as well as to balance the individual variation of body size in groups all weights were put into ratio with bodyweight. As sham groups showed no significant differences in the weight ratios at any timepoint this seems to be a valid procedure to achieve comparable data. Furthermore ventricular weight to bodyweight ratios are often used as parameter for hypertrophy and allow direct comparison of hypertrophy between males and females.

Hypertrophy in males and females with myocardial infarction was similar at 7 and 42 days post-MI. Females with MI always showed a trend towards higher weight ratios than males however this did not turn out to be significant at these two time points. Nevertheless there was a difference in morphology between the genders on day 21. Females with MI showed a significant increase compared to either females with sham or males with MI in all four weight ratios measured. *These results suggests a faster development of hypertrophy post-MI in females.* Statistical analysis confirmed this hypothesis as it shows a significant interaction of gender, timepoint and infarction of both ventricular weight to bodyweight and right ventricular weight to bodyweight ratio.

This finding is confirmed by studies evaluating the effect of estrogens on post-MI remodeling[170, 171, 172]. Interestingly it is contradicted by two studies one using a physiologic hormone status[149] and another using gonadectomy and subsequent sex-hormone replacement[186]. Both studies showed increased hypertrophy in males[149] and animals receiving testosterone respectively[186]. Cavasin et al.

published a study on a mouse model using a mouse model of myocardial infarction with physiologic hormone status and reported a higher left ventricular to bodyweight ratio in females but a higher myocyte cross sectional area in males[148]. This shows clearly that weight ratios do not strongly correlate with myocyte volume. Another interesting finding was reported by Litwin et al. on a model similar to the one used in this study. They reported higher left ventricular to bodyweight ratios for females with MI but a tendency towards higher right ventricular to bodyweight ratios in males 6 weeks post-MI[188].
The debate on sex-specific differences in hypertrophy is not concluded yet. The differences seen in the results might be caused by differences in timepoints of evaluation since this study showed the highest difference between the sexes 21 days post-MI but further work has to be done to elucidate this process.

## 4.2 In-Vivo Hemodynamics

The smaller size of female hearts also reflects as smaller end-diastolic and end-systolic diameters and subsequently higher fractional shortening in echocardiography. This is to be seen at both 21 and 42 days in sham operated animals. Infarction increases the diameters in both sexes and decreases fractional shortening in the same time. Significantly increased diameters and lowered fractional shortening is to be seen at both 21 and 42 days. However at 42 days there is a trend towards smaller diameters and improved fractional shortening in females with MI compared in males. This trend turns out to be statistically significant for end-systolic diameter. In contrary *at 21 days although there are statistically significant differences in sham operated animals, diameters and fractional shortening in MI groups are the same.* Statistical analysis confirmed the influence of gender on echocardiographic parameters showing a significant interaction of gender and infarction for end-systolic diameter and fractional shortening and a significant interaction of gender, infarction and timepoint for end-diastolic diameter. Correlating to the ventricular failure developed after 42 days lung and liver wet to dry ratios as marker for edema are increased. There seems to be no difference in lung congestion between males and females. However males show a significantly higher liver congestion than males, which serves as an indicator for right ventricular function. This might be caused by right ventricular decompensation of males whereas females still compensate the increased load on the right ventricle secondary to left ventricular failure. Statistical analysis confirmed the latter by showing a significant interaction of gender and infarction on liver wet to dry ratio.

These findings are supported by studies examining the effect of estrogen on post-MI remodeling[170, 171, 172], physiological hormone status[188] as well as clinical research[143] all showing no significant influence of sex or estrogen on fractional shortening or ventricular diameters. However this findings are contradicted by two studies, one using a model of physiological hormone status and MI in mice[148] an a clinical study on one-year outcome post-MI[30]. The reason for this inconsistency is not yet clear, however estrogen seems to have no positive effect on post-MI myocardial function.

## 4.3 Endothelial Function

As discussed above secondary endothelial dysfunction post-MI is a field with diverging results. This study showed no endothelial dysfunction in both sexes at 7 and 42 days post-MI. Basal NO release was reduced at 7 days in both sexes and in males only 42 days post-MI. However the interesting part is an up-regulation of EDHF pathways seen at day 7 in both sexes and at day 42 in females only. This is confirmed by blocking EDHF pathway using TEA a $K^+$-channel blocker or miconazole a cytochrome p450 antagonist. It seems like at 7 days post-MI endothelial dysfunction is prohibited by up-regulation of EDHF pathways and this up-regulation is still prominent in females 42 days post-MI. Again the *timepoint of analysis plays a crucial role in finding differences.*

The absence of endothelial dysfunction post-MI well correlates with previous findings of preserved endothelial function in Sprague-Dawley rats[109, 110]. Interestingly basal NO release was restored in female rats at 6 weeks post-MI. This might be due to the stimulating effects of estrogens of eNOS[194], restoring basal NO release[195]. Interestingly one study using estrogen receptor-$\beta$ knock-out mice suggested that estrogens only show this effects in males[196]. This is supported by a clinical study on young healthy men showing reduced flow mediated dilatation when medicated with aromatase-inhibitors[197]. Endothelial dysfunction in post-MI heart failure is a multi-factorial process. The data obtained in this study suggests to add sex as one of this factors.

## 4.4 Gene-expression profiling

Gene-expression profiling using genechip® technology is a sensitive approach. The huge number of targets evaluated is a huge statistical challenge. Nevertheless it is a way of screening to get an overall idea of what is going on at transcription level. Up-regulation was the predominant answer in this study at both timepoints in

both genders. However *at 7 days there was significantly more up-regulation in males than in females.* A contrary picture showed at day 42 post-MI. However over the whole time more targets were significantly changed in females than in males comparing MI with sham groups. Interestingly only a small subset of targets were the same in males and females on both timepoints. The rest of the targets were only changed in either males or females. A similar picture can be seen when comparing 7 to 42 days in each sex separately. Only a small subset of targets is significantly changed in both 7 and 42 days the rest is either changed at 7 or at 42 days. In both sexes the number of significantly changed targets decreases with time. Go annotations give a pattern over transcriptional programs activated in the tissue at the moment of the examination. Therefore the processes activated can easily be spotted out. At 7 days the groups reacted similar in both males and females suggesting no huge differences between the genders. A contrary picture was seen at 42 days. In nearly all functional groups there were differences between males and females. *This finding suggests that although different targets are expressed at day 7 post-MI in males and females, the basic transcriptional programs activated are the same.* At day 42 post-MI this seems to be different. The different targets activated in males and females seem to be caused by a different transcriptional program activated. Once again timepoint proved to be crucial to discover gender-specific differences.

The only comparable work to this study has been published by Weinberg et al. in 2003[147]. They used a model of pressure overload and evaluated gender-specific differences in early and late hypertrophic response. Interestingly their finding quite confirms the results of this study. Only a small subset of targets were significantly changed comparing the genders in both acute and chronic phase of pressure overload hypertrophy. The majority of targets is either changed in males or females. Furthermore comparing acute with chronic banding again only a small subset was changed in both groups. The majority was either changed in acute or chronic setting of pressure overload. And correlating to the findings of this study the number of significantly changed targets decreased from acute to chronic. However one difference is to be seen: They found more targets significantly changed in males than in females in acute phase whereas there were about the same number of targets changed in chronic phase. This contradicts the findings in this study where females showed more targets significantly changed at all timepoints. Gene-expression profiling is as mentioned above a very sensitive tool to monitor processes in cells as well as in tissues. However there are certain drawbacks of this technology. The huge amount of data gained by Genechips put new challenges on bioinformatic analysis and statistics. Due to the huge amount of comparisons

made there will for sure be some significant differences. Like in many methods genechips only give a snapshot at a certain time (the time of snap-freezing the sample) of the transcriptional status in the cell. This study and many others showed the importance of timepoint upon the result of evaluation. Furthermore a huge amount of targets measured on genechips or their function are unknown at the moment. This demonstrates once again our little understanding of processes in sub-cellular level and the huge potential there is for upcoming research. As a result of this problems genechip data is reviewed very critical in the scientific society and it is correct to do so. Time will prove the strength and weaknesses of this and similar technologies.

## 4.5 Assembling the Pieces

The point that was stressed most throughout this chapter was time. And it seems like time is the factor gluing the pieces of this study together. All parameters showing differences show these in a time dependent manner. At day 7 post-MI in early remodeling not many differences were to be seen. In morphology and echocardiography the biggest contrast between the groups were observed at day 21 post-MI, with females showing an adverse progress compared to males. These two parameters didn't show that much contrast 42 days post-MI. In contrary endothelial function and gene-expression profiling showed the highest contrast at this late phase of remodeling. However it is to note that day 21 has not been evaluated in this two analyses. Morphologic and echocardiographic data suggests that females do not react different than males in sense of quantity but rather in velocity of adverse development. The reason of this differences might lay in the differential targets expressed in early remodeling. Although the transcriptional program in early remodeling seems to be similar between males and females there are targets expressed in only one of the sexes. Some of this targets might cause a faster development of hypertrophy and reduced hemodynamics in females. This correlates well with clinical as well as basic research findings. There is evidence for higher 1 year mortality[8, 29] and more frequent development of congestive heart failure in women[8]. Furthermore there are reports of worse prognosis for women post-MI especially in young age[176, 177]. Premenopausal status seems to worsen development post-MI. Although estrogen seems to be protective against the development of coronary artery disease at the moment an myocardial infarction happens this effect doesn't seem to be existent or even detrimental. The often cited better outcome in congestive heart failure in women seems to be caused by a difference in etiology rather than a real benefit in prognosis[135, 136, 140, 141].

Estrogen seems to have no beneficial effects concerning morphologic and functional parameters in basic research[170, 171, 172, 188] as well as in at least one double blind placebo controlled clinical trial[169]. However the phantom of beneficial effects of estrogens on the cardiovascular system is still in the mind of many researchers and practitioners. This idea seems to be untrue for post-MI remodeling. Critical evaluation of the influence of estrogens on other cardiovascular diseases have to follow.

## 4.6 Limitations of this Study

As post-MI remodeling is a very dynamic process snap shots, like the ones in this study, always render an incomplete picture. Little can be said about the dynamics of processes and therefore on the outcome. It only allows to do statements on the three selected timepoints. Since there are reports of more pronounced hypertrophy in males and this study reported a later onset of hypertrophy in males it might well be that at a later timepoint the hypertrophy of males could be more pronounced than in females. The same thing is to say about echocardiographic parameters. Results in endothelial dysfunction are very species and even strain specific. The results reported by this study should therefore be critically viewed if applied to another strain or species. Genechips as described above have a lot of limitations. Pooling strategy as used in this study should only be considered a screening tool and the results reported above should be seen in this light. To confirm these findings the results will be verified using a second independent method for a selected subset of targets.

## 4.7 Conclusion

Gender-specific differences do exist in post-MI remodeling in morphology, hemodynamics, endothelial function and gene-expression profile. This differences are highly time dependent. Furthermore *the main difference is not a difference in quantity or quality but in velocity of development of congestive heart failure post-MI*. Further research has to be done to understand this highly dynamic process.

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# Appendix A

# Appendix

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## A.2 Disclaimer

The fundamental problem of todays science and those doing it is to assume there is only one reality and that all of it's elements can be quantified and understood. What we know today is only the least common denominator of the subjective realities of those speaking up and telling them. This work, seen in this perspective, describes only the personal truth of the author and might not be valid in the readers reality.

# Appendix B

# Geneexpression Tables

## B.1 Probesets significantly changed comparing mS7 vs. mM7

| Probe Set ID | Gene Symbol | SLR2 | annotation |
|---|---|---|---|
| 1367661_at | S100a6 | 1,48 | cell cycle / development |
| 1367776_at | Cdc2a | 1,68 | cell cycle / development |
| 1368527_at | Ptgs2 | 1,7 | cell cycle / development |
| 1369084_a_at | Bok | 1,01 | cell cycle / development |
| 1369735_at | Gas6 | 1,03 | cell cycle / development |
| 1369968_at | Ptn | 1,51 | cell cycle / development |
| 1370267_at | Gsk3b | 1,76 | cell cycle / development |
| 1370282_at | RGD:61950 | 1,11 | cell cycle / development |
| 1370294_a_at | Cdc20 | 1,29 | cell cycle / development |
| 1370458_at | Hdgfrp3 | 1,62 | cell cycle / development |
| 1371527_at | Emp1 | 1,68 | cell cycle / development |
| 1371947_at | Ndn predicted | 1,38 | cell cycle / development |
| 1372685_at | Cdkn3 predicted | 3,5 | cell cycle / development |
| 1377064_at | Dusp6 | 1,08 | cell cycle / development |
| 1383075_at | Ccnd1 | 1,09 | cell cycle / development |
| 1387004_at | Nbl1 | 2,47 | cell cycle / development |
| 1387122_at | Plagl1 | 1,37 | cell cycle / development |
| 1387391_at | Cdkn1a | 3,38 | cell cycle / development |
| 1388479_at | Dpysl3 | 1,13 | cell cycle / development |
| 1390343_at | Ccnc | 1,72 | cell cycle / development |
| 1398362_at | Notch2 | 1,59 | cell cycle / development |
| 1369351_at | Cntn3 | -1,03 | cell cycle / development |
| 1372016_at | Gadd45b | -1,4 | cell cycle / development |
| 1377100_at | Aprin predicted | -1,43 | cell cycle / development |
| 1387226_at | Inexa | -1,2 | cell cycle / development |
| 1387927_a_at | Olfm1 | -1,49 | cell cycle / development |
| 1367570_at | Tagln | 1,07 | cell structure / motility |
| 1367574_at | Vim | 1,12 | cell structure / motility |
| 1368404_at | Dbn1 | 1,4 | cell structure / motility |

Continued on Next Page...

Table B.1 – Continued

| Probe Set ID | Gene Symbol | SLR2 | annotation |
|---|---|---|---|
| 1368824_at | Cald1 | 1,04 | cell structure / motility |
| 1368838_at | Tpm4 | 1,07 | cell structure / motility |
| 1369976_at | Dnclc1 | 1,13 | cell structure / motility |
| 1370033_at | RGD:620885 | 1,17 | cell structure / motility |
| 1370287_a_at | Tpm1 | 1,28 | cell structure / motility |
| 1370339_at | Tpm3 | 1,29 | cell structure / motility |
| 1370792_at | Mapre1 | 1,08 | cell structure / motility |
| 1370863_at | Krt2-5 | 2,08 | cell structure / motility |
| 1370949_at | Marcks | 1,32 | cell structure / motility |
| 1371184_x_at | Tpm3 | 2,16 | cell structure / motility |
| 1371239_s_at | Tpm3 | 1,29 | cell structure / motility |
| 1371530_at | Krt2-8 | 1,9 | cell structure / motility |
| 1371700_at | Mfap4 predicted | 1,56 | cell structure / motility |
| 1371895_at | Krt1-14 predicted | 2,9 | cell structure / motility |
| 1372325_at | Emilin1 predicted | 3,07 | cell structure / motility |
| 1372516_at | Kif22 predicted | 1,87 | cell structure / motility |
| 1373674_at | Mfap5 predicted | 2,62 | cell structure / motility |
| 1376185_at | RGD:1359118 | 1,5 | cell structure / motility |
| 1376924_a_at | Palmd predicted | 1,05 | cell structure / motility |
| 1386948_at | Nes | 1,81 | cell structure / motility |
| 1388111_at | Eln | 2,28 | cell structure / motility |
| 1388155_at | Krt1-18 | 4,43 | cell structure / motility |
| 1389189_at | Actn1 | 1,98 | cell structure / motility |
| 1398294_at | Actn1 | 1,45 | cell structure / motility |
| 1398303_s_at | Tpm3 | 1,3 | cell structure / motility |
| 1398888_at | H3f3b | 1,02 | cell structure / motility |
| 1367562_at | Sparc | 1,06 | cell surface / extracellular matrix |
| 1367581_a_at | Spp1 | 1,69 | cell surface / extracellular matrix |
| 1367712_at | Timp1 | 1,84 | cell surface / extracellular matrix |
| 1367849_at | Sdc1 | 1,11 | cell surface / extracellular matrix |
| 1367860_a_at | Mmp14 | 2,17 | cell surface / extracellular matrix |
| 1368171_at | Lox | 2,6 | cell surface / extracellular matrix |
| 1368172_a_at | Lox | 2,38 | cell surface / extracellular matrix |
| 1368347_at | Col5a3 | 4,85 | cell surface / extracellular matrix |
| 1368441_at | Msln | 1,15 | cell surface / extracellular matrix |
| 1368474_at | Vcam1 | 2,07 | cell surface / extracellular matrix |
| 1368829_at | Fbn1 | 1,4 | cell surface / extracellular matrix |
| 1369793_a_at | Mcam | 1,16 | cell surface / extracellular matrix |
| 1369955_at | Col5a1 | 1,39 | cell surface / extracellular matrix |
| 1370155_at | Col1a2 | 1,77 | cell surface / extracellular matrix |
| 1370234_at | Fn1 | 2,85 | cell surface / extracellular matrix |
| 1370301_at | Mmp2 | 1,09 | cell surface / extracellular matrix |
| 1370864_at | Col1a1 | 2,35 | cell surface / extracellular matrix |

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Table B.1 – Continued

| Probe Set ID | Gene Symbol | SLR2 | annotation |
|---|---|---|---|
| 1370895_at | Col5a2 | 2,23 | cell surface / extracellular matrix |
| 1370959_at | Col3a1 | 1,39 | cell surface / extracellular matrix |
| 1371349_at | LOC294337 | 1,66 | cell surface / extracellular matrix |
| 1371369_at | Col6a2 predicted | 1,99 | cell surface / extracellular matrix |
| 1372897_at | LOC497831 | 1,39 | cell surface / extracellular matrix |
| 1373401_at | — | 4,82 | cell surface / extracellular matrix |
| 1373463_at | Col5a2 | 2,17 | cell surface / extracellular matrix |
| 1373947_at | Dpt predicted | 1,56 | cell surface / extracellular matrix |
| 1374726_at | Fndc1 predicted | 1,89 | cell surface / extracellular matrix |
| 1374933_at | Mcam | 1,11 | cell surface / extracellular matrix |
| 1375144_at | Timp2 | 1,47 | cell surface / extracellular matrix |
| 1376099_at | Col5a1 | 1,69 | cell surface / extracellular matrix |
| 1376198_at | Asam | 1,48 | cell surface / extracellular matrix |
| 1386879_at | Lgals3 | 1,46 | cell surface / extracellular matrix |
| 1386912_at | Pcolce | 1,14 | cell surface / extracellular matrix |
| 1387351_at | Fbn1 | 2,3 | cell surface / extracellular matrix |
| 1387854_at | Col1a2 | 2,07 | cell surface / extracellular matrix |
| 1388054_a_at | Cspg2 | 1,33 | cell surface / extracellular matrix |
| 1388116_at | Col1a1 | 1,86 | cell surface / extracellular matrix |
| 1388138_at | Thbs4 | 1,51 | cell surface / extracellular matrix |
| 1388142_at | Cspg2 | 1,61 | cell surface / extracellular matrix |
| 1388143_at | Col18a1 | 1,5 | cell surface / extracellular matrix |
| 1388936_at | Cdh11 | 1,08 | cell surface / extracellular matrix |
| 1389533_at | Fbln2 | 1,36 | cell surface / extracellular matrix |
| 1393891_at | Col8a1 predicted | 1,4 | cell surface / extracellular matrix |
| 1367931_a_at | Ptbp1 | 1,02 | gene / protein expression |
| 1368321_at | Egr1 | 1,49 | gene / protein expression |
| 1368726_a_at | Zfp347 | 1,63 | gene / protein expression |
| 1370054_at | Cdkn2c | 1,28 | gene / protein expression |
| 1370510_a_at | Arntl | 2,07 | gene / protein expression |
| 1371293_at | — | 1,06 | gene / protein expression |
| 1374857_at | LOC499709 | 2,13 | gene / protein expression |
| 1376009_at | Mgea6 predicted | 1,05 | gene / protein expression |
| 1377433_at | Zfp580 predicted | 1,09 | gene / protein expression |
| 1385243_at | Maf | 1,04 | gene / protein expression |
| 1389404_at | Fkhl18 predicted | 1,88 | gene / protein expression |
| 1398350_at | Basp1 | 1,66 | gene / protein expression |
| 1368511_at | Bhlhb3 | -1,37 | gene / protein expression |
| 1368632_at | Foxg1 | -1,88 | gene / protein expression |
| 1368784_at | Acf | -1,78 | gene / protein expression |
| 1369063_at | Anp32a | -1,93 | gene / protein expression |
| 1370541_at | Nr1d2 | -1,27 | gene / protein expression |

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Table B.1 – Continued

| Probe Set ID | Gene Symbol | SLR2 | annotation |
|---|---|---|---|
| 1372266_at | Rev3l predicted | -1,26 | gene / protein expression |
| 1373763_at | Zfp297b | -2,79 | gene / protein expression |
| 1377013_at | — | -1,07 | gene / protein expression |
| 1387874_at | Dbp | -2,24 | gene / protein expression |
| 1390430_at | Nr1d2 | -1,22 | gene / protein expression |
| 1368394_at | Sfrp4 | 1,08 | gene / protein expression |
| 1371048_at | Foxe1 | 1,17 | gene / protein expression |
| 1371504_at | RGD1561181 predicted | 1,07 | gene / protein expression |
| 1374137_at | Elf1 | 1,28 | gene / protein expression |
| 1374477_at | Prrx2 predicted | 1,48 | gene / protein expression |
| 1374891_at | Brf2 | 1,05 | gene / protein expression |
| 1389701_at | Pgr | 1,01 | gene / protein expression |
| 1369850_at | Ugt2a1 | -1,24 | gene / protein expression |
| 1371967_at | Mrpl16 | -1,06 | gene / protein expression |
| 1374847_at | Lztr1 predicted | -1,02 | gene / protein expression |
| 1387430_at | Hsf2 | -1,09 | gene / protein expression |
| 1392566_at | Maf | 1,31 | gene / proteine expression |
| 1367850_at | LOC498276 | 2,22 | immune response |
| 1367973_at | Ccl2 | 2,74 | immune response |
| 1367998_at | Slpi /// LOC296356 | 1,13 | immune response |
| 1368000_at | C3 | 1,54 | immune response |
| 1368238_at | Pap | 1,98 | immune response |
| 1369672_at | Alox5ap | 1,11 | immune response |
| 1370892_at | C4a /// C4-2 | 1,7 | immune response |
| 1370928_at | Litaf | 1,04 | immune response |
| 1376574_at | C1qr1 | 1,04 | immune response |
| 1376652_at | C1qa predicted | 1,17 | immune response |
| 1387125_at | S100a9 | 1,35 | immune response |
| 1387396_at | Hamp | 1,14 | immune response |
| 1387687_at | Igsf6 | 1,14 | immune response |
| 1387868_at | Lbp | 1,51 | immune response |
| 1387902_a_at | LOC500180 /// LOC500183 | 4,34 | immune response |
| 1387952_a_at | Cd44 | 1,24 | immune response |
| 1388272_at | Igh-1a predicted | 1,6 | immune response |
| 1388602_at | Adn | 2,56 | immune response |
| 1389123_at | RGD:1303200 | 1,44 | immune response |
| 1389470_at | Bf | 1,15 | immune response |
| 1390659_at | Cd44 | 1,88 | immune response |
| 1398246_s_at | Fcgr3 /// LOC498276 | 2,13 | immune response |
| 1376734_at | Nov | 1,18 | intracellular signaling / cell cell communication |

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Table B.1 – Continued

| Probe Set ID | Gene Symbol | SLR2 | annotation |
|---|---|---|---|
| 1367584_at | Anxa2 | 1,16 | intracellular signaling / cell-cell communication |
| 1367614_at | Anxa1 | 1,46 | intracellular signaling / cell-cell communication |
| 1367631_at | Ctgf | 1,92 | intracellular signaling / cell-cell communication |
| 1367813_at | Ppp1r14a | 1,19 | intracellular signaling / cell-cell communication |
| 1367844_at | Gnai2 | 1,13 | intracellular signaling / cell-cell communication |
| 1367846_at | S100a4 | 1,86 | intracellular signaling / cell-cell communication |
| 1367859_at | Tgfb3 | 1,22 | intracellular signaling / cell-cell communication |
| 1367940_at | Cmkor1 | 1,1 | intracellular signaling / cell-cell communication |
| 1368176_at | Rara | 1,41 | intracellular signaling / cell-cell communication |
| 1368408_at | Gprk5 | 1,21 | intracellular signaling / cell-cell communication |
| 1368706_at | Tm4sf4 | 2,77 | intracellular signaling / cell-cell communication |
| 1368883_at | Nov | 1,09 | intracellular signaling / cell-cell communication |
| 1369407_at | Tnfrsf11b | 3,89 | intracellular signaling / cell-cell communication |
| 1369484_at | Wisp2 | 1,85 | intracellular signaling / cell-cell communication |
| 1369771_at | Irs1 | 1,13 | intracellular signaling / cell-cell communication |
| 1370055_at | Rab3d | 1,79 | intracellular signaling / cell-cell communication |
| 1370256_at | Fzd1 | 1,49 | intracellular signaling / cell-cell communication |
| 1370948_a_at | Marcks | 1,14 | intracellular signaling / cell-cell communication |
| 1371644_at | Ptk9 predicted | 1,2 | intracellular signaling / cell-cell communication |
| 1371785_at | Tnfrsf12a | 1,26 | intracellular signaling / cell-cell communication |
| 1372031_at | Dab2 | 1,01 | intracellular signaling / cell-cell communication |
| 1372168_s_at | Igfbp6 | 1,91 | intracellular signaling / cell-cell communication |

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Table B.1 – Continued

| Probe Set ID | Gene Symbol | SLR2 | annotation |
|---|---|---|---|
| 1372835_at | Rhoj predicted | 1,49 | intracellular signaling / cell-cell communication |
| 1373611_at | Il17r predicted | 1,05 | intracellular signaling / cell-cell communication |
| 1373911_at | Postn predicted | 4,53 | intracellular signaling / cell-cell communication |
| 1374730_at | Tyrobp | 1,42 | intracellular signaling / cell-cell communication |
| 1375043_at | Fos | 5,83 | intracellular signaling / cell-cell communication |
| 1376425_at | Tgfb2 | 1,01 | intracellular signaling / cell-cell communication |
| 1379766_at | Tg | 1,22 | intracellular signaling / cell-cell communication |
| 1386890_at | S100a10 | 1,07 | intracellular signaling / cell-cell communication |
| 1387276_at | RGD:621187 | 1,31 | intracellular signaling / cell-cell communication |
| 1387625_at | Igfbp6 | 2,66 | intracellular signaling / cell-cell communication |
| 1388469_at | — | 1,86 | intracellular signaling / cell-cell communication |
| 1389905_at | Pepd | 1,11 | intracellular signaling / cell-cell communication |
| 1390119_at | Sfrp2 | 2,68 | intracellular signaling / cell-cell communication |
| 1397161_a_at | Itsn | 1,19 | intracellular signaling / cell-cell communication |
| 1398304_at | Fzd2 | 1,11 | intracellular signaling / cell-cell communication |
| 1368303_at | Per2 | -1,89 | intracellular signaling / cell-cell communication |
| 1371615_at | Dgat2 | -1,03 | intracellular signaling / cell-cell communication |
| 1371776_at | Pik3r1 | -1,16 | intracellular signaling / cell-cell communication |
| 1373666_at | Rapgef5 | -1,3 | intracellular signaling / cell-cell communication |
| 1387224_at | Dgkb | -1,2 | intracellular signaling / cell-cell communication |
| 1387504_at | Il1rl2 | -1,07 | intracellular signaling / cell-cell communication |
| 1389931_at | Crhr2 | -1,17 | intracellular signaling / cell-cell communication |

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Table B.1 – Continued

| Probe Set ID | Gene Symbol | SLR2 | annotation |
|---|---|---|---|
| 1398438_at | Gtpbp3 | -1,54 | intracellular signaling / cell-cell communication |
| 1371732_at | Dpt predicted | 1,38 | intradellular signaling / cell-cell communication |
| 1367668_a_at | Scd2 | 1,05 | metabolism |
| 1367856_at | G6pdx | 1,11 | metabolism |
| 1367896_at | Ca3 | 1,76 | metabolism |
| 1368003_at | Aldh1a2 | 1,04 | metabolism |
| 1368128_at | Pla2g2a | 1,1 | metabolism |
| 1368878_at | Idi1 | 1,6 | metabolism |
| 1370051_at | Tgm1 | 3,54 | metabolism |
| 1370154_at | Lyz | 1,22 | metabolism |
| 1370161_at | Ssg1 | 1,49 | metabolism |
| 1370862_at | Apoe | 1,4 | Metabolism |
| 1371537_at | — | 1,15 | metabolism |
| 1371774_at | Sat | 1,23 | metabolism |
| 1372229_at | — | 1,15 | metabolism |
| 1376089_at | — | 1,07 | metabolism |
| 1388650_at | Top2a | 4,49 | metabolism |
| 1388924_at | Angptl4 | 1,44 | metabolism |
| 1389871_at | Got2 | 1,35 | metabolism |
| 1367734_at | Akr1b4 | -1 | metabolism |
| 1367839_at | Fdft1 | -1,11 | metabolism |
| 1368188_at | Hpd | -1,04 | metabolism |
| 1369292_at | Hsd17b1 | -1,52 | metabolism |
| 1370019_at | Sult1a1 | -2,42 | metabolism |
| 1370187_at | Pccb | -1,22 | metabolism |
| 1370952_at | Gstm2 | -1,22 | metabolism |
| 1372382_at | Prkag2 | -1,27 | metabolism |
| 1376753_at | Fpgt | -1,27 | metabolism |
| 1376883_at | MGC93920 | -1,21 | metabolism |
| 1387703_a_at | Usp2 | -1,43 | metabolism |
| 1388210_at | Mte1 | -1,53 | metabolism |
| 1388617_at | Bphl predicted | -1,17 | metabolism |
| 1367564_at | Nppa | 2,13 | neurohumoral response |
| 1368912_at | Trh | 4,64 | neurohumoral response |
| 1384240_at | Agtr1a | 1,15 | neurohumoral response |
| 1370012_at | Ptgis | 1,01 | neurohumoral response |
| 1367655_at | Tmsb10 | 1,73 | others or unknown |
| 1367686_at | RAMP4 | 1,07 | others or unknown |
| 1368187_at | Gpnmb | 1,87 | others or unknown |
| 1368528_at | Mic2l1 | 1,41 | others or unknown |
| 1368555_at | Cd37 | 1,99 | others or unknown |
| 1368821_at | Fstl1 | 1,8 | others or unknown |
| 1368822_at | Fstl1 | 1,73 | others or unknown |

Continued on Next Page...

Table B.1 – Continued

| Probe Set ID | Gene Symbol | SLR2 | annotation |
|---|---|---|---|
| 1368840_at | Lr8 | 1,3 | others or unknown |
| 1369422_at | Fap | 1,28 | others or unknown |
| 1369648_at | Calcrl | 1,04 | others or unknown |
| 1370312_at | Spon1 | 1,32 | others or unknown |
| 1370347_at | Pdlim7 | 1,14 | others or unknown |
| 1370383_s_at | RT1-Db1 | 1,05 | others or unknown |
| 1370389_at | LOC497844 | 1,56 | others or unknown |
| 1370967_at | — | 1,24 | others or unknown |
| 1371033_at | RT1-Bb | 1,22 | others or unknown |
| 1371331_at | Fstl1 | 1,76 | others or unknown |
| 1371368_at | Sec61a1 | 1,57 | others or unknown |
| 1371432_at | Vat1 predicted | 1,37 | others or unknown |
| 1371447_at | Plac8 predicted | 1,41 | others or unknown |
| 1371462_at | Igfbp4 | 1,1 | others or unknown |
| 1371583_at | Rbm3 | 1,31 | others or unknown |
| 1371731_at | MGC72974 | 1,46 | others or unknown |
| 1371782_at | RGD:1359688 | 1,26 | others or unknown |
| 1371803_at | Gm2a | 1,02 | others or unknown |
| 1371832_at | Leo1 | 3,94 | others or unknown |
| 1371843_at | RGD:1359165 | 1,1 | others or unknown |
| 1371861_at | — | 1,17 | others or unknown |
| 1371922_at | — | 1,32 | others or unknown |
| 1371924_at | Olfml3 predicted | 1,27 | others or unknown |
| 1371927_at | — | 1,29 | others or unknown |
| 1371970_at | LOC499322 | 3,83 | others or unknown |
| 1372006_at | — | 1,98 | others or unknown |
| 1372042_at | Cklfsf3 predicted | 1 | others or unknown |
| 1372219_at | MGC109519 | 1,13 | others or unknown |
| 1372256_at | — | 1,06 | others or unknown |
| 1372286_at | LOC302313 | 1,19 | others or unknown |
| 1372293_at | — | 1,97 | others or unknown |
| 1372301_at | Aebp1 predicted | 1,28 | others or unknown |
| 1372308_at | — | 1,19 | others or unknown |
| 1372640_at | LOC499410 | 1,99 | others or unknown |
| 1372729_at | Procr predicted | 1,18 | others or unknown |
| 1372756_at | — | 1,04 | others or unknown |
| 1372824_at | Plekhf2 predicted | 1,14 | others or unknown |
| 1372870_at | Kdelr3 predicted | 1,12 | others or unknown |
| 1372947_at | Pls3 | 1,22 | others or unknown |
| 1373000_at | LOC317181 | 4,34 | others or unknown |
| 1373054_at | Cdw92 | 1,55 | others or unknown |
| 1373128_at | RGD:1359365 | 1,09 | others or unknown |
| 1373152_at | RGD:1359545 | 1,25 | others or unknown |

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Table B.1 – Continued

| Probe Set ID | Gene Symbol | SLR2 | annotation |
|---|---|---|---|
| 1373156_at | RGD:1359132 | 1,29 | others or unknown |
| 1373221_at | — | 1,67 | others or unknown |
| 1373250_at | — | 1,93 | others or unknown |
| 1373290_at | LOC312299 | 1,73 | others or unknown |
| 1373347_at | Acbd3 | 1,59 | others or unknown |
| 1373416_at | RGD1311673 predicted | 1,06 | others or unknown |
| 1373421_at | Tgif predicted | 1,29 | others or unknown |
| 1373460_at | LOC501103 | 1,18 | others or unknown |
| 1373471_at | Rnf166 | 1,43 | others or unknown |
| 1373487_at | Spon1 | 1,31 | others or unknown |
| 1373628_at | — | 3,07 | others or unknown |
| 1373673_at | — | 1,4 | others or unknown |
| 1373699_at | — | 1,42 | others or unknown |
| 1373727_at | LOC499856 | 2,37 | others or unknown |
| 1373750_at | Leprel2 predicted | 1,37 | others or unknown |
| 1373781_a_at | — | 1,65 | others or unknown |
| 1373823_at | LOC498709 | 1,75 | others or unknown |
| 1373882_at | — | 1,06 | others or unknown |
| 1373962_at | — | 1,12 | others or unknown |
| 1374061_at | RGD1307606 predicted | 1,07 | others or unknown |
| 1374172_at | — | 1,8 | others or unknown |
| 1374204_at | Wsb1 predicted | 1,12 | others or unknown |
| 1374238_at | — | 1,18 | others or unknown |
| 1374276_at | — | 1,08 | others or unknown |
| 1374529_at | Thbs1 | 2,18 | others or unknown |
| 1374564_at | Dtx2 | 1,25 | others or unknown |
| 1374666_at | Pcf11 predicted | 1,15 | others or unknown |
| 1374696_at | — | 2,3 | others or unknown |
| 1374759_at | Galntl1 predicted | 1,07 | others or unknown |
| 1374775_at | Mki67 predicted /// LOC310382 /// LOC366937 | 3,69 | others or unknown |
| 1374779_at | F13a | 1,17 | others or unknown |
| 1374809_at | — | 1,35 | others or unknown |
| 1375010_at | Cd68 predicted | 1,03 | others or unknown |
| 1375170_at | S100a11 predicted | 1,35 | others or unknown |
| 1375267_at | RGD:1303221 | 1,7 | others or unknown |
| 1375420_at | Tp53i11 predicted | 1,38 | others or unknown |
| 1375422_at | — | 1,05 | others or unknown |

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Table B.1 – Continued

| Probe Set ID | Gene Symbol | SLR2 | annotation |
|---|---|---|---|
| 1375523_at | Marcks | 1,35 | others or unknown |
| 1375575_at | — | 1,14 | others or unknown |
| 1375857_at | LOC309499 | 1,28 | others or unknown |
| 1375862_at | — | 1,04 | others or unknown |
| 1375962_at | — | 1,04 | others or unknown |
| 1376100_at | RGD1305887 predicted | 2,88 | others or unknown |
| 1376105_at | Col14a1 predicted | 1,35 | others or unknown |
| 1376377_at | RGD1565114 predicted | 1,29 | others or unknown |
| 1376379_a_at | RGD1309906 | 1,05 | others or unknown |
| 1376831_at | RGD1308747 predicted | 5,85 | others or unknown |
| 1376900_at | Aptx | 1,25 | others or unknown |
| 1376905_at | — | 1,48 | others or unknown |
| 1376943_at | — | 1,18 | others or unknown |
| 1377056_at | — | 1,17 | others or unknown |
| 1377086_at | C1qtnf3 predicted | 2,14 | others or unknown |
| 1377092_at | — | 1,2 | others or unknown |
| 1377421_at | — | 1,2 | others or unknown |
| 1377461_at | RGD1561952 predicted | 1,11 | others or unknown |
| 1377832_at | Plk4 predicted | 1,29 | others or unknown |
| 1379702_at | — | 2,7 | others or unknown |
| 1379747_at | Prss35 | 4,48 | others or unknown |
| 1382849_at | — | 3,29 | others or unknown |
| 1383912_at | — | 1,63 | others or unknown |
| 1386154_at | RGD1304927 predicted | 1,07 | others or unknown |
| 1386461_at | — | 1,06 | others or unknown |
| 1387774_at | Ywhaz | 1,01 | others or unknown |
| 1388395_at | G0s2 predicted | 1,54 | others or unknown |
| 1388408_at | RGD1307129 predicted | 1,79 | others or unknown |
| 1388425_at | RGD1305890 | 1,11 | others or unknown |
| 1388439_at | LOC360627 | 1,07 | others or unknown |
| 1388478_at | — | 1,15 | others or unknown |
| 1388484_at | Ube2c predicted | 1,37 | others or unknown |
| 1388527_at | — | 1,7 | others or unknown |
| 1388541_at | — | 1,66 | others or unknown |
| 1388569_at | Serpinf1 | 1,27 | others or unknown |
| 1388596_at | Cotl1 predicted | 1 | others or unknown |
| 1388674_at | Cdkn1a | 1,28 | others or unknown |

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Table B.1 – Continued

| Probe Set ID | Gene Symbol | SLR2 | annotation |
|---|---|---|---|
| 1388786_at | — | 1,17 | others or unknown |
| 1388893_at | RGD:1359293 | 1,29 | others or unknown |
| 1388902_at | Loxl1 predicted | 3,69 | others or unknown |
| 1388985_at | LOC310926 /// LOC501211 | 1,32 | others or unknown |
| 1388990_at | Mki67ip | 1 | others or unknown |
| 1389006_at | Mpeg1 | 1,13 | others or unknown |
| 1389020_at | — | 1,78 | others or unknown |
| 1389039_at | — | 1,02 | others or unknown |
| 1389129_at | RGD1308952 | 3,14 | others or unknown |
| 1389208_at | LOC363495 | 1,01 | others or unknown |
| 1389368_at | Magi1 predicted | 1,11 | others or unknown |
| 1389383_at | — | 1,22 | others or unknown |
| 1389408_at | Rrm2 | 1,92 | others or unknown |
| 1389419_at | — | 1,03 | others or unknown |
| 1389424_at | — | 1,04 | others or unknown |
| 1389435_at | — | 1,18 | others or unknown |
| 1389490_at | Cd164l1 predicted | 1,85 | others or unknown |
| 1389500_at | — | 1,82 | others or unknown |
| 1389553_at | RGD:1359528 | 1,6 | others or unknown |
| 1389617_at | — | 1,15 | others or unknown |
| 1389722_at | — | 1,13 | others or unknown |
| 1389756_at | Melk predicted | 1,42 | others or unknown |
| 1389809_at | — | 1,31 | others or unknown |
| 1390122_at | RGD1565175 predicted | 1,08 | others or unknown |
| 1390145_at | — | 1,68 | others or unknown |
| 1390249_at | RGD1305464 predicted | 1,19 | others or unknown |
| 1390298_at | — | 1,47 | others or unknown |
| 1390536_at | — | 1,29 | others or unknown |
| 1390604_s_at | Itgb3bp predicted | 3,36 | others or unknown |
| 1390698_at | — | 1,25 | others or unknown |
| 1390708_at | — | 1,93 | others or unknown |
| 1392819_at | Ms4a11 predicted | 1,44 | others or unknown |
| 1392939_at | — | 1,42 | others or unknown |
| 1392958_at | LOC498035 | 1,16 | others or unknown |
| 1393860_at | — | 2,34 | others or unknown |
| 1394080_at | — | 1,34 | others or unknown |
| 1398373_at | B3galt3 predicted | 1,25 | others or unknown |

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Table B.1 – Continued

| Probe Set ID | Gene Symbol | SLR2 | annotation |
|---|---|---|---|
| 1398380_at | RGD1311476 predicted | 1,1 | others or unknown |
| 1398421_at | — | 1,01 | others or unknown |
| 1398445_at | — | 1,17 | others or unknown |
| 1398464_at | — | 1,74 | others or unknown |
| 1367741_at | Herpud1 | -1,62 | others or unknown |
| 1368495_at | Rln1 | -1,21 | others or unknown |
| 1371405_at | — | -1,11 | others or unknown |
| 1371479_at | LOC500939 | -1,5 | others or unknown |
| 1371623_at | RGD1309248 predicted | -1,02 | others or unknown |
| 1372091_at | RGD:1303258 | -1,55 | others or unknown |
| 1372248_at | Sesn1 predicted | -1,11 | others or unknown |
| 1372400_at | RGD1563853 predicted | -1,4 | others or unknown |
| 1372474_at | — | -1,15 | others or unknown |
| 1372676_at | RGD1304560 predicted | -1,71 | others or unknown |
| 1372920_at | — | -1,65 | others or unknown |
| 1373254_at | — | -1,25 | others or unknown |
| 1373444_at | — | -1,06 | others or unknown |
| 1373708_at | MGC125034 | -1,06 | others or unknown |
| 1373930_at | — | -1,09 | others or unknown |
| 1374088_at | — | -1,02 | others or unknown |
| 1374347_at | — | -1,1 | others or unknown |
| 1374374_x_at | RGD1308066 predicted | -1,71 | others or unknown |
| 1374688_at | — | -1,02 | others or unknown |
| 1375053_at | — | -1,06 | others or unknown |
| 1375346_at | RGD1563941 predicted | -1,4 | others or unknown |
| 1375445_at | — | -1,58 | others or unknown |
| 1375464_at | RGD1564982 predicted | -1,24 | others or unknown |
| 1375849_at | — | -1,19 | others or unknown |
| 1375911_at | RGD:735140 | -1,4 | others or unknown |
| 1376139_at | Plxna3_mapped | -1,56 | others or unknown |
| 1376155_at | RGD1561110 predicted | -1,07 | others or unknown |
| 1376243_at | LOC304692 | -1,49 | others or unknown |
| 1376495_at | — | -1,06 | others or unknown |
| 1376626_at | MGC94941 | -1,01 | others or unknown |
| 1376678_at | RGD1562438 predicted | -1,3 | others or unknown |
| 1376746_at | Ldhd predicted | -3,49 | others or unknown |

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Table B.1 – Continued

| Probe Set ID | Gene Symbol | SLR2 | annotation |
|---|---|---|---|
| 1377297_at | — | -1,58 | others or unknown |
| 1377365_at | RGD1311019 predicted | -1,04 | others or unknown |
| 1377380_at | — | -1,14 | others or unknown |
| 1377381_at | — | -1,28 | others or unknown |
| 1377419_at | — | -2,12 | others or unknown |
| 1377772_at | Tmeff1 | -1,19 | others or unknown |
| 1385438_at | — | -1,09 | others or unknown |
| 1385866_at | — | -1,35 | others or unknown |
| 1386212_at | Spna1 predicted | -1,24 | others or unknown |
| 1386466_at | — | -1,21 | others or unknown |
| 1389219_at | LOC498312 | -1,48 | others or unknown |
| 1389314_at | Nvl predicted | -1,24 | others or unknown |
| 1389460_at | — | -1,16 | others or unknown |
| 1389632_at | — | -2,82 | others or unknown |
| 1389800_at | — | -1,01 | others or unknown |
| 1389864_at | — | -1,8 | others or unknown |
| 1390161_at | RGD:1359578 | -1,52 | others or unknown |
| 1390164_at | — | -1,24 | others or unknown |
| 1390171_at | — | -1,11 | others or unknown |
| 1390540_at | — | -1,02 | others or unknown |
| 1392798_at | Pdia2 predicted | -1,08 | others or unknown |
| 1394061_at | — | -1,25 | others or unknown |
| 1398440_at | — | -1,71 | others or unknown |
| 1367559_at | Ftl1 | 1,12 | transport |
| 1367939_at | Rbp1 | 2,18 | transport |
| 1368419_at | Cp | 2,47 | transport |
| 1368420_at | Cp | 1,47 | transport |
| 1368565_at | Slc1a3 | 1,91 | transport |
| 1369269_at | Galnt1 | 1,17 | transport |
| 1370228_at | Tf /// Srprb predicted | 1,13 | transport |
| 1370248_at | Fxyd6 | 1 | transport |
| 1371029_at | Pkd1 | 1,01 | transport |
| 1375633_at | RGD:1303043 | 1,17 | transport |
| 1386913_at | Gp38 | 1,03 | transport |
| 1387011_at | Lcn2 | 1,24 | transport |
| 1387058_at | Pctp | 1,11 | transport |
| 1387287_a_at | Abcc9 | 1,2 | transport |
| 1387519_at | Vamp1 | 1,05 | transport |
| 1387794_at | Fcna | 1,43 | transport |
| 1388292_at | Kcnj3 | 1,03 | transport |
| 1367650_at | Lcn7 | -1,11 | transport |
| 1368304_at | Fmo3 | -1,15 | transport |
| 1369625_at | Aqp1 | -1,01 | transport |

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Table B.1 – Continued

| Probe Set ID | Gene Symbol | SLR2 | annotation |
|---|---|---|---|
| 1369668_x_at | Vps52 | -1,2 | transport |
| 1370103_at | Hcn1 | -1,12 | transport |
| 1373657_at | Slc31a2 | -1,11 | transport |
| 1374741_at | Esrra | -1,07 | transport |
| 1387053_at | Fmo1 | -1,03 | transport |

## B.2 Probesets significantly changed comparing fS7 vs. fM7

| Probe Set ID | Gene Symbol | SLR2 | annotation |
|---|---|---|---|
| 1367776_at | Cdc2a | 1,5 | cell cycle / development |
| 1367866_at | Fbln5 | 1,01 | cell cycle / development |
| 1367875_at | Gak | 1,15 | cell cycle / development |
| 1368125_at | Slc12a4 | 1,56 | cell cycle / development |
| 1368527_at | Ptgs2 | 2,33 | cell cycle / development |
| 1369197_at | Apaf1 | 1,39 | cell cycle / development |
| 1369262_at | Casp8 | 3,21 | cell cycle / development |
| 1369530_at | Isl2 | 1,92 | cell cycle / development |
| 1369665_a_at | Il18 | 1,17 | cell cycle / development |
| 1369735_at | Gas6 | 1,09 | cell cycle / development |
| 1369941_at | Dap | 1,05 | cell cycle / development |
| 1370247_a_at | Pmp22 | 1,1 | cell cycle / development |
| 1370282_at | RGD:61950 | 1,62 | cell cycle / development |
| 1370295_at | Nme1 | 1,17 | cell cycle / development |
| 1370328_at | Dkk3 | 1,22 | cell cycle / development |
| 1371527_at | Emp1 | 1,12 | cell cycle / development |
| 1371551_at | Traf4 predicted | 1,16 | cell cycle / development |
| 1373914_at | Scgf | 2,13 | cell cycle / development |
| 1374739_at | LOC500727 | 1,08 | cell cycle / development |
| 1375168_at | Hdac7a | 1,41 | cell cycle / development |
| 1386938_at | Anpep | 1,49 | cell cycle / development |
| 1387143_at | Ppp1r9b | 1,05 | cell cycle / development |
| 1388099_a_at | Tfpt | 1,41 | cell cycle / development |
| 1388479_at | Dpysl3 | 1,5 | cell cycle / development |
| 1389555_at | RGD:1302974 | 1,41 | cell cycle / development |
| 1398362_at | Notch2 | 1,4 | cell cycle / development |
| 1368545_at | Cflar | -1,28 | cell cycle / development |
| 1369068_at | Cul5 | -1,87 | cell cycle / development |
| 1369192_at | Cdkn1b | -2,47 | cell cycle / development |
| 1371131_a_at | Txnip | -1,06 | cell cycle / development |
| 1372520_at | Mcl1 | -1,03 | cell cycle / development |
| 1372926_at | Timp3 | -1,95 | cell cycle / development |
| 1375872_at | Fcmd predicted | -1,25 | cell cycle / development |

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Table B.2 – Continued

| Probe Set ID | Gene Symbol | SLR2 | annotation |
|---|---|---|---|
| 1385839_x_at | Tm2d1 predicted | -1,1 | cell cycle / development |
| 1388105_at | D123 | -1,47 | cell cycle / development |
| 1398813_at | Ube1c | -1,08 | cell cycle / development |
| 1368202_a_at | Dab2 | 1,2 | cell cycle /development |
| 1367570_at | Tagln | 1,79 | cell structure / motility |
| 1367574_at | Vim | 1,02 | cell structure / motility |
| 1368404_at | Dbn1 | 1,11 | cell structure / motility |
| 1368838_at | Tpm4 | 1,15 | cell structure / motility |
| 1369942_at | Actn4 | 1,07 | cell structure / motility |
| 1370033_at | RGD:620885 | 1,23 | cell structure / motility |
| 1370158_at | Myh10 | 1,29 | cell structure / motility |
| 1370307_at | Agrn | 1,01 | cell structure / motility |
| 1370339_at | Tpm3 | 1,07 | cell structure / motility |
| 1370340_x_at | Tpm3 | 1,11 | cell structure / motility |
| 1370462_at | Hmmr | 1,41 | cell structure / motility |
| 1370857_at | RGD:621676 | 1,4 | cell structure / motility |
| 1371139_at | Pls3 | 3,1 | cell structure / motility |
| 1371239_s_at | Tpm3 | 1,05 | cell structure / motility |
| 1371575_at | Msn | 1,03 | cell structure / motility |
| 1371653_at | — | 1,08 | cell structure / motility |
| 1371700_at | Mfap4 predicted | 2,06 | cell structure / motility |
| 1372325_at | Emilin1 predicted | 2,12 | cell structure / motility |
| 1372516_at | Kif22 predicted | 1,02 | cell structure / motility |
| 1373591_at | Arfip2 | 1,02 | cell structure / motility |
| 1373674_at | Mfap5 predicted | 2,14 | cell structure / motility |
| 1373897_at | — | 1,79 | cell structure / motility |
| 1375367_at | RGD:1359203 | 1,09 | cell structure / motility |
| 1376766_at | Fmnl1 predicted | 1,15 | cell structure / motility |
| 1379936_at | Tpm1 | 1,92 | cell structure / motility |
| 1386925_at | Arpc1b | 1,41 | cell structure / motility |
| 1386948_at | Nes | 1,06 | cell structure / motility |
| 1387402_at | Myh9 | 1,32 | cell structure / motility |
| 1388111_at | Eln | 1,75 | cell structure / motility |
| 1388139_at | Myh2 | 1,09 | cell structure / motility |
| 1388460_at | Capg predicted | 1,09 | cell structure / motility |
| 1388932_at | Lama5 | 1,46 | cell structure / motility |
| 1389189_at | Actn1 | 1,56 | cell structure / motility |
| 1398294_at | Actn1 | 1,42 | cell structure / motility |
| 1398303_s_at | Tpm3 | 1,39 | cell structure / motility |
| 1399147_at | Dncli1 | 3,68 | cell structure / motility |
| 1370738_a_at | Trdn | -3,13 | cell structure / motility |
| 1375542_at | Rdx | -1,11 | cell structure / motility |
| 1376924_a_at | Palmd predicted | -1,4 | cell structure / motility |

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Table B.2 – Continued

| Probe Set ID | Gene Symbol | SLR2 | annotation |
|---|---|---|---|
| 1367562_at | Sparc | 2,09 | cell surface / extracellular matrix |
| 1367581_a_at | Spp1 | 1,44 | cell surface / extracellular matrix |
| 1367594_at | Bgn | 1,34 | cell surface / extracellular matrix |
| 1367712_at | Timp1 | 1,63 | cell surface / extracellular matrix |
| 1367744_at | Maged2 | 1,43 | cell surface / extracellular matrix |
| 1367860_a_at | Mmp14 | 1,97 | cell surface / extracellular matrix |
| 1368171_at | Lox | 2,13 | cell surface / extracellular matrix |
| 1368172_a_at | Lox | 1,62 | cell surface / extracellular matrix |
| 1368347_at | Col5a3 | 3,21 | cell surface / extracellular matrix |
| 1368530_at | Mmp12 | 2,41 | cell surface / extracellular matrix |
| 1368829_at | Fbn1 | 2,31 | cell surface / extracellular matrix |
| 1369793_a_at | Mcam | 1,12 | cell surface / extracellular matrix |
| 1369955_at | Col5a1 | 2,29 | cell surface / extracellular matrix |
| 1370043_at | Alcam | 1,61 | cell surface / extracellular matrix |
| 1370130_at | RGD:619921 | 1,29 | cell surface / extracellular matrix |
| 1370155_at | Col1a2 | 2,64 | cell surface / extracellular matrix |
| 1370234_at | Fn1 | 2,95 | cell surface / extracellular matrix |
| 1370864_at | Col1a1 | 2,51 | cell surface / extracellular matrix |
| 1370895_at | Col5a2 | 2,05 | cell surface / extracellular matrix |
| 1370959_at | Col3a1 | 1,87 | cell surface / extracellular matrix |
| 1371032_at | Nid1 | 1,03 | cell surface / extracellular matrix |
| 1371349_at | LOC294337 | 1,5 | cell surface / extracellular matrix |
| 1371369_at | Col6a2 predicted | 2,04 | cell surface / extracellular matrix |
| 1372439_at | Col4a1 predicted | 1,02 | cell surface / extracellular matrix |
| 1372897_at | LOC497831 | 1,54 | cell surface / extracellular matrix |
| 1373245_at | Col4a1 predicted | 1,55 | cell surface / extracellular matrix |
| 1373401_at | — | 3,15 | cell surface / extracellular matrix |
| 1373463_at | Col5a2 | 2,01 | cell surface / extracellular matrix |
| 1373947_at | Dpt predicted | 1,9 | cell surface / extracellular matrix |
| 1374726_at | Fndc1 predicted | 2,52 | cell surface / extracellular matrix |
| 1376099_at | Col5a1 | 1,45 | cell surface / extracellular matrix |
| 1386879_at | Lgals3 | 1,28 | cell surface / extracellular matrix |
| 1386912_at | Pcolce | 1,18 | cell surface / extracellular matrix |
| 1387351_at | Fbn1 | 2,27 | cell surface / extracellular matrix |
| 1387854_at | Col1a2 | 2,41 | cell surface / extracellular matrix |
| 1388054_a_at | Cspg2 | 1,71 | cell surface / extracellular matrix |
| 1388116_at | Col1a1 | 2,81 | cell surface / extracellular matrix |
| 1388138_at | Thbs4 | 2,59 | cell surface / extracellular matrix |
| 1388142_at | Cspg2 | 1,12 | cell surface / extracellular matrix |
| 1388143_at | Col18a1 | 1,88 | cell surface / extracellular matrix |
| 1388459_at | Col18a1 | 4,5 | cell surface / extracellular matrix |
| 1388936_at | Cdh11 | 1,31 | cell surface / extracellular matrix |

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Table B.2 – Continued

| Probe Set ID | Gene Symbol | SLR2 | annotation |
|---|---|---|---|
| 1389533_at | Fbln2 | 1,29 | cell surface / extracellular matrix |
| 1389966_at | Col6a3 predicted | 1,73 | cell surface / extracellular matrix |
| 1393891_at | Col8a1 predicted | 2,65 | cell surface / extracellular matrix |
| 1368321_at | Egr1 | 1,08 | gene / protein expression |
| 1368510_at | Gata1 | 1,18 | gene / protein expression |
| 1368571_at | Cyln2 | 1,29 | gene / protein expression |
| 1370054_at | Cdkn2c | 1,64 | gene / protein expression |
| 1370159_at | Smarcd2 | 1,09 | gene / protein expression |
| 1372483_at | Zfp469 predicted | 1,35 | gene / protein expression |
| 1372653_at | Fkbp11 predicted | 1,13 | gene / protein expression |
| 1373599_at | — | 1,35 | gene / protein expression |
| 1374154_at | — | 1,05 | gene / protein expression |
| 1375218_at | Tgfb1i4 | 1,01 | gene / protein expression |
| 1375249_at | Eif2c1 predicted | 1,13 | gene / protein expression |
| 1375661_at | Sox11 | 1,55 | gene / protein expression |
| 1376325_at | — | 1,16 | gene / protein expression |
| 1378038_at | Ptbp2 | 1,02 | gene / protein expression |
| 1378140_at | Arl11 predicted | 1,77 | gene / protein expression |
| 1387060_at | Copeb | 1,2 | gene / protein expression |
| 1387169_at | Tle3 | 1,43 | gene / protein expression |
| 1387343_at | Cebpd | 1,48 | gene / protein expression |
| 1388761_at | Hdac1 predicted | 4,42 | gene / protein expression |
| 1389432_at | RGD:1303084 | 1,11 | gene / protein expression |
| 1390415_at | — | 1,57 | gene / protein expression |
| 1398350_at | Basp1 | 1,66 | gene / protein expression |
| 1368249_at | Klf15 | -1,24 | gene / protein expression |
| 1369737_at | Crem | -2,41 | gene / protein expression |
| 1370751_at | RGD:727924 | -1,66 | gene / protein expression |
| 1372266_at | Rev3l predicted | -1,12 | gene / protein expression |
| 1374857_at | LOC499709 | -1,31 | gene / protein expression |
| 1376884_a_at | Rpl3l predicted | -1,12 | gene / protein expression |
| 1388901_at | Fkbp5 predicted | -1,04 | gene / protein expression |
| 1367804_at | Apcs | 1,13 | gene / protein expression |
| 1368394_at | Sfrp4 | 2,2 | gene / protein expression |
| 1371400_at | Thrsp | 1,05 | gene / protein expression |
| 1372367_at | — | 1,03 | gene / protein expression |
| 1373499_at | Gas5 | 1,75 | gene / protein expression |
| 1387036_at | Hes1 | 1,12 | gene / protein expression |
| 1389137_at | Cit | 1,18 | gene / protein expression |
| 1390046_at | Adam8 predicted | 1,06 | gene / protein expression |
| 1368376_at | Nr0b2 | -1,01 | gene / protein expression |

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Table B.2 – Continued

| Probe Set ID | Gene Symbol | SLR2 | annotation |
|---|---|---|---|
| 1370474_at | Thrb | -1,4 | gene / protein expression |
| 1371504_at | RGD1561181 predicted | -1,58 | gene / protein expression |
| 1372245_at | Wdr39 | -1,03 | gene / protein expression |
| 1372269_at | Med6 predicted | -1,1 | gene / protein expression |
| 1376121_at | Phf10 | -1,13 | gene / protein expression |
| 1376805_at | Rnf2 | -1,21 | gene / protein expression |
| 1367998_at | Slpi /// LOC296356 | 1,26 | immune response |
| 1368000_at | C3 | 1,27 | immune response |
| 1368393_at | C1qr1 | 2,16 | immune response |
| 1368558_s_at | Aif1 | 1,14 | immune response |
| 1370847_at | Spon2 | 1,61 | immune response |
| 1370892_at | C4a /// C4-2 | 1,14 | immune response |
| 1370904_at | RGD:735053 | 1,12 | immune response |
| 1371015_at | Mx1 | 1,04 | immune response |
| 1371079_at | Fcgr2b | 1,73 | immune response |
| 1371262_at | Igha /// LOC314492 /// RGD:1359626 /// LOC500731 /// LOC500733 /// LOC500734 /// LOC500735 /// LOC500736 /// LOC501425 /// LOC503065 /// LOC503070 | 1,21 | immune response |
| 1374334_at | Igha | 1,16 | immune response |
| 1387868_at | Lbp | 1,09 | immune response |
| 1387902_a_at | LOC500180 /// LOC500183 | 2,76 | immune response |
| 1387952_a_at | Cd44 | 1,07 | immune response |
| 1387969_at | Cxcl10 | 1,82 | immune response |
| 1388130_at | Zyx | 1,04 | immune response |
| 1388272_at | Igh-1a predicted | 4,92 | immune response |
| 1388602_at | Adn | 1,02 | immune response |
| 1368494_at | S100a8 | -1,42 | immune response |
| 1369305_at | Rab3il1 | 1,05 | intracelluar signaling / cell-cell communication |
| 1368114_at | Fgf13 | -1,37 | intracelluar signaling / cell-cell communication |
| 1376734_at | Nov | 1,14 | intracellular signaling / cell cell communication |

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Table B.2 – Continued

| Probe Set ID | Gene Symbol | SLR2 | annotation |
|---|---|---|---|
| 1367584_at | Anxa2 | 1,57 | intracellular signaling / cell-cell communication |
| 1367631_at | Ctgf | 1,56 | intracellular signaling / cell-cell communication |
| 1367844_at | Gnai2 | 1,31 | intracellular signaling / cell-cell communication |
| 1367846_at | S100a4 | 2,23 | intracellular signaling / cell-cell communication |
| 1367859_at | Tgfb3 | 1,58 | intracellular signaling / cell-cell communication |
| 1368010_at | Ptpn6 | 1,03 | intracellular signaling / cell-cell communication |
| 1368808_at | Cap1 | 1,03 | intracellular signaling / cell-cell communication |
| 1368883_at | Nov | 1,09 | intracellular signaling / cell-cell communication |
| 1368940_at | P2ry2 | 1,06 | intracellular signaling / cell-cell communication |
| 1369260_a_at | Mpp4 | 1,37 | intracellular signaling / cell-cell communication |
| 1369263_at | Wnt5a | 1,51 | intracellular signaling / cell-cell communication |
| 1369407_at | Tnfrsf11b | 1,77 | intracellular signaling / cell-cell communication |
| 1369443_at | Angptl2 | 1,51 | intracellular signaling / cell-cell communication |
| 1369484_at | Wisp2 | 3,05 | intracellular signaling / cell-cell communication |
| 1369645_at | Oprl1 | 1,14 | intracellular signaling / cell-cell communication |
| 1369646_at | Oprl | 1,08 | intracellular signaling / cell-cell communication |
| 1369736_at | Emp1 | 1,4 | intracellular signaling / cell-cell communication |
| 1370603_a_at | Ptprc | 1,01 | intracellular signaling / cell-cell communication |
| 1370642_s_at | Pdgfrb /// LOC497724 | 1,04 | intracellular signaling / cell-cell communication |
| 1371113_a_at | Tfrc | 1,21 | intracellular signaling / cell-cell communication |
| 1371487_at | Sh3bgrl3 predicted | 1,05 | intracellular signaling / cell-cell communication |
| 1371632_at | — | 1,01 | intracellular signaling / cell-cell communication |

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Table B.2 – Continued

| Probe Set ID | Gene Symbol | SLR2 | annotation |
|---|---|---|---|
| 1372168_s_at | Igfbp6 | 2,23 | intracellular signaling / cell-cell communication |
| 1372935_at | — | 1,38 | intracellular signaling / cell-cell communication |
| 1373425_at | LOC365842 | 1,3 | intracellular signaling / cell-cell communication |
| 1373911_at | Postn predicted | 2,85 | intracellular signaling / cell-cell communication |
| 1374730_at | Tyrobp | 1 | intracellular signaling / cell-cell communication |
| 1375043_at | Fos | 1,33 | intracellular signaling / cell-cell communication |
| 1375224_at | Phlda3 predicted | 1,71 | intracellular signaling / cell-cell communication |
| 1376425_at | Tgfb2 | 2,36 | intracellular signaling / cell-cell communication |
| 1385814_at | Map3k3 predicted | 1,29 | intracellular signaling / cell-cell communication |
| 1387276_at | RGD:621187 | 1,05 | intracellular signaling / cell-cell communication |
| 1387444_at | Ptprh | 1,01 | intracellular signaling / cell-cell communication |
| 1387523_at | Ptgdr /// LOC498475 | 1,21 | intracellular signaling / cell-cell communication |
| 1387625_at | Igfbp6 | 1,99 | intracellular signaling / cell-cell communication |
| 1388469_at | — | 1,22 | intracellular signaling / cell-cell communication |
| 1388750_at | Tfrc | 1,18 | intracellular signaling / cell-cell communication |
| 1389315_at | Git2 | 1,52 | intracellular signaling / cell-cell communication |
| 1390119_at | Sfrp2 | 2,63 | intracellular signaling / cell-cell communication |
| 1392672_at | Scgf | 1,37 | intracellular signaling / cell-cell communication |
| 1393669_at | RGD:1359415 | 2,6 | intracellular signaling / cell-cell communication |
| 1398304_at | Fzd2 | 2,57 | intracellular signaling / cell-cell communication |
| 1398345_at | — | 1,3 | intracellular signaling / cell-cell communication |
| 1368132_at | Tob1 | -1,17 | intracellular signaling / cell-cell communication |

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Table B.2 – Continued

| Probe Set ID | Gene Symbol | SLR2 | annotation |
|---|---|---|---|
| 1368358_a_at | Ptprr | -1,34 | intracellular signaling / cell-cell communication |
| 1368854_at | Vsnl1 | -1,08 | intracellular signaling / cell-cell communication |
| 1368924_at | Ghr | -1,26 | intracellular signaling / cell-cell communication |
| 1369152_at | Ppp3r1 | -1,39 | intracellular signaling / cell-cell communication |
| 1369352_at | Hipk3 | -1,1 | intracellular signaling / cell-cell communication |
| 1370061_at | Rab3b | -1,46 | intracellular signaling / cell-cell communication |
| 1371060_at | Trim23 | -1,81 | intracellular signaling / cell-cell communication |
| 1371776_at | Pik3r1 | -1,02 | intracellular signaling / cell-cell communication |
| 1374235_at | Dscr1l1 | -1 | intracellular signaling / cell-cell communication |
| 1374989_at | Asb12 | -1,1 | intracellular signaling / cell-cell communication |
| 1375692_at | Mapk1 | -1,1 | intracellular signaling / cell-cell communication |
| 1382105_at | Gnb5 | -4,65 | intracellular signaling / cell-cell communication |
| 1382375_at | Wnt5a | -1,1 | intracellular signaling / cell-cell communication |
| 1386950_at | Ppp1cb | -2,33 | intracellular signaling / cell-cell communication |
| 1388048_a_at | Inpp4b | -1,46 | intracellular signaling / cell-cell communication |
| 1388305_at | Araf | -1,06 | intracellular signaling / cell-cell communication |
| 1371732_at | Dpt predicted | 1,35 | intradellular signaling / cell-cell communication |
| 1367497_at | Ptdss1 | 1,08 | metabolism |
| 1367708_a_at | Fasn | 1,25 | metabolism |
| 1368027_at | Tbxas1 | 1,32 | metabolism |
| 1368259_at | Ptgs1 | 1,14 | metabolism |
| 1368370_at | Adcy4 | 1,19 | metabolism |
| 1369460_at | Slc7a2 | 1,04 | metabolism |
| 1369929_at | Psap | 1,02 | metabolism |
| 1370154_at | Lyz | 1,59 | metabolism |
| 1370161_at | Ssg1 | 1,26 | metabolism |
| 1370220_at | Scpep1 | 1,26 | metabolism |
| 1370862_at | Apoe | 1,79 | Metabolism |

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Table B.2 – Continued

| Probe Set ID | Gene Symbol | SLR2 | annotation |
|---|---|---|---|
| 1371774_at | Sat | 1,13 | metabolism |
| 1373150_at | Comtd1 predicted | 1,07 | metabolism |
| 1373600_at | LOC300173 | 1,36 | metabolism |
| 1374976_a_at | Soat1 | 1,87 | metabolism |
| 1383303_at | Sah | 1,3 | metabolism |
| 1383945_at | Umpk predicted | 1,22 | metabolism |
| 1387376_at | Aox1 | 1,83 | metabolism |
| 1387570_at | Manea | 1,32 | metabolism |
| 1388650_at | Top2a | 2,47 | metabolism |
| 1389688_at | Leprel1 | 1,74 | metabolism |
| 1390420_at | Cpxm1 predicted | 1,25 | metabolism |
| 1390588_at | — | 2,22 | metabolism |
| 1398349_at | Ak2 | 1,12 | metabolism |
| 1399162_a_at | Ddb1 | 1,28 | metabolism |
| 1367544_at | Rnf111 predicted | -1,15 | metabolism |
| 1367908_at | Gcsh | -1,11 | metabolism |
| 1368814_at | Aldh6a1 | -1,43 | metabolism |
| 1369150_at | Pdk4 | -1,39 | metabolism |
| 1369629_at | Adk | -1,23 | metabolism |
| 1369785_at | Ppat | -1,09 | metabolism |
| 1370019_at | Sult1a1 | -1,81 | metabolism |
| 1370237_at | Hadhsc | -1,01 | metabolism |
| 1370385_at | Pla2g6 | -1,42 | metabolism |
| 1372323_at | Sardh | -1,06 | metabolism |
| 1372524_at | — | -1,17 | metabolism |
| 1373201_at | Dbt | -1,33 | metabolism |
| 1384466_at | RGD:1359368 | -1,93 | metabolism |
| 1387022_at | Aldh1a1 | -1,07 | metabolism |
| 1387206_at | B4galt6 | -1,28 | metabolism |
| 1387896_at | Scp2 | -1,08 | metabolism |
| 1388210_at | Mte1 | -2,68 | metabolism |
| 1388211_s_at | Cte1 /// Mte1 | -1,73 | metabolism |
| 1388410_at | Ugp2 predicted | -1,07 | metabolism |
| 1388617_at | Bphl predicted | -1,06 | metabolism |
| 1389114_at | RGD1309144 | -1,01 | metabolism |
| 1389548_at | Adhfe1 predicted | -2 | metabolism |
| 1389572_at | Me3 predicted | -1,02 | metabolism |
| 1389989_at | Atrx | -4,72 | metabolism |
| 1390388_at | Fech predicted | -1,08 | metabolism |
| 1367564_at | Nppa | 2,62 | neurohumoral response |
| 1370012_at | Ptgis | 1,64 | neurohumoral response |

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Table B.2 – Continued

| Probe Set ID | Gene Symbol | SLR2 | annotation |
|---|---|---|---|
| 1367768_at | Lxn | 1,61 | others or unknown |
| 1367986_at | Ptgfrn | 1,04 | others or unknown |
| 1367993_at | Rsn | 1,06 | others or unknown |
| 1368187_at | Gpnmb | 2,73 | others or unknown |
| 1368247_at | Hspa1a /// Hspa1b | 1,05 | others or unknown |
| 1368276_at | Syp | 1,23 | others or unknown |
| 1368399_a_at | Pgcp | 1,12 | others or unknown |
| 1368676_at | Dnch2 /// LOC497827 | 1,6 | others or unknown |
| 1368821_at | Fstl1 | 1,83 | others or unknown |
| 1368822_at | Fstl1 | 2,37 | others or unknown |
| 1368840_at | Lr8 | 1,56 | others or unknown |
| 1368976_at | Cd38 | 1,01 | others or unknown |
| 1369422_at | Fap | 1,46 | others or unknown |
| 1369453_at | Epn1 | 1,12 | others or unknown |
| 1369723_at | Xylt2 | 1,25 | others or unknown |
| 1369947_at | Ctsk | 1,27 | others or unknown |
| 1370000_at | Nucb2 | 1,01 | others or unknown |
| 1370347_at | Pdlim7 | 1,44 | others or unknown |
| 1370383_s_at | RT1-Db1 | 1,34 | others or unknown |
| 1370394_at | RGD:1359626 /// LOC500728 | 2,77 | others or unknown |
| 1370883_at | RT1-Da | 1,22 | others or unknown |
| 1370885_at | Ctsz | 1,24 | others or unknown |
| 1370887_at | Tgfb1i1 | 1,36 | others or unknown |
| 1370964_at | Ass | 1,18 | others or unknown |
| 1371033_at | RT1-Bb | 1,19 | others or unknown |
| 1371037_at | Pros1 | 1,01 | others or unknown |
| 1371194_at | Tnfaip6 | 1,47 | others or unknown |
| 1371331_at | Fstl1 | 2,18 | others or unknown |
| 1371368_at | Sec61a1 | 1,23 | others or unknown |
| 1371382_at | LOC293860 | 1,38 | others or unknown |
| 1371411_at | Plxnb2 predicted | 1,21 | others or unknown |
| 1371412_a_at | Nrep | 1,27 | others or unknown |
| 1371432_at | Vat1 predicted | 1,25 | others or unknown |
| 1371447_at | Plac8 predicted | 1,42 | others or unknown |
| 1371462_at | Igfbp4 | 1,46 | others or unknown |
| 1371563_at | Rcc2 predicted | 1,21 | others or unknown |
| 1371583_at | Rbm3 | 1,37 | others or unknown |
| 1371735_at | — | 1,49 | others or unknown |
| 1371771_at | — | 1,62 | others or unknown |
| 1371782_at | RGD:1359688 | 1,3 | others or unknown |
| 1371784_at | RGD:1303226 | 1,43 | others or unknown |

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Table B.2 – Continued

| Probe Set ID | Gene Symbol | SLR2 | annotation |
|---|---|---|---|
| 1371803_at | Gm2a | 1,32 | others or unknown |
| 1371847_at | — | 1,07 | others or unknown |
| 1371924_at | Olfml3 predicted | 1,28 | others or unknown |
| 1371927_at | — | 1,24 | others or unknown |
| 1372006_at | — | 1,35 | others or unknown |
| 1372042_at | Cklfsf3 predicted | 1,24 | others or unknown |
| 1372050_at | — | 1,25 | others or unknown |
| 1372063_at | LOC497938 | 1,7 | others or unknown |
| 1372125_at | Gpx7 predicted | 1,33 | others or unknown |
| 1372146_at | — | 1,53 | others or unknown |
| 1372174_at | Peflin | 1,06 | others or unknown |
| 1372219_at | MGC109519 | 1,3 | others or unknown |
| 1372285_at | — | 1,32 | others or unknown |
| 1372293_at | — | 1,38 | others or unknown |
| 1372301_at | Aebp1 predicted | 1,74 | others or unknown |
| 1372357_at | Tbc1d20 | 1,09 | others or unknown |
| 1372410_at | C1qtnf6 predicted | 1,62 | others or unknown |
| 1372447_at | — | 1,01 | others or unknown |
| 1372640_at | LOC499410 | 5,14 | others or unknown |
| 1372655_at | — | 1,09 | others or unknown |
| 1372658_at | Dmn | 1,08 | others or unknown |
| 1372772_at | — | 1,12 | others or unknown |
| 1372778_at | — | 1,03 | others or unknown |
| 1372870_at | Kdelr3 predicted | 1,3 | others or unknown |
| 1372979_at | — | 1,09 | others or unknown |
| 1373000_at | LOC317181 | 1,47 | others or unknown |
| 1373054_at | Cdw92 | 1,37 | others or unknown |
| 1373127_at | LOC502656 | 1,13 | others or unknown |
| 1373128_at | RGD:1359365 | 1,08 | others or unknown |
| 1373204_at | RGD1310725 predicted | 1,27 | others or unknown |
| 1373214_at | Kdelc1 | 1,1 | others or unknown |
| 1373250_at | — | 1,29 | others or unknown |
| 1373458_at | Bex4 | 1,27 | others or unknown |
| 1373514_at | RGD1308168 predicted | 1,29 | others or unknown |
| 1373536_at | — | 1,21 | others or unknown |
| 1373561_at | RGD:1359458 | 1,08 | others or unknown |
| 1373592_at | MGC94010 | 1,16 | others or unknown |
| 1373628_at | — | 2,57 | others or unknown |
| 1373672_at | — | 1,76 | others or unknown |
| 1373673_at | — | 1,24 | others or unknown |
| 1373727_at | LOC499856 | 2,24 | others or unknown |

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Table B.2 – Continued

| Probe Set ID | Gene Symbol | SLR2 | annotation |
|---|---|---|---|
| 1373750_at | Leprel2 predicted | 1,23 | others or unknown |
| 1373781_a_at | — | 1,1 | others or unknown |
| 1373860_at | Sox4 predicted | 1,36 | others or unknown |
| 1373882_at | — | 1,21 | others or unknown |
| 1373889_at | LOC498022 | 1,06 | others or unknown |
| 1374081_at | — | 1,12 | others or unknown |
| 1374121_at | — | 1,42 | others or unknown |
| 1374172_at | — | 1,86 | others or unknown |
| 1374176_at | RGD1308059 predicted | 1,12 | others or unknown |
| 1374247_at | Stab1 predicted | 2,68 | others or unknown |
| 1374276_at | — | 1,21 | others or unknown |
| 1374381_at | — | 1,38 | others or unknown |
| 1374383_at | — | 1,18 | others or unknown |
| 1374453_at | — | 1,39 | others or unknown |
| 1374529_at | Thbs1 | 1,74 | others or unknown |
| 1374627_at | — | 1,2 | others or unknown |
| 1374666_at | Pcf11 predicted | 1,23 | others or unknown |
| 1374670_at | RGD1307722 predicted | 1,07 | others or unknown |
| 1374709_at | — | 1,06 | others or unknown |
| 1374759_at | Galntl1 predicted | 1,74 | others or unknown |
| 1374762_at | — | 1,17 | others or unknown |
| 1374798_at | Tor1aip2 | 1,04 | others or unknown |
| 1374831_at | Athl1 predicted | 1,02 | others or unknown |
| 1374851_at | Ixl predicted | 1,15 | others or unknown |
| 1374939_at | — | 1,13 | others or unknown |
| 1375010_at | Cd68 predicted | 1,64 | others or unknown |
| 1375054_at | — | 1,02 | others or unknown |
| 1375056_at | LOC289589 | 1,22 | others or unknown |
| 1375123_at | Sox4 predicted | 1,03 | others or unknown |
| 1375170_at | S100a11 predicted | 1,52 | others or unknown |
| 1375187_at | — | 1,26 | others or unknown |
| 1375248_at | RGD:1359220 | 1,3 | others or unknown |
| 1375267_at | RGD:1303221 | 1,15 | others or unknown |
| 1375523_at | Marcks | 1,57 | others or unknown |
| 1375575_at | — | 1,01 | others or unknown |
| 1375593_at | — | 1,34 | others or unknown |
| 1375724_at | RGD1563612 predicted | 1,22 | others or unknown |
| 1375862_at | — | 1,46 | others or unknown |
| 1375921_at | — | 1,43 | others or unknown |

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Table B.2 – Continued

| Probe Set ID | Gene Symbol | SLR2 | annotation |
|---|---|---|---|
| 1375998_at | — | 1,59 | others or unknown |
| 1376028_at | LOC303514 | 1,15 | others or unknown |
| 1376045_at | — | 1,13 | others or unknown |
| 1376100_at | RGD1305887 predicted | 1,54 | others or unknown |
| 1376105_at | Col14a1 predicted | 1,14 | others or unknown |
| 1376152_at | — | 1,01 | others or unknown |
| 1376321_at | Fam38a predicted | 1,24 | others or unknown |
| 1376332_at | RGD1560268 predicted | 1,13 | others or unknown |
| 1376353_at | Actr5 predicted | 1,31 | others or unknown |
| 1376459_at | RGD1563580 predicted | 1,05 | others or unknown |
| 1376799_a_at | Crlf1 predicted | 1,41 | others or unknown |
| 1376821_at | — | 1,18 | others or unknown |
| 1376831_at | RGD1308747 predicted | 1,54 | others or unknown |
| 1376905_at | — | 1,31 | others or unknown |
| 1376980_at | — | 3,41 | others or unknown |
| 1376998_a_at | — | 3,74 | others or unknown |
| 1377024_at | — | 1,23 | others or unknown |
| 1377086_at | C1qtnf3 predicted | 4,81 | others or unknown |
| 1377239_at | Apbb1ip predicted | 1,39 | others or unknown |
| 1378016_at | — | 1,22 | others or unknown |
| 1378367_at | — | 1,29 | others or unknown |
| 1380822_at | — | 1,03 | others or unknown |
| 1380979_a_at | RGD1309414 predicted | 1 | others or unknown |
| 1383013_at | RGD1565099 predicted | 1,07 | others or unknown |
| 1383100_at | RGD1306343 predicted | 1,24 | others or unknown |
| 1383175_a_at | RGD1306959 predicted | 1,57 | others or unknown |
| 1383684_at | Asf1b predicted | 1,75 | others or unknown |
| 1384288_at | — | 1,22 | others or unknown |
| 1384847_at | — | 1,14 | others or unknown |
| 1384934_at | — | 1,49 | others or unknown |
| 1385236_at | RGD1304856 predicted | 1,58 | others or unknown |
| 1385241_at | — | 1,72 | others or unknown |

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Table B.2 – Continued

| Probe Set ID | Gene Symbol | SLR2 | annotation |
|---|---|---|---|
| 1385458_a_at | RGD1306959 predicted | 1,26 | others or unknown |
| 1386041_a_at | RGD:1359220 | 1,03 | others or unknown |
| 1386160_at | Thh predicted | 1,13 | others or unknown |
| 1386744_x_at | — | 4,77 | others or unknown |
| 1387166_at | Aipl1 | 1,13 | others or unknown |
| 1387897_at | Cnp1 | 1,1 | others or unknown |
| 1387946_at | Lgals3bp | 1 | others or unknown |
| 1388148_a_at | Lrpap1 | 1,18 | others or unknown |
| 1388166_at | RGD:1359202 /// LOC299458 /// LOC314509 /// LOC366747 | 1,52 | others or unknown |
| 1388339_at | Pea15 predicted | 1,15 | others or unknown |
| 1388340_at | RGD:1303041 | 1,43 | others or unknown |
| 1388416_at | Lrp1 predicted | 1,23 | others or unknown |
| 1388439_at | LOC360627 | 1,59 | others or unknown |
| 1388482_at | — | 1,48 | others or unknown |
| 1388484_at | Ube2c predicted | 2 | others or unknown |
| 1388519_at | Sec61b predicted | 1,04 | others or unknown |
| 1388527_at | — | 2,07 | others or unknown |
| 1388569_at | Serpinf1 | 1,17 | others or unknown |
| 1388596_at | Cotl1 predicted | 1,78 | others or unknown |
| 1388628_at | RGD:1303327 | 1,15 | others or unknown |
| 1388773_at | LOC299339 | 1,08 | others or unknown |
| 1388784_at | Csf1r | 1,05 | others or unknown |
| 1388786_at | — | 1,53 | others or unknown |
| 1388902_at | Loxl1 predicted | 2,37 | others or unknown |
| 1389020_at | — | 2,01 | others or unknown |
| 1389039_at | — | 1,09 | others or unknown |
| 1389048_at | RGD:620739 | 1,71 | others or unknown |
| 1389263_at | Rai14 predicted | 1,56 | others or unknown |
| 1389295_at | Olfml2b predicted | 1,37 | others or unknown |
| 1389306_at | — | 2,64 | others or unknown |
| 1389408_at | Rrm2 | 1,7 | others or unknown |
| 1389419_at | — | 3,8 | others or unknown |
| 1389435_at | — | 1,02 | others or unknown |
| 1389490_at | Cd164l1 predicted | 2,22 | others or unknown |

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Table B.2 – Continued

| Probe Set ID | Gene Symbol | SLR2 | annotation |
|---|---|---|---|
| 1389600_at | LOC301748 /// LOC316186 /// LOC360998 /// LOC363306 /// LOC363320 /// LOC363433 /// LOC498374 /// LOC501091 /// LOC501092 /// LOC501093 /// LOC501221 /// LOC501225 /// LOC501226 /// LOC501245 /// LOC501250 /// LOC501253 /// LOC501393 /// LOC501396 /// LOC | 4,55 | others or unknown |
| 1389637_at | RGD1309338 predicted | 1,18 | others or unknown |
| 1389640_at | — | 1,08 | others or unknown |
| 1389695_at | — | 1,43 | others or unknown |
| 1389698_at | — | 1,06 | others or unknown |
| 1389707_at | — | 2,21 | others or unknown |
| 1389809_at | — | 1,02 | others or unknown |
| 1389864_at | — | 1,06 | others or unknown |
| 1389889_at | RGD1306404 predicted | 1,09 | others or unknown |
| 1390175_at | RGD1565319 predicted | 1,02 | others or unknown |
| 1390177_at | — | 1,29 | others or unknown |
| 1390200_at | RGD1304816 predicted | 1,73 | others or unknown |
| 1390249_at | RGD1305464 predicted | 1,74 | others or unknown |
| 1390277_at | RGD1560646 predicted | 1,27 | others or unknown |
| 1390306_at | — | 1,32 | others or unknown |
| 1390708_at | — | 1,67 | others or unknown |
| 1391484_at | Socs7 predicted | 1,17 | others or unknown |
| 1391544_at | — | 1,15 | others or unknown |
| 1392534_at | Tmepai predicted | 1,25 | others or unknown |

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Table B.2 – Continued

| Probe Set ID | Gene Symbol | SLR2 | annotation |
|---|---|---|---|
| 1392938_s_at | RGD1306959 predicted | 1,37 | others or unknown |
| 1393643_at | Rcn predicted | 1,09 | others or unknown |
| 1398348_at | — | 1,37 | others or unknown |
| 1367522_at | RGD1566014 predicted | -1,05 | others or unknown |
| 1367728_at | Tsn | -1,28 | others or unknown |
| 1368013_at | Ddit4l | -1,3 | others or unknown |
| 1368208_at | Cml1 | -1,28 | others or unknown |
| 1368770_at | Gcnt1 | -1,97 | others or unknown |
| 1368843_at | Yme1l1 | -1,24 | others or unknown |
| 1368944_at | Dlgh1 | -1,25 | others or unknown |
| 1369070_at | Pex12 | -1,44 | others or unknown |
| 1369076_at | Tmem33 | -1,24 | others or unknown |
| 1369591_at | Csn10 | -1,06 | others or unknown |
| 1370198_at | Trdn | -1,24 | others or unknown |
| 1371405_at | — | -1,19 | others or unknown |
| 1371443_at | RGD1304567 | -1,02 | others or unknown |
| 1371715_at | MGC112883 | -1,01 | others or unknown |
| 1371744_at | — | -1,03 | others or unknown |
| 1371766_at | — | -1,17 | others or unknown |
| 1371956_at | — | -1,01 | others or unknown |
| 1371965_at | RGD1303272 | -1,17 | others or unknown |
| 1371970_at | LOC499322 | -2,78 | others or unknown |
| 1372011_at | Gda | -1,18 | others or unknown |
| 1372101_at | Ppap2b | -1,07 | others or unknown |
| 1372248_at | Sesn1 predicted | -1,23 | others or unknown |
| 1372312_at | Ltv1 | -1,07 | others or unknown |
| 1372372_at | RGD1306952 predicted | -1,15 | others or unknown |
| 1372534_at | — | -1,39 | others or unknown |
| 1372586_at | Ube2d3 | -1,21 | others or unknown |
| 1372627_at | — | -1,08 | others or unknown |
| 1372676_at | RGD1304560 predicted | -1,71 | others or unknown |
| 1372713_at | RGD1309550 | -1,04 | others or unknown |
| 1373011_at | LOC619558 | -1,16 | others or unknown |
| 1373142_at | Ghitm | -1,11 | others or unknown |
| 1373178_at | — | -1,09 | others or unknown |
| 1373253_at | Acbd4 | -1,25 | others or unknown |
| 1373266_at | RGD1306327 | -1,16 | others or unknown |
| 1373568_at | — | -1,03 | others or unknown |
| 1373652_at | — | -1,04 | others or unknown |
| 1373765_at | — | -1,96 | others or unknown |
| 1373773_at | Gpm6a | -1,39 | others or unknown |

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Table B.2 – Continued

| Probe Set ID | Gene Symbol | SLR2 | annotation |
|---|---|---|---|
| 1373859_at | — | -1,59 | others or unknown |
| 1374088_at | — | -1,22 | others or unknown |
| 1374148_at | LOC498009 | -3,13 | others or unknown |
| 1374218_at | Iqsec2 predicted | -1,09 | others or unknown |
| 1374237_at | Lmod1 predicted | -1,02 | others or unknown |
| 1374278_at | — | -1,56 | others or unknown |
| 1374318_at | — | -1,09 | others or unknown |
| 1374348_at | RGD1308111 predicted | -1,02 | others or unknown |
| 1374408_at | RGD1309199 | -1,14 | others or unknown |
| 1374454_at | — | -1,67 | others or unknown |
| 1374515_at | RGD1306437 predicted | -1,1 | others or unknown |
| 1374527_at | RGD1308525 predicted | -1,39 | others or unknown |
| 1374562_at | — | -1,01 | others or unknown |
| 1374605_at | RGD1309660 predicted | -1,22 | others or unknown |
| 1374652_at | — | -1,5 | others or unknown |
| 1374676_at | Mob | -1,2 | others or unknown |
| 1374753_at | MGC93684 | -1,02 | others or unknown |
| 1374770_at | Asah1 | -1,11 | others or unknown |
| 1375099_at | — | -1,25 | others or unknown |
| 1375422_at | — | -1,49 | others or unknown |
| 1375644_at | LOC498824 | -1,02 | others or unknown |
| 1375911_at | RGD:735140 | -1,45 | others or unknown |
| 1376049_at | LOC312030 | -1,15 | others or unknown |
| 1376058_at | Mtus1 | -1,05 | others or unknown |
| 1376094_at | Hint3 | -1,06 | others or unknown |
| 1376175_at | LOC498174 | -2,67 | others or unknown |
| 1376280_at | RGD1307284 predicted | -1,11 | others or unknown |
| 1376282_at | — | -1,12 | others or unknown |
| 1376376_at | — | -1,03 | others or unknown |
| 1376484_at | RGD1559624 predicted | -1,75 | others or unknown |
| 1376581_at | RGD1309138 predicted | -3,07 | others or unknown |
| 1376620_at | — | -1,24 | others or unknown |
| 1376746_at | Ldhd predicted | -1,57 | others or unknown |
| 1376770_at | RGD1559565 predicted | -1,04 | others or unknown |
| 1376843_at | Bmpr2 | -1,53 | others or unknown |

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Table B.2 – Continued

| Probe Set ID | Gene Symbol | SLR2 | annotation |
|---|---|---|---|
| 1376861_at | LOC317312 /// LOC501648 | -1,53 | others or unknown |
| 1376868_at | — | -1,05 | others or unknown |
| 1377069_at | — | -1,15 | others or unknown |
| 1377072_at | — | -1,7 | others or unknown |
| 1377213_at | — | -1,09 | others or unknown |
| 1377297_at | — | -1,52 | others or unknown |
| 1377448_at | RGD1307901 predicted | -1,09 | others or unknown |
| 1377807_a_at | — | -1,27 | others or unknown |
| 1379500_at | LOC498404 | -1,06 | others or unknown |
| 1380883_at | — | -1,53 | others or unknown |
| 1382255_at | — | -1,03 | others or unknown |
| 1382959_at | — | -1,07 | others or unknown |
| 1383058_at | — | -1,15 | others or unknown |
| 1383686_at | — | -1,01 | others or unknown |
| 1384309_at | — | -1,19 | others or unknown |
| 1385697_at | — | -1,28 | others or unknown |
| 1386185_at | — | -2,91 | others or unknown |
| 1386514_at | Hapln4 predicted | -2,5 | others or unknown |
| 1386856_a_at | Samd4b | -1,57 | others or unknown |
| 1387636_a_at | Cdtw1 | -1,03 | others or unknown |
| 1387929_at | RGD:620149 | -1,4 | others or unknown |
| 1388307_at | Tde2 | -1,12 | others or unknown |
| 1388382_at | LOC361985 | -1,21 | others or unknown |
| 1388471_at | RGD1307494 predicted | -1,56 | others or unknown |
| 1388526_at | — | -1,32 | others or unknown |
| 1388573_at | — | -1,08 | others or unknown |
| 1388689_at | — | -1,28 | others or unknown |
| 1388696_at | Ufd1l | -1,08 | others or unknown |
| 1388766_at | Mtx2 predicted | -1,01 | others or unknown |
| 1388799_at | Klhl7 predicted | -1,1 | others or unknown |
| 1389075_at | — | -1,28 | others or unknown |
| 1389111_at | — | -1,01 | others or unknown |
| 1389147_at | — | -1,62 | others or unknown |
| 1389229_at | Acpl2 | -1,08 | others or unknown |
| 1389230_at | Arrdc3 | -1,42 | others or unknown |
| 1389252_at | — | -1,06 | others or unknown |
| 1389332_at | — | -1,1 | others or unknown |
| 1389411_at | — | -1,13 | others or unknown |
| 1389460_at | — | -1,45 | others or unknown |
| 1389464_at | Lnx1 predicted | -1,18 | others or unknown |

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Table B.2 – Continued

| Probe Set ID | Gene Symbol | SLR2 | annotation |
|---|---|---|---|
| 1389551_at | Lactb2 predicted | -1,06 | others or unknown |
| 1389632_at | — | -1,28 | others or unknown |
| 1389694_at | — | -1,23 | others or unknown |
| 1389729_at | MGC94142 | -1,19 | others or unknown |
| 1389907_at | Zbtb8os predicted | -1,11 | others or unknown |
| 1390042_at | MGC109491 | -1,39 | others or unknown |
| 1390101_at | RGD1560252 predicted | -1,04 | others or unknown |
| 1390139_a_at | RGD1306073 predicted | -1,02 | others or unknown |
| 1390408_at | LOC317444 | -1,44 | others or unknown |
| 1390606_at | RGD1564108 predicted | -1,72 | others or unknown |
| 1391272_at | LOC499942 | -1,07 | others or unknown |
| 1391428_at | — | -1,26 | others or unknown |
| 1392633_at | — | -1,74 | others or unknown |
| 1392683_at | — | -1,01 | others or unknown |
| 1392778_at | — | -3,38 | others or unknown |
| 1392929_at | RGD1565616 predicted | -1,24 | others or unknown |
| 1393018_at | RGD1565534 predicted | -1,17 | others or unknown |
| 1393239_at | — | -1,21 | others or unknown |
| 1393798_at | Atrx | -1,66 | others or unknown |
| 1394347_at | LOC501069 | -2,46 | others or unknown |
| 1398966_at | — | -1,06 | others or unknown |
| 1398973_at | RGD1564625 predicted | -1,11 | others or unknown |
| 1399129_at | — | -1,01 | others or unknown |
| 1367939_at | Rbp1 | 2 | transport |
| 1368207_at | Fxyd5 | 1,35 | transport |
| 1368242_at | Kcnb1 | 1,38 | transport |
| 1368419_at | Cp | 1,06 | transport |
| 1368565_at | Slc1a3 | 1,03 | transport |
| 1369384_at | Gria4 | 1,82 | transport |
| 1369639_at | Gja1 | 1,19 | transport |
| 1369743_a_at | P2rx4 | 1,47 | transport |
| 1370228_at | Tf /// Srprb predicted | 1,35 | transport |
| 1370248_at | Fxyd6 | 1,02 | transport |
| 1370516_at | Slc15a3 | 1,42 | transport |
| 1370966_at | Hcn2 | 1,16 | transport |
| 1373658_at | — | 1,78 | transport |

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Table B.2 – Continued

| Probe Set ID | Gene Symbol | SLR2 | annotation |
|---|---|---|---|
| 1373932_at | Cybb | 1,5 | transport |
| 1375633_at | RGD:1303043 | 1,9 | transport |
| 1376344_at | Cybrd1 | 1,43 | transport |
| 1386913_at | Gp38 | 1,04 | transport |
| 1387871_at | Cfl1 | 1,01 | transport |
| 1388140_at | Rab13 | 1,24 | transport |
| 1388494_at | — | 1,7 | transport |
| 1398330_at | Stxbp1 | 1,29 | transport |
| 1368304_at | Fmo3 | -1,2 | transport |
| 1369526_at | Acadsb | -1,14 | transport |
| 1370588_a_at | Slc8a1 | -1,44 | transport |
| 1372142_at | Asna1 predicted | -1,03 | transport |
| 1373074_at | RGD1307279 | -1,01 | transport |
| 1373953_at | Slc4a1ap predicted | -1,08 | transport |
| 1374741_at | Esrra | -1,04 | transport |
| 1375783_at | Grik5 | -1,44 | transport |
| 1376560_at | LOC362652 | -1,3 | transport |
| 1382775_at | Ryr2 | -1,08 | transport |
| 1384609_a_at | RGD1311456 predicted | -5,35 | transport |
| 1386911_at | Atp1a2 | -1,04 | transport |
| 1387455_a_at | Vldlr | -1,02 | transport |
| 1389912_at | Ensa | -1,05 | transport |
| 1398313_a_at | Kcnk3 | -1,19 | transport |

## B.3 Probesets significantly changed comparing mS42 vs. mM42

| Probe Set ID | Gene Symbol | SLR2 | annotation |
|---|---|---|---|
| 1387032_at | Cck | -1,67 | cell cycle / development |
| 1368828_at | Gata6 | 1,01 | cell cycle / development |
| 1368722_at | Lta | -1,04 | cell cycle / development |
| 1387776_at | Tgm2 | 1,20 | cell cycle / development |
| 1370282_at | RGD:61950 | 1,27 | cell cycle / development |
| 1368466_a_at | Odf2 | 2,96 | cell cycle / development |
| 1387391_at | Cdkn1a | 1,14 | cell cycle / development |
| 1387274_at | Dlx5 | -1,72 | cell cycle / development |
| 1385265_a_at | — | 1,39 | cell cycle / development |
| 1368189_at | Dhcr7 | -1,06 | cell cycle / development |
| 1368144_at | Rgs2 | 1,23 | cell cycle / development |
| 1368125_at | Slc12a4 | 3,15 | cell cycle / development |
| 1376178_at | Ddit3 | -1,44 | cell cycle / development |

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Table B.3 – Continued

| Probe Set ID | Gene Symbol | SLR2 | annotation |
|---|---|---|---|
| 1374173_at | Hexb | -1,09 | cell cycle / development |
| 1371527_at | Emp1 | 1,04 | cell cycle / development |
| 1376307_a_at | Drb1 | 1,35 | cell cycle / development |
| 1371315_at | Myl7 predicted | 3,53 | cell structure / motility |
| 1375542_at | Rdx | 1,53 | cell structure / motility |
| 1387617_at | Tpm3 | -1,07 | cell structure / motility |
| 1371700_at | Mfap4 predicted | 1,44 | cell structure / motility |
| 1371139_at | Pls3 | 1,73 | cell structure / motility |
| 1368404_at | Dbn1 | 1,00 | cell structure / motility |
| 1369476_at | Efnb1 | 1,12 | cell surface / extracellular matrix |
| 1369327_at | Pdzk3 | 1,16 | cell surface / extracellular matrix |
| 1388054_a_at | Cspg2 | 1,76 | cell surface / extracellular matrix |
| 1387854_at | Col1a2 | 1,26 | cell surface / extracellular matrix |
| 1388142_at | Cspg2 | 1,56 | cell surface / extracellular matrix |
| 1387351_at | Fbn1 | 1,20 | cell surface / extracellular matrix |
| 1370927_at | Col12a1 | 1,50 | cell surface / extracellular matrix |
| 1370993_at | Lamc1 | 1,53 | cell surface / extracellular matrix |
| 1388138_at | Thbs4 | 1,05 | cell surface / extracellular matrix |
| 1367594_at | Bgn | 1,18 | cell surface / extracellular matrix |
| 1367712_at | Timp1 | 1,06 | cell surface / extracellular matrix |
| 1393891_at | Col8a1 predicted | 1,29 | cell surface / extracellular matrix |
| 1390430_at | Nr1d2 | -1,12 | gene / protein expression |
| 1368702_at | Pawr | 2,30 | gene / protein expression |
| 1369067_at | Nr4a3 | 1,68 | gene / protein expression |
| 1387876_at | Stat5b | -1,14 | gene / protein expression |
| 1387874_at | Dbp | -2,60 | gene / protein expression |
| 1377902_a_at | Rad52 predicted | -1,44 | gene / protein expression |
| 1370510_a_at | Arntl | 1,35 | gene / protein expression |
| 1371293_at | — | 1,40 | gene / protein expression |
| 1387374_at | Tcf12 | 1,67 | gene / protein expression |
| 1368997_at | Tceb3 | 1,10 | gene / protein expression |
| 1373804_at | Foxp1 | 1,15 | gene / protein expression |
| 1398911_at | Mrpl2 | -1,20 | gene / protein expression |
| 1390659_at | Cd44 | 1,44 | immune response |
| 1368238_at | Pap | 4,84 | immune response |
| 1387396_at | Hamp | 1,20 | immune response |
| 1387902_a_at | LOC500180 /// LOC500183 | 1,18 | immune response |
| 1387072_at | Prkwnk1 | 1,04 | intracellular signaling / cell-cell communication |
| 1373911_at | Postn predicted | 3,10 | intracellular signaling / cell-cell communication |
| 1398438_at | Gtpbp3 | -1,24 | intracellular signaling / cell-cell communication |

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Table B.3 – Continued

| Probe Set ID | Gene Symbol | SLR2 | annotation |
|---|---|---|---|
| 1375231_a_at | Cxxc5 | -1,02 | intracellular signaling / cell-cell communication |
| 1371081_at | Rapgef4 | -1,27 | intracellular signaling / cell-cell communication |
| 1376393_at | Ralgps2 | -1,14 | intracellular signaling / cell-cell communication |
| 1370728_at | Il13ra1 | 4,68 | intracellular signaling / cell-cell communication |
| 1371615_at | Dgat2 | -1,00 | intracellular signaling / cell-cell communication |
| 1392467_at | Impa2 | -1,74 | intracellular signaling / cell-cell communication |
| 1368290_at | Cyr61 | -2,25 | intracellular signaling / cell-cell communication |
| 1392672_at | Scgf | 1,17 | intracellular signaling / cell-cell communication |
| 1367631_at | Ctgf | 1,44 | intracellular signaling / cell-cell communication |
| 1389315_at | Git2 | 1,15 | intracellular signaling / cell-cell communication |
| 1388712_at | — | 2,66 | intracellular signaling / cell-cell communication |
| 1369640_at | Gja1 | 1,04 | intracellular signaling / cell-cell communication |
| 1368849_at | Csnk1g3 | 1,42 | intracellular signaling / cell-cell communication |
| 1369736_at | Emp1 | 1,26 | intracellular signaling / cell-cell communication |
| 1388249_at | Rapgef1 | 1,95 | intracellular signaling / cell-cell communication |
| 1388104_at | Gpr48 | 1,12 | intracellular signaling / cell-cell communication |
| 1368685_at | Cspg4 | 1,04 | intracellular signaling / cell-cell communication |
| 1387641_at | Rab5a | 1,04 | intracellular signaling / cell-cell communication |
| 1369352_at | Hipk3 | 1,47 | intracellular signaling / cell-cell communication |
| 1368505_at | Rgs4 | 1,09 | intracellular signaling / cell-cell communication |
| 1370256_at | Fzd1 | 1,30 | intracellular signaling / cell-cell communication |
| 1369152_at | Ppp3r1 | 1,02 | intracellular signaling / cell-cell communication |

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Table B.3 – Continued

| Probe Set ID | Gene Symbol | SLR2 | annotation |
|---|---|---|---|
| 1368408_at | Gprk5 | 1,43 | intracellular signaling / cell-cell communication |
| 1369492_at | Aadac | -1,26 | metabolism |
| 1369365_at | Pde3a | 1,08 | metabolism |
| 1370523_a_at | — | -1,08 | metabolism |
| 1367896_at | Ca3 | 1,26 | metabolism |
| 1368188_at | Hpd | -1,11 | metabolism |
| 1386889_at | Scd2 | 1,20 | metabolism |
| 1387154_at | Npy | 1,40 | neurohumoral response |
| 1367564_at | Nppa | 3,81 | neurohumoral response |
| 1373159_at | — | -1,11 | others or unknown |
| 1373543_at | RGD1564382 predicted | -1,54 | others or unknown |
| 1373021_at | — | -1,05 | others or unknown |
| 1373078_at | — | -1,02 | others or unknown |
| 1373152_at | RGD:1359545 | 1,06 | others or unknown |
| 1369326_at | Akap6 | 1,02 | others or unknown |
| 1373781_a_at | — | 1,65 | others or unknown |
| 1373778_at | — | -1,11 | others or unknown |
| 1373771_at | — | -1,10 | others or unknown |
| 1370394_at | RGD:1359626 /// LOC500728 | 1,15 | others or unknown |
| 1374078_at | RGD1560612 predicted | 1,12 | others or unknown |
| 1369107_at | Sftpa1 | 1,48 | others or unknown |
| 1373628_at | — | 1,21 | others or unknown |
| 1372849_at | — | 1,03 | others or unknown |
| 1373535_at | Enah predicted | 1,47 | others or unknown |
| 1373699_at | — | -1,07 | others or unknown |
| 1370887_at | Tgfb1i1 | 1,05 | others or unknown |
| 1372213_at | LOC500300 | -1,51 | others or unknown |
| 1371331_at | Fstl1 | 1,07 | others or unknown |
| 1368247_at | Hspa1a /// Hspa1b | 1,19 | others or unknown |
| 1372440_at | Serpine2 | 1,58 | others or unknown |
| 1370198_at | Trdn | -1,07 | others or unknown |
| 1370236_at | Ppt | 1,02 | others or unknown |
| 1370806_at | Retsat | -1,35 | others or unknown |
| 1368531_at | Prlpc1 | -2,44 | others or unknown |
| 1371028_at | Tgoln2 | 1,15 | others or unknown |
| 1372640_at | LOC499410 | 1,88 | others or unknown |
| 1372620_at | Anp32e predicted | 1,25 | others or unknown |
| 1372576_at | — | 1,13 | others or unknown |
| 1373284_at | Sav1 predicted | 1,29 | others or unknown |

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Table B.3 – Continued

| Probe Set ID | Gene Symbol | SLR2 | annotation |
|---|---|---|---|
| 1373282_at | RGD1306651 predicted | -1,33 | others or unknown |
| 1369519_at | Edn1 | -1,03 | others or unknown |
| 1372820_at | — | 1,17 | others or unknown |
| 1372025_at | Apeg3 | -1,45 | others or unknown |
| 1374105_at | Hig1 | -1,06 | others or unknown |
| 1371998_at | MGC124888 | 1,03 | others or unknown |
| 1371970_at | LOC499322 | 4,40 | others or unknown |
| 1371927_at | — | 2,10 | others or unknown |
| 1371687_at | Canx | 1,10 | others or unknown |
| 1368944_at | Dlgh1 | 1,18 | others or unknown |
| 1389203_at | RGD1307036 predicted | 2,20 | others or unknown |
| 1389172_at | Enh | 1,97 | others or unknown |
| 1389020_at | — | 1,11 | others or unknown |
| 1388902_at | Loxl1 predicted | 1,03 | others or unknown |
| 1388781_at | — | 1,10 | others or unknown |
| 1388689_at | — | -1,19 | others or unknown |
| 1388569_at | Serpinf1 | 1,00 | others or unknown |
| 1388395_at | G0s2 predicted | 1,06 | others or unknown |
| 1388192_at | Rwdd3 | 2,81 | others or unknown |
| 1386597_s_at | Spdy1 | 3,09 | others or unknown |
| 1384446_at | — | -1,05 | others or unknown |
| 1384967_at | Sart2 predicted | -1,06 | others or unknown |
| 1385458_a_at | RGD1306959 predicted | 1,43 | others or unknown |
| 1385697_at | — | -3,41 | others or unknown |
| 1388824_at | — | 1,06 | others or unknown |
| 1388802_at | — | 1,62 | others or unknown |
| 1374974_at | — | 1,32 | others or unknown |
| 1386622_at | RGD1565247 predicted | 1,32 | others or unknown |
| 1385826_at | — | 1,28 | others or unknown |
| 1392938_s_at | RGD1306959 predicted | 1,67 | others or unknown |
| 1390741_at | RGD1304737 predicted | -1,23 | others or unknown |
| 1391454_at | — | 1,04 | others or unknown |
| 1391599_at | — | -1,23 | others or unknown |
| 1392407_at | RGD1561419 predicted | 1,04 | others or unknown |
| 1390586_at | — | -1,04 | others or unknown |
| 1392778_at | — | -1,45 | others or unknown |
| 1390168_a_at | Zcsl3 predicted | -1,64 | others or unknown |
| 1393268_at | — | 1,04 | others or unknown |

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Table B.3 – Continued

| Probe Set ID | Gene Symbol | SLR2 | annotation |
|---|---|---|---|
| 1393860_at | — | 3,13 | others or unknown |
| 1393993_at | — | -1,16 | others or unknown |
| 1398463_at | — | -1,33 | others or unknown |
| 1398348_at | — | 1,09 | others or unknown |
| 1385871_at | Dhx36 predicted | -1,08 | others or unknown |
| 1389259_at | — | 1,55 | others or unknown |
| 1389368_at | Magi1 predicted | 2,12 | others or unknown |
| 1389612_at | — | 1,01 | others or unknown |
| 1389694_at | — | -1,13 | others or unknown |
| 1389419_at | — | 1,65 | others or unknown |
| 1374473_at | — | -1,14 | others or unknown |
| 1376072_at | RGD1309973 /// LOC501188 | -1,26 | others or unknown |
| 1374529_at | Thbs1 | 1,42 | others or unknown |
| 1376799_a_at | Crlf1 predicted | 1,04 | others or unknown |
| 1376665_at | — | 1,16 | others or unknown |
| 1376937_at | LOC304020 | 1,02 | others or unknown |
| 1376993_at | Amotl1 predicted | 1,15 | others or unknown |
| 1376827_at | — | 1,20 | others or unknown |
| 1375769_at | Trim41 predicted | 1,09 | others or unknown |
| 1375123_at | Sox4 predicted | 2,18 | others or unknown |
| 1399164_a_at | — | -1,06 | others or unknown |
| 1375089_at | Filip1 | 1,20 | others or unknown |
| 1375911_at | RGD:735140 | -1,34 | others or unknown |
| 1376800_at | — | -1,06 | others or unknown |
| 1374187_at | — | 1,60 | others or unknown |
| 1377475_at | — | 1,16 | others or unknown |
| 1379242_at | — | 3,17 | others or unknown |
| 1374233_at | RGD1308326 predicted | 1,64 | others or unknown |
| 1377239_at | Apbb1ip predicted | 1,33 | others or unknown |
| 1383102_at | — | 1,48 | others or unknown |
| 1383175_a_at | RGD1306959 predicted | 1,50 | others or unknown |
| 1374172_at | — | 1,02 | others or unknown |
| 1374164_at | — | -1,04 | others or unknown |
| 1379814_at | — | -5,22 | others or unknown |
| 1374448_at | Reck predicted | 1,07 | others or unknown |
| 1377118_at | RGD1308517 | 1,07 | others or unknown |
| 1374237_at | Lmod1 predicted | -1,21 | others or unknown |
| 1377224_at | — | 2,09 | others or unknown |

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Table B.3 – Continued

| Probe Set ID | Gene Symbol | SLR2 | annotation |
|---|---|---|---|
| 1374313_at | Bpy2ip1 predicted | 1,76 | others or unknown |
| 1374316_at | — | 1,02 | others or unknown |
| 1377094_at | — | -1,32 | others or unknown |
| 1374343_at | — | 1,47 | others or unknown |
| 1373932_at | Cybb | 1,71 | transport |
| 1368046_at | RGD:620059 | 4,24 | transport |
| 1368419_at | Cp | 2,12 | transport |
| 1390237_at | Timm8a | -1,18 | transport |
| 1374532_at | Ptges2 predicted | 1,03 | transport |
| 1371102_x_at | Hbb | 2,30 | transport |
| 1387543_at | Slc5a7 | 1,08 | transport |
| 1377362_at | Kcnab1 | 1,13 | transport |
| 1370588_a_at | Slc8a1 | 1,65 | transport |
| 1386951_at | Ndufa5 | -1,14 | transport |
| 1387420_at | Clic4 | 1,11 | transport |
| 1369410_at | — | -1,04 | transport |
| 1370239_at | Hba-a1 /// RGD:1359364 | 3,37 | transport |
| 1367553_x_at | Hbb | 2,93 | transport |
| 1387719_at | Clcn1 | -1,24 | transport |
| 1388064_a_at | Slc1a3 | 1,34 | transport |
| 1369741_at | Kcnj3 | -1,00 | transport |
| 1369668_x_at | Vps52 | -1,20 | transport |
| 1388608_x_at | Hba-a1 | 1,73 | transport |
| 1371245_a_at | — | 4,16 | transport |
| 1386372_at | Rab3ip | -1,19 | transport |
| 1368889_at | Vti1a | -1,02 | transport |
| 1370240_x_at | Hba-a1 /// RGD:1359364 | 3,37 | transport |

## B.4 Probesets significantly changed comparing fS42 vs. fM42

| Probe Set ID | Gene Symbol | SLR2 | annotation |
|---|---|---|---|
| 1383075_at | Ccnd1 | 1,42 | cell cycle / development |
| 1392890_at | Pafah1b1 | 1,52 | cell cycle / development |
| 1371827_at | Syvn1 | 1,07 | cell cycle / development |
| 1368527_at | Ptgs2 | 1,32 | cell cycle / development |
| 1369968_at | Ptn | 1,49 | cell cycle / development |
| 1373577_at | Nrp | 1,31 | cell cycle / development |
| 1371527_at | Emp1 | 1,77 | cell cycle / development |
| 1388970_at | Rasip1 predicted | 1,18 | cell cycle / development |

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Table B.4 – Continued

| Probe Set ID | Gene Symbol | SLR2 | annotation |
|---|---|---|---|
| 1368819_at | Itgb1 | 1,51 | cell cycle / development |
| 1388867_at | MGC112830 | 1,09 | cell cycle / development |
| 1390100_s_at | Bat3 | 1,01 | cell cycle / development |
| 1371064_at | Pcm1 | -1,20 | cell cycle / development |
| 1369530_at | Isl2 | -1,20 | cell cycle / development |
| 1389384_at | Hrpap20 | 1,47 | cell cycle / development |
| 1387270_at | Hhex | 1,28 | cell cycle / development |
| 1368939_a_at | Ntrk3 | -1,08 | cell cycle / development |
| 1372759_at | Cdk9 | 1,01 | cell cycle / development |
| 1398813_at | Ube1c | 1,31 | cell cycle / development |
| 1388096_at | Kitl | 2,62 | cell cycle / development |
| 1372520_at | Mcl1 | 1,36 | cell cycle / development |
| 1371528_at | Fkbp8 | -1,05 | cell cycle / development |
| 1372926_at | Timp3 | 1,17 | cell cycle / development |
| 1367587_at | Csh1l1 | -2,79 | cell cycle / development |
| 1371545_at | Pecam | 1,06 | cell structure / motility |
| 1373674_at | Mfap5 predicted | 2,14 | cell structure / motility |
| 1388111_at | Eln | 1,17 | cell structure / motility |
| 1371327_a_at | Actg predicted /// LOC295810 | 1,05 | cell structure / motility |
| 1370949_at | Marcks | 1,57 | cell structure / motility |
| 1371700_at | Mfap4 predicted | 1,41 | cell structure / motility |
| 1370738_a_at | Trdn | 2,25 | cell structure / motility |
| 1369212_s_at | Epb4.1l1 | -1,14 | cell structure / motility |
| 1373363_at | Map1b | 1,16 | cell structure / motility |
| 1399147_at | Dncli1 | 1,34 | cell structure / motility |
| 1371315_at | Myl7 predicted | 1,39 | cell structure / motility |
| 1368404_at | Dbn1 | 1,08 | cell structure / motility |
| 1375469_at | Smarca4 | -2,89 | cell structure / motility |
| 1371765_at | H2a | 1,16 | cell structure / motility |
| 1376924_a_at | Palmd predicted | 1,51 | cell structure / motility |
| 1387351_at | Fbn1 | 1,66 | cell surface / extracellular matrix |
| 1387854_at | Col1a2 | 1,52 | cell surface / extracellular matrix |
| 1376198_at | Asam | 1,75 | cell surface / extracellular matrix |
| 1390112_at | Efemp1 predicted | 1,18 | cell surface / extracellular matrix |
| 1393891_at | Col8a1 predicted | 1,30 | cell surface / extracellular matrix |
| 1388312_at | — | 1,94 | cell surface / extracellular matrix |
| 1367860_a_at | Mmp14 | 1,25 | cell surface / extracellular matrix |
| 1368172_a_at | Lox | 2,51 | cell surface / extracellular matrix |
| 1370895_at | Col5a2 | 1,30 | cell surface / extracellular matrix |
| 1367594_at | Bgn | 1,09 | cell surface / extracellular matrix |
| 1368829_at | Fbn1 | 1,74 | cell surface / extracellular matrix |
| 1388138_at | Thbs4 | 1,78 | cell surface / extracellular matrix |

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Table B.4 – Continued

| Probe Set ID | Gene Symbol | SLR2 | annotation |
|---|---|---|---|
| 1370234_at | Fn1 | 1,22 | cell surface / extracellular matrix |
| 1367749_at | Lum | 1,76 | cell surface / extracellular matrix |
| 1376711_at | Cldn11 | -1,34 | cell surface / extracellular matrix |
| 1371518_at | Nid | 1,10 | cell surface / extracellular matrix |
| 1368474_at | Vcam1 | 1,13 | cell surface / extracellular matrix |
| 1387144_at | Itga1 | 1,33 | cell surface / extracellular matrix |
| 1388054_a_at | Cspg2 | 1,18 | cell surface / extracellular matrix |
| 1370130_at | RGD:619921 | 1,20 | cell surface / extracellular matrix |
| 1370510_a_at | Arntl | 1,03 | gene / protein expression |
| 1387644_at | Btc | -1,51 | gene / protein expression |
| 1372151_at | Tcerg1 predicted | 1,27 | gene / protein expression |
| 1371293_at | — | 1,12 | gene / protein expression |
| 1373264_at | Zbed3 | 1,48 | gene / protein expression |
| 1388313_at | Rps25 | 1,09 | gene / protein expression |
| 1387874_at | Dbp | -1,39 | gene / protein expression |
| 1375545_at | Rbm9 predicted | 1,14 | gene / protein expression |
| 1390234_at | Sf3b1 | 1,06 | gene / protein expression |
| 1368511_at | Bhlhb3 | -1,01 | gene / protein expression |
| 1374154_at | — | 1,44 | gene / protein expression |
| 1376437_at | Dhx33 predicted | 2,56 | gene / protein expression |
| 1368632_at | Foxg1 | -1,60 | gene / protein expression |
| 1375190_at | Kctd13 | -1,51 | gene / protein expression |
| 1399046_at | Top1 | 1,15 | gene / protein expression |
| 1390430_at | Nr1d2 | -1,32 | gene / protein expression |
| 1369067_at | Nr4a3 | 1,20 | gene / protein expression |
| 1389851_at | Zfp36l2 predicted | -1,07 | gene / protein expression |
| 1382005_at | Rod1 | 1,77 | gene / protein expression |
| 1372367_at | — | 1,04 | gene / protein expression |
| 1389446_at | Snrpa1 predicted | -1,60 | gene / protein expression |
| 1371670_at | Exosc4 predicted | -1,14 | gene / protein expression |
| 1372575_at | Wbp11 | 1,03 | gene / protein expression |
| 1371489_at | Rnf4 | 2,21 | gene / protein expression |
| 1371430_at | Dag1 | 1,31 | gene / protein expression |
| 1388576_at | Eif3s9 | -1,16 | gene / protein expression |
| 1375019_at | Hnrph3 predicted | 1,07 | gene / protein expression |
| 1389141_at | Orc2l | -1,21 | gene / protein expression |
| 1375907_at | Ascc1 | -1,23 | gene / protein expression |
| 1374137_at | Elf1 | 2,04 | gene / protein expression |
| 1374425_at | Tle1 predicted | 1,22 | gene / protein expression |
| 1368308_at | Myc | 1,27 | gene / protein expression |

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Table B.4 – Continued

| Probe Set ID | Gene Symbol | SLR2 | annotation |
|---|---|---|---|
| 1373764_at | Zfml predicted | 1,93 | gene / protein expression |
| 1387036_at | Hes1 | 1,06 | gene / protein expression |
| 1389689_at | Vars2l | 1,07 | gene / protein expression |
| 1369912_at | Crk | 1,01 | gene / protein expression |
| 1376811_a_at | Cpsf6 predicted | 1,25 | gene / protein expression |
| 1369679_a_at | Nfia | 1,25 | gene / protein expression |
| 1377029_at | Rora predicted | -1,26 | gene / protein expression |
| 1379685_at | Sfrs15 | 1,14 | gene / protein expression |
| 1372254_at | Serping1 | 1,06 | immune response |
| 1388272_at | Igh-1a predicted | 2,02 | immune response |
| 1387902_a_at | LOC500180 /// LOC500183 | 3,36 | immune response |
| 1367850_at | LOC498276 | 1,74 | immune response |
| 1398246_s_at | Fcgr3 /// LOC498276 | 1,16 | immune response |
| 1388212_a_at | RT1-S3 | 1,04 | immune response |
| 1376652_at | C1qa predicted | 1,26 | immune response |
| 1387893_at | C1s /// LOC500313 | 1,73 | immune response |
| 1368760_at | Cxcl2 | 1,27 | immune response |
| 1368238_at | Pap | 1,55 | immune response |
| 1368490_at | Cd14 | 1,41 | immune response |
| 1387134_at | Slfn3 | 1,91 | immune response |
| 1368332_at | Gbp2 | 1,18 | immune response |
| 1369202_at | Mx2 | 1,02 | immune response |
| 1370892_at | C4a /// C4-2 | 1,25 | immune response |
| 1387029_at | Cfh | 2,08 | immune response |
| 1389123_at | RGD:1303200 | 1,51 | immune response |
| 1371635_at | Gpr175 | -1,20 | intracelluar signaling / cell-cell communication |
| 1374369_at | Raph1 predicted | 1,09 | intracelluar signaling / cell-cell communication |
| 1373803_a_at | Ghr | 1,08 | intracellular signaling / cell-cell communication |
| 1387277_at | Lyn | -1,42 | intracellular signaling / cell-cell communication |
| 1382778_at | Dusp6 | 1,04 | intracellular signaling / cell-cell communication |
| 1383017_at | — | 1,03 | intracellular signaling / cell-cell communication |
| 1387659_at | Gda | 1,14 | intracellular signaling / cell-cell communication |
| 1373911_at | Postn predicted | 2,06 | intracellular signaling / cell-cell communication |

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Table B.4 – Continued

| Probe Set ID | Gene Symbol | SLR2 | annotation |
|---|---|---|---|
| 1388818_at | Araf | -1,10 | intracellular signaling / cell-cell communication |
| 1388800_at | Rab5a | 1,11 | intracellular signaling / cell-cell communication |
| 1387625_at | Igfbp6 | 1,02 | intracellular signaling / cell-cell communication |
| 1376425_at | Tgfb2 | 1,17 | intracellular signaling / cell-cell communication |
| 1386950_at | Ppp1cb | 1,94 | intracellular signaling / cell-cell communication |
| 1390711_at | — | 1,45 | intracellular signaling / cell-cell communication |
| 1369806_at | Adrb1 | -1,12 | intracellular signaling / cell-cell communication |
| 1369732_a_at | St3gal2 | 1,47 | intracellular signaling / cell-cell communication |
| 1389905_at | Pepd | 1,90 | intracellular signaling / cell-cell communication |
| 1369443_at | Angptl2 | 1,32 | intracellular signaling / cell-cell communication |
| 1371235_at | Grm6 | -1,02 | intracellular signaling / cell-cell communication |
| 1390119_at | Sfrp2 | 1,75 | intracellular signaling / cell-cell communication |
| 1370061_at | Rab3b | -1,15 | intracellular signaling / cell-cell communication |
| 1390707_at | Rgs10 | 1,31 | intracellular signaling / cell-cell communication |
| 1369484_at | Wisp2 | 2,10 | intracellular signaling / cell-cell communication |
| 1367912_at | Ltbp1 | 1,26 | intracellular signaling / cell-cell communication |
| 1398355_at | Trpm7 | 2,54 | intracellular signaling / cell-cell communication |
| 1367631_at | Ctgf | 1,16 | intracellular signaling / cell-cell communication |
| 1399027_at | RGD:619921 | 1,11 | intracellular signaling / cell-cell communication |
| 1367619_at | Pgrmc1 | 1,43 | intracellular signaling / cell-cell communication |
| 1371081_at | Rapgef4 | 1,18 | intracellular signaling / cell-cell communication |
| 1372503_at | Tnfsf12 | 1,15 | intracellular signaling / cell-cell communication |

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Table B.4 – Continued

| Probe Set ID | Gene Symbol | SLR2 | annotation |
|---|---|---|---|
| 1388305_at | Araf | 1,17 | intracellular signaling / cell-cell communication |
| 1388462_at | Sbk1 | -1,08 | intracellular signaling / cell-cell communication |
| 1370891_at | Cd48 | 1,05 | intracellular signaling / cell-cell communication |
| 1372733_at | — | 1,11 | intracellular signaling / cell-cell communication |
| 1370728_at | Il13ra1 | 2,17 | intracellular signaling / cell-cell communication |
| 1370642_s_at | Pdgfrb /// LOC497724 | 1,34 | intracellular signaling / cell-cell communication |
| 1388057_a_at | Dlgap1 | 1,37 | intracellular signaling / cell-cell communication |
| 1371732_at | Dpt predicted | 1,08 | intradellular signaling / cell-cell communication |
| 1372323_at | Sardh | 1,06 | metabolism |
| 1373201_at | Dbt | 1,01 | metabolism |
| 1367856_at | G6pdx | 1,13 | metabolism |
| 1373062_at | Sulf1 | 2,94 | metabolism |
| 1367627_at | Gatm | 1,22 | metabolism |
| 1367668_a_at | Scd2 | 1,47 | metabolism |
| 1368891_at | Gnpat | 1,56 | metabolism |
| 1370489_a_at | Plcb4 | 1,74 | metabolism |
| 1370523_a_at | — | 2,20 | metabolism |
| 1373381_at | Herc4 | 1,08 | metabolism |
| 1399162_a_at | Ddb1 | 1,12 | metabolism |
| 1368906_at | Pgk1 | 1,17 | metabolism |
| 1368128_at | Pla2g2a | 1,58 | metabolism |
| 1368806_at | Sepp1 | 1,15 | metabolism |
| 1374976_a_at | Soat1 | 2,00 | metabolism |
| 1369292_at | Hsd17b1 | 2,50 | metabolism |
| 1368331_at | Ctbs | 1,47 | metabolism |
| 1368215_at | Tpp1 | 1,02 | metabolism |
| 1387219_at | Adm | 1,30 | metabolism |
| 1390588_at | — | -2,43 | metabolism |
| 1387506_at | Foxa3 | -1,70 | metabolism |
| 1393946_at | Fusip1 | 1,32 | metabolism |
| 1389567_at | Scap predicted | -1,26 | metabolism |
| 1367564_at | Nppa | 2,02 | neurohumoral response |
| 1383251_at | Parp2 predicted | 1,01 | others or unknown |
| 1372444_at | Kif5b | 1,38 | others or unknown |
| 1372400_at | RGD1563853 predicted | 2,00 | others or unknown |
| 1371636_at | — | 1,04 | others or unknown |

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Table B.4 – Continued

| Probe Set ID | Gene Symbol | SLR2 | annotation |
|---|---|---|---|
| 1388746_at | — | 1,50 | others or unknown |
| 1372435_at | — | -1,07 | others or unknown |
| 1371652_at | — | 1,13 | others or unknown |
| 1388689_at | — | 2,92 | others or unknown |
| 1388635_at | RGD1309744 predicted | 1,17 | others or unknown |
| 1371756_at | Krt5 | -1,04 | others or unknown |
| 1371919_at | RGD:1302935 | 1,00 | others or unknown |
| 1388578_at | LOC289378 | -1,05 | others or unknown |
| 1371969_at | — | 1,26 | others or unknown |
| 1389072_at | — | 1,85 | others or unknown |
| 1389249_at | Sh2bp1 | 1,21 | others or unknown |
| 1389220_at | — | 1,33 | others or unknown |
| 1371250_at | Pf4 | 1,22 | others or unknown |
| 1389147_at | — | 2,05 | others or unknown |
| 1371274_at | CysS | -1,02 | others or unknown |
| 1371313_at | RGD1565656 predicted | 1,18 | others or unknown |
| 1388879_at | — | 1,37 | others or unknown |
| 1371331_at | Fstl1 | 1,09 | others or unknown |
| 1388766_at | Mtx2 predicted | 1,24 | others or unknown |
| 1371394_x_at | LOC498989 | -1,66 | others or unknown |
| 1371412_a_at | Nrep | 1,51 | others or unknown |
| 1389070_at | — | -1,00 | others or unknown |
| 1371472_at | — | 1,09 | others or unknown |
| 1371475_at | Rnase4 | 1,30 | others or unknown |
| 1389020_at | — | 1,98 | others or unknown |
| 1372063_at | LOC497938 | 2,99 | others or unknown |
| 1388882_at | Fkbp3 predicted | 1,16 | others or unknown |
| 1371583_at | Rbm3 | 1,23 | others or unknown |
| 1389095_at | Boc predicted | 3,11 | others or unknown |
| 1372713_at | RGD1309550 | 1,60 | others or unknown |
| 1388557_at | — | 1,96 | others or unknown |
| 1372567_at | — | 1,38 | others or unknown |
| 1388166_at | RGD:1359202 /// LOC299458 /// LOC314509 /// LOC366747 | 1,41 | others or unknown |
| 1372576_at | — | -1,08 | others or unknown |
| 1372620_at | Anp32e predicted | 1,13 | others or unknown |
| 1372627_at | — | 1,55 | others or unknown |
| 1375038_at | — | 2,13 | others or unknown |

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Table B.4 – Continued

| Probe Set ID | Gene Symbol | SLR2 | annotation |
|---|---|---|---|
| 1373992_at | RGD:1359421 /// LOC498871 /// LOC498872 | 1,07 | others or unknown |
| 1383162_at | — | 1,81 | others or unknown |
| 1372721_at | — | 1,04 | others or unknown |
| 1372748_at | RGD1307436 predicted | 1,14 | others or unknown |
| 1372809_at | LOC290595 | -1,13 | others or unknown |
| 1372818_at | Colec12 | 1,04 | others or unknown |
| 1372828_at | Msrb2 | -1,32 | others or unknown |
| 1372840_at | RGD1560093 predicted | 2,33 | others or unknown |
| 1372870_at | Kdelr3 predicted | 1,09 | others or unknown |
| 1388420_at | LOC361100 | 1,62 | others or unknown |
| 1389253_at | Vnn1 predicted | 1,30 | others or unknown |
| 1389332_at | — | 1,32 | others or unknown |
| 1372064_at | Cxcl16 | 1,44 | others or unknown |
| 1372101_at | Ppap2b | 1,70 | others or unknown |
| 1388527_at | — | 1,73 | others or unknown |
| 1372167_at | — | 1,82 | others or unknown |
| 1372265_at | RGD1304719 | 1,16 | others or unknown |
| 1371970_at | LOC499322 | -4,58 | others or unknown |
| 1372282_at | RGD1307506 predicted | 1,39 | others or unknown |
| 1372301_at | Aebp1 predicted | 1,94 | others or unknown |
| 1388408_at | RGD1307129 predicted | 1,15 | others or unknown |
| 1388347_at | LOC362934 | 1,39 | others or unknown |
| 1388339_at | Pea15 predicted | 1,47 | others or unknown |
| 1388338_at | — | -1,23 | others or unknown |
| 1388307_at | Tde2 | 2,03 | others or unknown |
| 1373313_at | — | 1,23 | others or unknown |
| 1373954_at | RGD1305986 predicted | 1,65 | others or unknown |
| 1388472_at | — | 1,48 | others or unknown |
| 1391560_at | — | 1,03 | others or unknown |
| 1391454_at | — | -1,28 | others or unknown |
| 1368353_at | Gfap | -1,37 | others or unknown |
| 1391428_at | — | 1,35 | others or unknown |
| 1390738_at | Bst2 | 1,04 | others or unknown |
| 1392900_at | LOC310756 | 1,02 | others or unknown |
| 1390709_at | — | 1,22 | others or unknown |
| 1390698_at | — | 2,12 | others or unknown |
| 1390688_at | Ddx50 | 1,20 | others or unknown |
| 1390672_at | — | -1,47 | others or unknown |

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Table B.4 – Continued

| Probe Set ID | Gene Symbol | SLR2 | annotation |
|---|---|---|---|
| 1390670_at | — | -1,14 | others or unknown |
| 1390661_at | Wdr20 | 1,76 | others or unknown |
| 1390604_s_at | Itgb3bp predicted | 3,66 | others or unknown |
| 1390568_at | Tubd1 predicted | -1,14 | others or unknown |
| 1368508_at | Psma3 /// Psma3l | 1,21 | others or unknown |
| 1399155_at | — | -1,35 | others or unknown |
| 1399154_at | Fbxl11 predicted | 1,32 | others or unknown |
| 1399116_at | — | 1,31 | others or unknown |
| 1399028_at | — | 1,10 | others or unknown |
| 1398973_at | RGD1564625 predicted | 1,51 | others or unknown |
| 1398945_at | — | 1,08 | others or unknown |
| 1398927_at | RGD1307161 | -1,43 | others or unknown |
| 1367655_at | Tmsb10 | 2,16 | others or unknown |
| 1392710_at | Wdfy1 | -1,32 | others or unknown |
| 1367741_at | Herpud1 | -1,19 | others or unknown |
| 1367768_at | Lxn | 1,63 | others or unknown |
| 1398596_at | — | 2,30 | others or unknown |
| 1394247_x_at | — | -1,46 | others or unknown |
| 1394234_x_at | — | 1,28 | others or unknown |
| 1393860_at | — | 1,52 | others or unknown |
| 1393417_at | — | -1,07 | others or unknown |
| 1393239_at | — | 1,08 | others or unknown |
| 1393130_at | — | 1,11 | others or unknown |
| 1390526_at | — | 1,01 | others or unknown |
| 1398866_at | Magi3 | 1,61 | others or unknown |
| 1389467_at | MGC108778 | 1,13 | others or unknown |
| 1390375_at | Akap8l | -1,05 | others or unknown |
| 1389525_at | Rnf149 | 1,18 | others or unknown |
| 1370236_at | Ppt | 1,18 | others or unknown |
| 1370312_at | Spon1 | 1,30 | others or unknown |
| 1370344_at | Hspa4 | 1,01 | others or unknown |
| 1398319_at | — | 1,39 | others or unknown |
| 1389601_at | — | 1,36 | others or unknown |
| 1389424_at | — | 1,04 | others or unknown |
| 1389383_at | — | 1,03 | others or unknown |
| 1389351_at | RGD:1359548 | 1,06 | others or unknown |
| 1389337_at | — | 1,00 | others or unknown |
| 1389329_at | Lgals8 | 1,70 | others or unknown |
| 1372872_at | LOC310958 | 1,17 | others or unknown |
| 1370899_at | — | 1,14 | others or unknown |
| 1370381_at | Pnrc1 | 1,54 | others or unknown |
| 1389986_at | — | 2,01 | others or unknown |

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Table B.4 – Continued

| Probe Set ID | Gene Symbol | SLR2 | annotation |
|---|---|---|---|
| 1371028_at | Tgoln2 | 1,20 | others or unknown |
| 1390477_at | — | -1,15 | others or unknown |
| 1390450_a_at | Ogn predicted | 1,84 | others or unknown |
| 1370394_at | RGD:1359626 /// LOC500728 | 1,99 | others or unknown |
| 1390300_at | — | 2,23 | others or unknown |
| 1390298_at | — | 1,02 | others or unknown |
| 1390259_at | — | 1,00 | others or unknown |
| 1390129_at | — | 1,20 | others or unknown |
| 1369186_at | Casp1 | 1,12 | others or unknown |
| 1390115_at | — | 1,03 | others or unknown |
| 1390538_at | — | -1,06 | others or unknown |
| 1389923_at | — | -1,09 | others or unknown |
| 1369670_at | Mox2 | 1,15 | others or unknown |
| 1389842_at | RGD1564664 predicted | -1,03 | others or unknown |
| 1389796_at | — | 2,05 | others or unknown |
| 1389774_at | — | 1,78 | others or unknown |
| 1369890_at | — | -1,00 | others or unknown |
| 1389728_at | Meis2 predicted | 1,36 | others or unknown |
| 1369938_at | Pank4 | -1,13 | others or unknown |
| 1389713_at | — | 1,05 | others or unknown |
| 1390024_at | — | 1,34 | others or unknown |
| 1384802_at | — | -1,30 | others or unknown |
| 1375646_at | Efcab2 predicted | 2,32 | others or unknown |
| 1375714_at | LOC365661 | 1,32 | others or unknown |
| 1375800_at | — | 1,12 | others or unknown |
| 1375821_at | — | -1,90 | others or unknown |
| 1375853_at | RGD1309995 predicted | 1,02 | others or unknown |
| 1375880_at | — | 1,22 | others or unknown |
| 1375990_a_at | — | 1,18 | others or unknown |
| 1376845_at | isg12(b) | 1,66 | others or unknown |
| 1376330_at | — | -1,11 | others or unknown |
| 1376905_at | — | 2,69 | others or unknown |
| 1375612_at | — | 1,22 | others or unknown |
| 1376049_at | LOC312030 | 1,59 | others or unknown |
| 1376104_at | RGD1308319 predicted | 1,88 | others or unknown |
| 1376214_at | — | 1,04 | others or unknown |
| 1376232_at | — | -1,08 | others or unknown |
| 1374770_at | Asah1 | 1,83 | others or unknown |
| 1376896_at | — | 1,48 | others or unknown |
| 1375215_x_at | RGD:1303133 | 2,17 | others or unknown |
| 1374858_at | Dhx29 predicted | 1,51 | others or unknown |

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Table B.4 – Continued

| Probe Set ID | Gene Symbol | SLR2 | annotation |
|---|---|---|---|
| 1374879_x_at | — | 1,92 | others or unknown |
| 1374953_at | LOC500420 | 1,04 | others or unknown |
| 1367489_at | — | 1,07 | others or unknown |
| 1385826_at | — | 1,14 | others or unknown |
| 1385697_at | — | 2,48 | others or unknown |
| 1375123_at | Sox4 predicted | 1,07 | others or unknown |
| 1387929_at | RGD:620149 | 1,11 | others or unknown |
| 1372640_at | LOC499410 | 2,40 | others or unknown |
| 1375635_at | — | 1,08 | others or unknown |
| 1375230_at | — | -1,11 | others or unknown |
| 1385333_at | — | 1,42 | others or unknown |
| 1375362_at | — | 1,45 | others or unknown |
| 1375422_at | — | 2,38 | others or unknown |
| 1375463_at | — | 1,44 | others or unknown |
| 1375535_at | — | 1,26 | others or unknown |
| 1384934_at | — | 1,19 | others or unknown |
| 1375595_at | — | 1,44 | others or unknown |
| 1379683_at | RGD1565079 predicted | 1,35 | others or unknown |
| 1377296_at | Tm6sf1 predicted | -1,04 | others or unknown |
| 1377720_x_at | — | 1,60 | others or unknown |
| 1377731_at | RGD1560600 predicted | 1,16 | others or unknown |
| 1377820_a_at | — | 1,09 | others or unknown |
| 1377823_at | — | 1,31 | others or unknown |
| 1377836_at | — | 3,30 | others or unknown |
| 1377995_at | RGD1311484 | -1,02 | others or unknown |
| 1378009_at | — | 1,11 | others or unknown |
| 1379361_at | Pex11a | -1,14 | others or unknown |
| 1383338_at | — | 3,40 | others or unknown |
| 1379739_at | — | 1,26 | others or unknown |
| 1379874_at | — | 2,07 | others or unknown |
| 1381504_at | LOC306805 | 1,86 | others or unknown |
| 1383321_at | Tpst1 predicted | 1,10 | others or unknown |
| 1382255_at | — | 1,25 | others or unknown |
| 1383306_at | — | 1,21 | others or unknown |
| 1379242_at | — | 1,58 | others or unknown |
| 1376376_at | — | 1,61 | others or unknown |
| 1376411_at | — | 1,07 | others or unknown |
| 1376440_at | Rnf139 predicted | 1,39 | others or unknown |
| 1387081_at | Rcn2 | 1,16 | others or unknown |
| 1376495_at | — | -1,08 | others or unknown |
| 1376575_at | — | 1,66 | others or unknown |

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Table B.4 – Continued

| Probe Set ID | Gene Symbol | SLR2 | annotation |
|---|---|---|---|
| 1376579_at | Lap3 | 1,58 | others or unknown |
| 1376588_at | — | 1,22 | others or unknown |
| 1376634_a_at | — | 3,78 | others or unknown |
| 1377224_at | — | 2,89 | others or unknown |
| 1376662_at | Ppp1r12a | 2,04 | others or unknown |
| 1376723_a_at | — | -1,19 | others or unknown |
| 1376746_at | Ldhd predicted | -1,42 | others or unknown |
| 1376778_at | — | 1,83 | others or unknown |
| 1383965_at | Ncbp2 predicted | 1,89 | others or unknown |
| 1376817_at | — | -1,45 | others or unknown |
| 1383912_at | — | 3,68 | others or unknown |
| 1377114_at | — | 1,15 | others or unknown |
| 1377141_at | LOC498685 | 1,20 | others or unknown |
| 1375134_at | — | 1,49 | others or unknown |
| 1384402_a_at | LOC289181 | 1,81 | others or unknown |
| 1386517_at | — | 2,31 | others or unknown |
| 1375921_at | — | 1,23 | others or unknown |
| 1373421_at | Tgif predicted | 2,79 | others or unknown |
| 1373876_at | — | -1,06 | others or unknown |
| 1373419_at | — | 1,00 | others or unknown |
| 1374751_at | — | 2,34 | others or unknown |
| 1374061_at | RGD1307606 predicted | 1,78 | others or unknown |
| 1386856_a_at | Samd4b | -1,12 | others or unknown |
| 1373862_at | LOC252889 | 1,34 | others or unknown |
| 1374166_at | — | 1,01 | others or unknown |
| 1374167_at | LOC361399 | 1,46 | others or unknown |
| 1374170_at | LOC498749 | 1,49 | others or unknown |
| 1375901_at | Mageh1 | 1,44 | others or unknown |
| 1373546_at | — | 1,03 | others or unknown |
| 1388799_at | Klhl7 predicted | 1,42 | others or unknown |
| 1373919_at | — | 2,13 | others or unknown |
| 1373152_at | RGD:1359545 | 1,59 | others or unknown |
| 1374081_at | — | 1,22 | others or unknown |
| 1373603_at | RGD1565744 predicted | 1,02 | others or unknown |
| 1373616_at | RGD1561936 predicted | 1,20 | others or unknown |
| 1373628_at | — | 2,74 | others or unknown |
| 1373673_at | — | 1,04 | others or unknown |
| 1387166_at | Aipl1 | -1,07 | others or unknown |
| 1373727_at | LOC499856 | 1,59 | others or unknown |
| 1373750_at | Leprel2 predicted | 1,62 | others or unknown |
| 1373759_at | — | 1,36 | others or unknown |

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Table B.4 – Continued

| Probe Set ID | Gene Symbol | SLR2 | annotation |
|---|---|---|---|
| 1373776_at | — | 1,02 | others or unknown |
| 1387266_at | Siah1a | 1,25 | others or unknown |
| 1373861_at | Ndfip2 predicted | 1,62 | others or unknown |
| 1372999_at | RGD1307008 predicted | 1,19 | others or unknown |
| 1388802_at | — | 1,03 | others or unknown |
| 1374529_at | Thbs1 | 1,84 | others or unknown |
| 1374530_at | — | 1,20 | others or unknown |
| 1374545_at | Rkhd2 predicted | 1,06 | others or unknown |
| 1374548_at | — | 1,35 | others or unknown |
| 1374563_at | — | 1,32 | others or unknown |
| 1374578_at | — | 1,87 | others or unknown |
| 1373078_at | — | -1,20 | others or unknown |
| 1373037_at | Ube2l6 | 1,04 | others or unknown |
| 1374454_at | — | 1,46 | others or unknown |
| 1374631_at | Obfc2b | 1,07 | others or unknown |
| 1374644_at | — | 1,35 | others or unknown |
| 1374652_at | — | 1,10 | others or unknown |
| 1374684_at | — | 2,07 | others or unknown |
| 1374695_at | — | 1,61 | others or unknown |
| 1372947_at | Pls3 | 1,39 | others or unknown |
| 1374705_at | — | 1,31 | others or unknown |
| 1374718_at | — | 1,40 | others or unknown |
| 1375962_at | — | 1,19 | others or unknown |
| 1374204_at | Wsb1 predicted | 1,44 | others or unknown |
| 1374214_at | — | 1,08 | others or unknown |
| 1374233_at | RGD1308326 predicted | 1,41 | others or unknown |
| 1374298_at | — | 1,71 | others or unknown |
| 1374299_at | Dhx9 predicted | 2,64 | others or unknown |
| 1374316_at | — | -1,19 | others or unknown |
| 1374456_at | — | 1,20 | others or unknown |
| 1373090_at | Ssr1 | 1,00 | others or unknown |
| 1374339_at | — | 1,01 | others or unknown |
| 1385933_at | — | 1,52 | others or unknown |
| 1385916_at | — | 1,53 | others or unknown |
| 1374435_at | — | 1,89 | others or unknown |
| 1373093_at | RGD1307599 predicted | 1,00 | others or unknown |
| 1388796_at | Gosr1 | 1,36 | transport |
| 1367598_at | Ttr | -1,02 | transport |
| 1388198_at | Nupl1 | 1,51 | transport |
| 1377386_at | Atp2c1 | -1,55 | transport |
| 1367748_at | Arf5 | -1,10 | transport |
| 1388052_a_at | Kcnq3 | -1,14 | transport |

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Table B.4 – Continued

| Probe Set ID | Gene Symbol | SLR2 | annotation |
|---|---|---|---|
| 1388140_at | Rab13 | 1,11 | transport |
| 1377190_at | RGD1306939 | 1,29 | transport |
| 1370248_at | Fxyd6 | 1,37 | transport |
| 1386372_at | Rab3ip | -1,40 | transport |
| 1369705_at | Xtrp3 | -1,24 | transport |
| 1369772_at | Slc6a9 | -2,17 | transport |
| 1389492_at | Arfgap1 | -1,33 | transport |
| 1370228_at | Tf /// Srprb predicted | 1,03 | transport |
| 1376344_at | Cybrd1 | 1,60 | transport |
| 1370240_x_at | Hba-a1 /// RGD:1359364 | 1,34 | transport |
| 1388608_x_at | Hba-a1 | 1,33 | transport |
| 1370739_x_at | Trdn | 1,51 | transport |
| 1371102_x_at | Hbb | 1,04 | transport |
| 1370934_at | Nup153 | 1,47 | transport |
| 1371004_at | Sort1 | 1,20 | transport |
| 1370239_at | Hba-a1 /// RGD:1359364 | 1,64 | transport |
| 1387600_at | Gabrp | -1,01 | transport |
| 1373657_at | Slc31a2 | 1,39 | transport |
| 1368533_at | Heph | 1,62 | transport |
| 1387054_at | Abcg1 | -1,16 | transport |
| 1387027_a_at | Lgals9 | 1,19 | transport |
| 1387543_at | Slc5a7 | -1,38 | transport |
| 1387008_at | Sfxn3 | 1,14 | transport |
| 1368990_at | Cyp1b1 | 1,07 | transport |
| 1376268_at | Arf6 | 1,34 | transport |
| 1386904_a_at | Cyb5 | -1,08 | transport |
| 1371929_at | Mlx | 1,00 | transport |

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