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**GENOMICS** 

Genomics 87 (2006) 616-632

www.elsevier.com/locate/ygeno

# Overlapping and distinct transcriptional regulator properties of the GLI1 and GLI2 oncogenes

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Received 22 September 2005; accepted 8 December 2005 Available online 24 January 2006

# Abstract

The GLI transcription factors mediate the hedgehog signal in development and carcinogenesis. Basal cell carcinoma can be caused by overexpression of either GL11 or GL12. Though GL11 and GL12 have identical or very similar DNA binding specificities, some of their activities are overlapping, some are clearly distinct. We analyzed target gene specificities of GL11 and constitutively active GL12 (GL12 $\Delta$ N) by global expression profiling in an inducible, well-characterized HaCaT keratinocyte expression system. Four hundred fifty-six genes up- or downregulated at least twofold were identified. GLI target gene profiles correlated well with the biological activities of these transcription factors in hair follicles and basal cell carcinoma. Upregulation of largely overlapping sets of target genes was effected by both factors, repression occurred predominantly in response to GL12. Also, significant quantitative differences in response to GL11 and GL12 $\Delta$ N were found for a small number of activated genes. Since we have not detected a putative processed GL12 repressor, these results point to specific but indirect target gene repression by GL12 $\Delta$ N via preferential activation of one or more negative regulators.

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Keywords: Basal cell carcinoma; GLI target genes; Global expression analysis; Keratinocytes; Transcriptional repression

The hedgehog (Hh) signaling pathway (reviewed in [1,2]) has been implicated not only in development, but also in the formation and maintenance of different tumors of skin, brain, prostate, upper gastrointestinal tract, and lung (reviewed in [3-8]). The tumorigenic effect of constitutive hedgehog signaling was first demonstrated in basal cell carcinoma (BCC), in which the majority of tumors are caused by the inactivation of the Hh receptor and negative pathway regulator PTCH [9-11]. In addition, mutations in SMOH leading to constitutive pathway activation have been found in sporadic BCC [12,13]. Pathway activation by overexpression of Sonic hedgehog (SHH) in human keratinocytes or mouse skin also leads to BCC-like features and changes in gene expression [14,15]. The zinc finger transcription factors GLI1 and GLI2, the main mediators of the hedgehog signal in skin, can both cause epithelial tumors with characteristics of BCC when overexpressed in the basal epidermal layer and the outer root sheath of the hair follicle in transgenic mice and frog skin [16-20]. Overlapping function between GLI1 and GLI2 in development, however, is apparent from the different phenotypes of single and compound mutants [21–27] and has most clearly been demonstrated by the rescue of the  $Gli2^{-/-}$  developmental phenotype in mice expressing Gli1 from the Gli2 locus, except for a subtle, unexplained skin phenotype [28]. GLI1 and GLI2 have been shown to have distinct as well as overlapping functions. Though GLI1 has been shown to have activator functions only [29-32], GLI2 can clearly act as an activator as proven by the substitution experiment referred to above, but there is also evidence for repressive function of GLI2 [24,30,32-34]. Differences in the biological activities of Gli1 and Gli2 exist, since Gli1<sup>-/-</sup> mice have no obvious phenotype, while homozygous  $Gli2^{-/-}$  mice die around birth and have abnormal lungs and neural tube and also defects in hair follicle development [21,27,35,36].

Data on the respective roles of GLI1 and GLI2 in tumorigenesis are less extensive. Using a conditional *Gli2* allele Hutchin et al. [37] showed that BCC-like tumor growth

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and maintenance depend on continuous expression of *Gli2* in tumor cells. GLI1 is the hedgehog target gene most consistently expressed at elevated levels in BCC and in the majority—if not all—Hh-associated tumors [16,38,39]. GLI1 has been shown to be important in growth and maintenance of prostate tumor cells [38,40]. GLI1 is also likely to play a critical role in medulloblastoma, where it is highly expressed. In *Gli1<sup>-/-</sup>* mice the incidence of medulloblastoma caused by constitutive Hh signaling [41] is severely reduced even though it can occur. Less is known about the role of GLI2 in Hh signaling-induced tumors.

To define the relative contributions of these transcription factors to carcinogenesis, we focused on basal cell carcinoma, where the action of GLI1 or GLI2 is sufficient to give rise to tumors. To assess on a molecular level the extent of overlapping and distinct target gene specificities of GLI1 and GLI2, we used conditional expression in the human keratinocyte cell line HaCaT [42], in which we have previously shown that (i) the response to GLI1 and GLI2 is similar to that of primary human keratinocytes and (ii) GLI1 and GLI2 can elicit expression patterns that resemble to a significant extent those of BCC [43]. Here, we have addressed by global expression profiling and QRT-PCR the target gene specificities of the transcriptional activators GLI1 and GLI2 $\Delta$ N, a constitutively active form of GLI2 lacking the N-terminal repression domain [44]. Human full-length GLI2 was recently described by Roessler and colleagues [34] and shows significantly lower transcriptional activator function than GLI2 $\Delta$ N in vitro. In vivo, in mouse hair follicle development, there is evidence that full activation of Gli2 depends on an event that requires the presence of Shh. In the absence of Shh, rescue of the phenotype can be achieved only by a constitutively active, N-terminally truncated Gli2 protein that closely resembles the human GLI2 $\Delta$ N [36]. Similarly, only truncated/activated Gli2 is able to mimic Shh-induced gene expression in isolated presomitic mesoderm [24,30]. Nterminally truncated Gli2 has also been shown to produce a more severe tumor phenotype than full-length Gli2 when expressed in the epidermis of transgenic mice [19]. The truncated human GLI2, GLI2 $\Delta$ N, is therefore a valuable tool to mimic the activated form of GLI2. When we used DNAarray technology to analyze the transcription profiles induced by conditionally expressed GLI2 $\Delta$ N and GLI1, we identified qualitative and quantitative similarities as well as differences in their target gene response. Only very few genes were upregulated exclusively by either GLI1 or GLI2 $\Delta$ N. The most striking difference between GLI1 and GLI2 $\Delta$ N was the very small number of genes repressed on induction of GLI1, while a large number were repressed after induction of GLI2 $\Delta$ N. In the absence of evidence for proteolytic processing and in view of the strongly activating properties of  $GLI2\Delta N$ , repression of target genes in this system is likely to be indirect, possibly by GLI2 specific activation of a repressor. The data provide evidence for selective activation of transcriptional programs by GLI1 and GLI2, which could have significant consequences for the execution of the hedgehog signal in keratinocytes.

# **Results and discussion**

# Differential induction and repression of GL11 and GL12 target genes

To compare GLI1 and GLI2 expression profiles in keratinocytes we used tetracycline-inducible HaCaT cell lines expressing GLI1 or an activated form of GLI2 (GLI2 $\Delta$ N) [43]. To minimize cell clone-specific effects we pooled four independent clones. Since a comparison of the relative effects of GLI1 and GLI2 $\Delta$ N has to be based on similar expression levels of the transcription factors, we first measured transgene expression by ORT-PCR at the RNA level. Both GLI1 and GLI2 $\Delta$ N were expressed at comparable levels in the induced cells used for the expression analysis (Fig. 1A). Fig. 1A shows that the increase in PTCH mRNA reflects the increase in GLI1 and GLI2 $\Delta$ N mRNA levels, implying similar transcriptional activity of both GLI proteins. We also demonstrated induction of GLI1 and GLI2 $\Delta$ N by Western blot (Fig. 1A, top). To compare activity and specificity of GLI1, GLI2 $\Delta$ N, and the newly described full-length GLI2 [34], we used luciferase assays on three different promoters: the known target genes PTCH [45] (C. Schmid, unpublished) and GLI1 [46] and an artificial promoter containing six tandem GLI binding sites [47] (Fig. 1B). Activation of all three promoters is strongest with GLI2 $\Delta$ N, followed by GLI1 and full-length GLI2. The relative activities of the three GLI proteins, however, vary widely on the three tested promoters. Differential activity of different GLI proteins on different promoters is frequently observed and may be partly responsible for different effects of the transcription factors as discussed below.

Approximately 12,000 PCR-amplified, sequence-verified EST clones on high-density filter arrays were hybridized with <sup>33</sup>P-labeled cDNA from GLI1- or GLI2 $\Delta$ N-expressing and control cells to determine expression levels after 24 and 72 h of tetracycline treatment (see Material and methods). In total, RNA levels of 456 genes represented by 512 EST clones were found to be increased or decreased at least twofold at one or both time points as judged by SAM (significance analysis of microarray) [48] (Table 1). Fig. 2 compares the inducing and repressing activities of GLI1 and GLI2 $\Delta$ N. Seventy-two hours after induction 68 genes were induced more than twofold by GLI1 and 138 by GLI2 $\Delta$ N, 46 of these were induced by both. Most genes upregulated by GLI2 $\Delta$ N were also upregulated by GLI1. The smaller number of genes responding to GLI1 than GLI2 $\Delta$ N may reflect the fact that for many genes the strength of the response was higher for GLI2 $\Delta$ N than for GLI1. For a very small number of genes there is such a large difference between the activation by the two transcription factors that expression of those genes can be considered specific to just GLI1 or GLI2. For GLI2 induction of BCL2 such specificity has previously been described [49]. Here we find GLI2 specificity also for FST, while TNC and CTSL are much more strongly activated by GLI1 than by GLI2 $\Delta$ N (Table 1 and Fig. 5). It is possible that a gene-specific threshold of GLI activity is required, but the detailed mechanism is not known.



Fig. 1. Transcriptional activity of GLI1 or GLI2 $\Delta$ N in HaCaT keratinocytes. (A) The induction in HaCaT cells of GLI1 and GLI2 $\Delta$ N under tetracycline control was determined by QRT-PCR and Western blot. Increase of the GLI1 or GLI2 $\Delta$ N transgene and the direct target gene PTCH mRNAs is shown after induction for the times indicated. GLI1 and GLI2 $\Delta$ N proteins (top) were detected using specific antibodies against GLI1 and GLI2. Samples were taken from tetracycline-treated and untreated double stable HaCaT cells as indicated. (B) Luciferase reporter assay comparing the activities of GLI1, GLI2 $\Delta$ N, and human full-length GLI2 on different promoter constructs. HaCaT cells were cotransfected with different reporter constructs (the synthetic reporter construct 6×GLIbs, PTCHprom, and GLI1prom) and NLS-Myc-tagged GLI1 (GLI1), Myc-tagged GLI2 $\Delta$ N (GLI2 $\Delta$ N), Myc-tagged full-length GLI2 (GLI2), or empty expression vector (pc).

Reduction of expression levels was observed for only 45 clones after 72 h of tetracycline treatment by GLI1 compared to 190 genes for GLI2 $\Delta$ N; 28 of these were repressed by both. The results are even more striking at the 24-h time point, at which twice as many genes were induced, but 17 times as many repressed by GLI2 $\Delta$ N compared to GLI1. A large majority of genes repressed by GLI2 $\Delta$ N are not affected by GLI1, while

only a very small number of genes repressed in response to GLI1 are unaffected by GLI2 $\Delta$ N expression. Most genes repressed by GLI1 are also repressed by GLI2 $\Delta$ N. Since in GLI1-expressing HaCaT cells endogenous GLI2 is also turned on after a delay [43], it is not possible to discriminate between a specific effect of GLI1 and an indirect effect via GLI1-induced expression of endogenous GLI2. These results show a clear difference between the regulatory effects of GLI1 and GLI2 $\Delta N$ in keratinocytes compatible with in vivo data in other systems showing only activating function for Gli1, but activating and repressing function for Gli2 [24,30,32–34]. It is surprising that repression can take place in the absence of the putative Nterminal repressor domain of GLI2 [30,34]. The data, however, do not address whether repression of target genes is caused directly by a GLI2 repressor function present also in GLI2 $\Delta N$ or indirectly by GLI2-mediated induction of an unknown repressor activity. Ci, the single Drosophila ortholog of the three mammalian GLI transcription factors, can act either as activator or as repressor of transcription. In the presence of Hh, an activated form of full-length 155-kDa Ci induces the expression of *Hh* target genes, while in the absence of Hh a proteolytically processed 75-kDa repressor form is localized to the nucleus and prevents the expression of Hh target genes (reviewed in [1,2]). Of the three mammalian GLI proteins [50], mouse Gli1 has been described as having only activating functions, which can be supplied also by mouse Gli2 [21,28]. Mouse Gli3 is an important repressor of *Hh* target genes in limb and neural development [51,52], but also has an activating function [24,53]. In vitro, all three GLI proteins have been shown to be able to act as dominant negative, if the protein is truncated C-terminally to the Zn-finger DNA binding domain [23,30,32,54], indicating the presence of activating domains in the deleted fragment. The structure of these molecules is similar to that of the in vivo-processed 75-kDa repressor form of Ci [23,32].

The repressor activity of C-terminally truncated Gli3 has been amply demonstrated in vivo and in vitro [23,51,54,55]. The in vivo repressor role of a corresponding truncated Gli2 protein is much less clear. Unlike Gli3, the repressing activity of Gli2 observed in some contexts is not responsive to the Hh signal. Truncated products of Gli2 have been observed after expression in frog embryos [23], COS cells [51], and *Drosophila melanogaster* [32], but there is no clear evidence for such a repressor form in the absence of ectopic overexpression.

Phosphorylation by protein kinase A (PKA) is a precondition for proteolytic processing of Ci and of Gli3 to a Cterminally truncated form with repressor activity [23,56–58]. In the expression analysis the large number of genes repressed in response to GLI2 $\Delta$ N could arise due to either direct repression by a modified form of GLI2 $\Delta$ N or another mechanism. We therefore first assayed for forskolin-induced PKA phosphorylation of the GLI proteins by immunoprecipitation using GLI1- and GLI2 $\Delta$ N-specific antibodies followed by detection using PKA substrate-specific antibody (Fig. 3A). We then looked for the appearance of proteolytically processed forms of the GLI proteins in Western blots of whole lysates from cells treated with tetracycline and forskolin, but only fulllength specific fragments were detected (Fig. 3B). We therefore conclude that detectable processing of the inducible GLI2 $\Delta$ N protein in a way comparable to that of Ci or GLI3 does not occur in HaCaT cells even though strong repression of target genes is observed.

# Groups of functionally related genes regulated by GL11 and GL12

Based on their molecular function and association with pathways, we grouped the differentially expressed genes according to gene map classification using Pathway Explorer (https://www.pathwayexplorer.genome.tugraz.at/) [59] (Fig. 4 and Table 1). As expected, cell cycle and proliferation are among the most highly represented classes. Two pathways known to interact with HH, WNT and TGF $\beta$ , also appear. These and other classes are discussed below in the context of skin, BCC, and hair follicles.

To verify a subset of the array data we used QRT-PCR (genes marked by superscript "b" in Table 1). For selected genes we refined the time resolution by a 12-h point (Fig. 5 and Table 2). The QRT-PCR data show good agreement with the array data for kinetics and level of induction. The higher fold-change values measured by QRT-PCR are a common phenomenon, likely to be due to the higher dynamic range of the PCR-based approach.

We have previously shown that  $GLI2\Delta N$  induces the expression of genes driving proliferation and represses epidermal differentiation markers [60]. We now compared these results to the GLI1 response and observed very little repression of differentiation markers such as KRT1, KRT10, IVL, SPRR2A (Table 2, bottom), DSG1, S100A8, and S100A9 (Table 1), while genes involved in promoting proliferation were induced also by GLI1 (Table 2, top), illustrating the distinct and overlapping specificities of the effects of the two related transcription factors. Cell cycle genes regulated by GLI1 and GLI2 $\Delta$ N include some cyclins, cyclin inhibitors, cyclindependent kinases, and other proteins involved in critical steps of cell cycle progression such as E2F1. Increased cell cycle progression is also seen in the mRNA increase of the classical markers MKI67 (Ki67), PCNA, and MAD2L1 (Table 1), a mitotic checkpoint protein induced by E2F1 [61].

Differential expression in response to GL11 or GL12 $\Delta$ N was also found for different proteases and their inhibitors, though this does not necessarily correlate with their activity since protease activity is mostly regulated at the posttranslational level. Of the members of the kallikrein family of serine proteases expressed in skin, KLK6 was highly and KLK5 and KLK10 were moderately induced by both GL11 and GL12 $\Delta$ N (Fig. 5A). The serine protease inhibitor Kazal-type 5 (SPINK5) (Table 1), which is coexpressed with kallikrein proteases in skin, is downregulated by GL12 $\Delta$ N only. Expression of several other serine protease inhibitors is also changed by GL1 expression: SERPINA1 and SERPINB2 are upregulated, while SERPINB3, SERPINB5, and SERPINB13 are turned down, as is the epithelial-specific protease inhibitor PI3 (SKALP/elafin) (Fig. 5D and Table 1). An example of the

complementary regulatory roles of GLI1 and GLI2 $\Delta N$  is the lysosomal cysteine protease cathepsin L (CTSL), which is also expressed in skin and hair follicles. CTSL is upregulated in response to GLI1 and to a lower extent by GLI2 $\Delta$ N, while its inhibitor cystatin A (CSTA) is downregulated by GLI2 $\Delta$ N only (Figs. 5B and 5D). The metalloproteases illustrate opposite effects in successive regulatory steps: MMP1, MMP10, MMP12, and MMP13 show a strong negative response to GLI2 $\Delta$ N and a weaker one to GLI1 expression (Table 1). From the higher time resolution of the QRT-PCR analysis for MMP1, MMP10, and MMP13 it is clear that repression is reversed at the 72-h time point (Fig. 5D, inset). This is likely to be mediated by the transcription factor FOXE1, a direct target gene of GLI2 [62], which strongly induces expression of these MMPs when expressed in HaCaT keratinocytes (data not shown).

GLI2 $\Delta$ N plays an essential role in hair follicle development [36] and is highly expressed in the outer root sheath (ORS) [46]. We found significant similarities between genes expressed in hair follicles and HaCaT cells expressing GLI2 $\Delta$ N. BCCs are another structure expressing GLI target genes. Some genes expressed in the ORS and in BCCs are upregulated by GLI2 $\Delta N$ in HaCaT cells (CTSL, FOXE1, BCL2) (Fig. 5C), while most of the downregulated genes (KRT1, KRT10, IVL, DSG1) (Fig. 5D and Table 1) are not normally present in the basal layer of epidermis, the ORS, and BCCs. The protease CTSL (see above) has also been localized to the ORS. Its importance in proper skin and hair morphology is underlined by the phenotype of CTSL-deficient mice, which develop epidermal hyperplasia, acanthosis, hyperkeratosis, and periodic hair loss [63-65]. CTSL is also elevated in BCC [66]. An important role in development and cycling of the hair follicle and skin homeostasis involves TGF $\beta$  signaling. Members of the TGF $\beta$ family are involved in the control of keratinocyte proliferation and differentiation during normal skin stratification (reviewed in [67–69]). We found upregulation of expression of the activin/ BMP antagonists follistatin (FST) and HTRA1 (PRSS11) (Fig. 5C and Table 1), pointing to inhibition of TGFB signaling by the HH/GLI pathway. Notably, FST was specifically induced by GLI2, while HTRA1 responded to both GLI1 and GLI2 $\Delta N$ . This correlates well with the expression of follistatin mRNA in mouse skin in the ORS of the hair follicle and in the basal layer of the epidermis [70]. In follistatin-deficient mice, hair follicle development is significantly retarded, while the number of hair follicles in wild-type embryonic skin explants treated with follistatin is increased [71]. Furthermore, the activators of TGF<sup>B</sup> signaling, BMP2 and BMP7, were downregulated by GLI2, as was their target gene ID1 (Table 1) [72-74], a basic helix-loop-helix transcription factor involved in mediating the effect of TGFB. TGFB receptor2 (TGFBR2) is also downregulated. Together, these results point to an inhibitory role of GLI2 on TGFB signaling in hair follicle development.

# Conclusions

Target gene expression after induction of GLI1 and GLI2 in HaCaT keratinocytes illustrates the proliferation enhancing

Table 1 Gene expression profiles of human epidermal cells in response to GLI1 and GLI2 $\Delta N$ 

GLI 24 h         GLI 72 h         GLI 24 h         GLI 72 h         GLI 72 h         GLI 72 h           SERPING <sup>345</sup> NM.00619         0.38         0.39         0.03         0.02         1           SERPING <sup>345</sup> NM.00611         0.48         0.39         0.02         00           RETTP <sup>35</sup> NM.00611         0.41         0.50         0.41         0.66         26, 29           CILI 74 NM.00617         0.43         0.44         0.15         0.66         1.25           ABCA <sup>44</sup> NM.00758         0.49         0.61         0.17         0.68           Pi <sup>354</sup> NM.00758         -         -         0.17         0.69           MMP1 <sup>34</sup> NM.00247         0.45         0.52         0.07         0.10         4, 25           MMP1 <sup>34</sup> NM.00285         -         0.27         0.26         0.14         11           SI00.49 <sup>36</sup> NM.00285         -         0.27         0.13         10         12           CICA4         NM.00285         -         0.23         0.38         0.14         11           VA252         NM.00285         -         0.27         0.15         2,3         1.5 <th>HUGO gene name</th> <th>NCBI acc. no.</th> <th>Fold induction/</th> <th>Pathway ID</th>	HUGO gene name	NCBI acc. no.	Fold induction/	Pathway ID			
SERFINES <sup>24</sup> NAL00019         0.38         0.39         0.043         0.02         1           SUD0A <sup>24</sup> NAL00512         0.64         -         0.12         0.02         10           KRT1 <sup>AA</sup> NAL00512         0.61         0.56         0.14         0.06         26, 29           KRT1 <sup>OPb</sup> NAL00529         -         0.63         0.22         0.06         1, 25           RCM <sup>10Pb</sup> NAL00538         0.30         0.26         0.22         0.06         1, 25           RACA4 <sup>10</sup> NAL00539         0.49         0.61         0.07         0.08         1, 25           RACA4 <sup>10</sup> NAL00247         0.45         0.52         0.07         0.10         4, 25           MAPH <sup>1</sup> <sup>24</sup> NAL00213         0.46         0.55         0.26         0.12         4, 25           SI00A9 <sup>24</sup> NAL00213         0.46         0.57         0.40         0.17         0.18         10           SI00A9 <sup>24</sup> NAL002613         -         -         0.26         0.14         11           VAA73         NAL00218         0.46         0.57         0.41         0.15         1.61         11         12			GLI1 24 h	GLI1 72 h	GLI2 24 h	GLI2 72 h	
SID0.8 <sup>ab</sup> NAL002964         0.05         0.24         0.09         0.02         10           JUNB <sup>ab</sup> NAL00229         -         0.38          0.05         2.2           JUNB <sup>ab</sup> NAL00229         -         0.38         0.41         0.05         2.0           CBLSLA         NAL00268         0.30         0.26         0.22         0.06         1.25           JUNB <sup>ab</sup> NAL00268         0.30         0.26         0.22         0.07         0.08           JED22709         NAL02478         -         -         0.17         0.09           MAPI 3 <sup>ab</sup> NAL00247         0.45         0.52         0.27         0.12         4.25           MAPI 3 <sup>ab</sup> NAL002421         0.46         0.65         0.39         0.12         4.25           STR2A <sup>ab</sup> NAL002421         0.46         0.65         0.39         0.14         11           VAX3         NAL002421         0.42         0.26         0.14         0.15           STR2A <sup>ab</sup> NAL00213         -         -         0.27         0.15         2.10           VAX3         NAL00203         -         -         0.23	SERPINB3 <sup>a,b</sup>	NM_006919	0.38	0.39	0.03	0.02	1
KRT1***NAL0001210.640.120.02KRT10**NAL002290.380.0520, 29KRT10**NAL002100.610.540.440.150.66P13**NAL002580.390.260.220.061.25ABCA4***NAL002590.490.610.770.081.25FL2220**NAL024770.450.520.070.104.25THBP*NAL002610.580.260.124.25STRRAA**NAL0026610.270.210.1310CLCA4NAL0026610.270.200.1423STRRAA**NAL005670.260.1411PLA22024*NAL005070.270.200.1441VAYANAL005010.270.152.10,11,19CLCS12NAL005020.270.152.10,11,19CLCA4NAL003010.230.1441PLA2202**NAL005030.500.4111PLA220**NAL005030.520.480.132.21CLC54NAL005030.230.151.5CMA*NAL005030.230.212.7CMA*NAL005130.130.222.2CMA*NAL005150.550.580.50.57<	S100A8 <sup>a,b</sup>	NM_002964	0.35	0.24	0.09	0.02	10
JUNB**NL.00229-0.83-0.850.610.650.640.650.660.750.660.750.670.750.	KRT1 <sup>a,b</sup>	NM_006121	0.64	-	0.12	0.02	
KRT10 <sup>bb</sup> NhL00021         0.61         0.63         0.64         0.65           CINLAL         NL002638         0.30         0.26         0.22         0.66         1.25           BASA         NL002638         0.39         0.61         0.77         0.06         1.25           FL22209P         NL024578         -         -         0.77         0.10         4.25           THBD*         NL00261         -         0.88         0.26         0.12         4.25           SMMP1 <sup>128</sup> NL00265         -         0.27         0.40         0.13         10           CLCA4         NL01285         0.40         0.37         0.21         0.14         41           FLA22704*         NL005051         -         0.27         0.40         0.13         10           CLCA4         NL012128         0.42         0.28         0.22         0.14         41           FLA22704*         NL000501         -         -         0.27         0.15         2.10.11.19           CL2C42         NL000512         -         -         0.27         0.15         2.10.11.19           CL2C42*         NL000513         -         -         0.2	JUNB <sup>a,b</sup>	NM_002229	-	0.38	-	0.05	26, 29
CBLXL4         NM.080617         0.43         0.44         0.15         0.06           ABCA4 <sup>b</sup> NM.00358         0.49         0.61         0.17         0.08           ABCA4 <sup>b</sup> NM.003578         -         -         0.17         0.08           MMP13 <sup>bh</sup> NM.00361         -         0.52         0.07         0.10         4.25           MMP1 <sup>bh</sup> NM.00361         -         0.53         0.20         0.12         4.25           MMP1 <sup>bh</sup> NM.00361         -         0.57         0.21         0.13         10           S100.9 <sup>bh</sup> NM.00285         -         0.27         0.40         0.13         10           CLCA4         NM.003127         -         -         0.26         0.14         11           VAV3*         NM.00300         -         0.23         0.35         0.14         41           VAV3*         NM.00513         -         -         0.16         0.17         28,38           CLTA*         NM.00213         -         -         0.13         0.12         14           L/WCR         A138981         0.60         0.49         0.32         0.18 <td< td=""><td>KRT10<sup>a,b</sup></td><td>NM_000421</td><td>0.61</td><td>0.50</td><td>0.14</td><td>0.06</td><td></td></td<>	KRT10 <sup>a,b</sup>	NM_000421	0.61	0.50	0.14	0.06	
Pipsh         NM. 002638         0.309         0.26         0.22         0.06         1.25           FL222709°         NM.024578         -         -         0.17         0.09           FL222709°         NM.024578         -         -         0.17         0.09           FL222709°         NM.024578         -         -         0.17         0.09           FL222709°         NM.00361         -         0.58         0.26         0.12         -           STBPREALA <sup>th</sup> NM.003988         0.40         0.37         0.21         0.13         10           CLCA4         NM.012128         0.42         0.28         0.22         0.14         11           PLA3C32A*         NM.00300         -         0.23         0.35         0.14         41           VAV3*         NM.00300         -         0.23         0.35         0.14         41           VAV3*         NM.003013         -         0.55         0.16         0.17         2.8.3           CLCA*         NM.002165         -         0.55         0.44         0.19         0.22         1.01.19           DL**         NM.002165         -         0.55         0.44 <td< td=""><td>CBLNL4</td><td>NM_080617</td><td>0.43</td><td>0.44</td><td>0.15</td><td>0.06</td><td></td></td<>	CBLNL4	NM_080617	0.43	0.44	0.15	0.06	
ABCA+ <sup>bh</sup> NM00350         0.49         0.61         0.17         0.08           EZ2270 <sup>00</sup> NM.024578         -         -         0.17         0.09         4.25           MMP13 <sup>bh</sup> NM.00361         -         0.52         0.07         0.10         4.25           MMP1 <sup>bh</sup> NM.00361         -         0.58         0.26         0.12         4.35           SIM0A9 <sup>bh</sup> NM.002421         0.46         0.65         0.39         0.12         4.25           SIM0A9 <sup>bh</sup> NM.002965         -         0.27         0.40         0.33         10           CIC.CA         NM.00127         -         -         0.23         0.35         0.14         11           VAV3*         NM.001613         -         -         0.23         0.35         0.14         41           VAV3*         NM.001613         -         -         0.32         0.16         0.17         28.38           GIA1 <sup>A</sup> NM.001613         -         -         0.13         0.17         28.38           GIA1 <sup>A</sup> NM.001613         -         -         0.13         0.18         0.17         28.38           GIA1 <sup>A</sup> <	PI3 <sup>a,b</sup>	NM_002638	0.30	0.26	0.22	0.06	1,25
FL22209 <sup>6</sup> NM.024578         -         -         0.17         0.09           FL22209 <sup>6</sup> NM.00361         -         0.58         0.26         0.12           THBD <sup>16</sup> NM.00361         -         0.58         0.26         0.12           SPRR2A <sup>ab</sup> NM.005988         0.40         0.37         0.21         0.13           SPRR2A <sup>ab</sup> NM.005985         0.42         0.22         0.22         0.14         23           CLCC44         NM.012128         0.42         0.22         0.22         0.14         23           CLCC47         NM.00300         -         0.23         0.35         0.14         41           VAV3 <sup>3</sup> NM.00300         -         0.23         0.35         0.14         41           VAV3 <sup>3</sup> NM.003015         -         -         0.15         2.10.11.19           CLC2 <sup>4</sup> NM.002165         -         0.55         0.44         0.17         1           DVAV3         NM.002165         -         0.52         0.47         0.23         0.22         27           OLFA4         NM.00433         -         -         0.19         0.22         22         2	ABCA4 <sup>a,b</sup>	NM_000350	0.49	0.61	0.17	0.08	
MMP (3 <sup>bb</sup> )         NML 002427         0.45         0.52         0.07         0.10         4.25           MMP ( <sup>bb</sup> )         NML 002421         0.46         0.65         0.39         0.12         4.25           MMP ( <sup>bb</sup> )         NML 002955          0.27         0.40         0.13         10           CLCA4         NML 002955          0.27         0.40         0.13         10           CLCA4         NML 002952          0.22         0.43         0.14         11           PLA3C2A*         NL 000300          0.23         0.35         0.14         41           VAV3*         NML 000155          1.85         0.16         0.17         28.38           GIA1*         NML 000165          1.85         0.16         0.17         28.38           CL2*         NML 000165          0.50         0.41         0.18         1           L/VCR         AL399981         0.60         0.49         0.32         0.16         0.20           CL2*         NL 000213          0.55         0.44         0.19         0.22         27           GIA1*         NL 000233 <td>FLJ22709<sup>a</sup></td> <td>NM_024578</td> <td>-</td> <td>-</td> <td>0.17</td> <td>0.09</td> <td></td>	FLJ22709 <sup>a</sup>	NM_024578	-	-	0.17	0.09	
THBD*         NML000361          0.58         0.26         0.12         4, 25           SPRR2Axb*         NML005985         0.40         0.37         0.21         0.13         10           SPRR2Axb*         NML005985         0.40         0.37         0.21         0.13         10           CLCA4         NML012128         0.42         0.28         0.22         0.14         23           CLCA4         NML005127         -         -         0.23         0.35         0.14         41           VAV3*         NML000513         -         -         -         0.16         0.17         28, 38           CLC2*         NML000813         -         -         0.18         0.17         1           L/CR         AL38981         0.60         0.49         0.32         0.18         0.17         1           L/CR         AL38981         0.60         0.49         0.32         0.18         0.17         1           L/CR         AL38981         0.60         0.49         0.32         0.18         0.17         1         2.1         0.11         10         1         0.17         1         0.1         0.12         1         <	MMP13 <sup>a,b</sup>	NM_002427	0.45	0.52	0.07	0.10	4, 25
MMP1 <sup>bh</sup> NM_002421         0.46         0.65         0.39         0.12         4, 25           SI00AP <sup>bh</sup> NM_002965          0.27         0.40         0.13         10           CLCA4         NM_012128         0.42         0.28         0.22         0.14         13           CLECSP2         NM_00300         -         -         0.26         0.14         11           VAV3*         NM_000301         -         -         0.27         0.15         3.5           CCL2*         NM_00030282         -         -         -         0.16         0.17         28.38           CCL2*         NM_000151         -         -         0.18         0.17         28.38           CSTA*b         NM_00513         -         -         0.18         0.17         28.38           LVCR         AL38981         0.60         0.49         0.32         0.18         1           D1P4*         NM_001515         0.58         0.29         0.57         0.20         1         1         1           D1F4*         NM_000433         -         0.47         0.23         0.22         2         2         2         2 <t< td=""><td>THBD<sup>a</sup></td><td>NM_000361</td><td>-</td><td>0.58</td><td>0.26</td><td>0.12</td><td></td></t<>	THBD <sup>a</sup>	NM_000361	-	0.58	0.26	0.12	
SPREA. <sup>Abb</sup> NNL.05988         0.40         0.37         0.21         0.13           CLCA4         NNL.012128         0.42         0.28         0.22         0.14         23           CLCA4         NNL.00300         -         0.23         0.35         0.14         41           PLA3C3C4*         NNL00013         -         0.23         0.35         0.14         41           VAV3*         NNL000155         -         -         0.15         2.10.11.1         2.10.11.1           VAV3*         NNL000165         -         1.85         0.16         0.17         2.8.38           CSTA <sup>A</sup> NNL002912         -         -         0.18         0.17         1           D1 <sup>45</sup> NNL002165         -         0.50         0.41         0.18         0.17         1           D1 <sup>45</sup> NNL002165         -         0.50         0.41         0.18         0.17         1         1           D1 <sup>45</sup> NNL002165         -         0.50         0.49         0.20         0.27         0.43         0.21         2.7           D14749         NNL002165         -         0.50         0.39         0.22         2.2	MMP1 <sup>a,b</sup>	NM_002421	0.46	0.65	0.39	0.12	4, 25
S100.40 <sup>bb</sup> NML.00296S          0.27         0.40         0.13         10           CLCA4         NML.001212B         0.42         0.28         0.22         0.14         11           PLA3C2AV         NML.003000         -         0.23         0.35         0.14         41           VAV3*         NML.00613         -         0.27         0.15         3.5           CC12*         NML.0005213         -         0.16         0.17         2.8.38           LNCR         AL3S9981         0.60         0.49         0.32         0.18           LNCR         AL3S9981         0.60         0.49         0.32         0.18           LNCR         AL3S9981         0.60         0.49         0.32         0.18           LNCR         AF402776         -         0.52         0.49         0.20         0.7           NCF2*         NML.00433         -         0.47         0.23         0.22         2.7           NCR2*         NML.00860         0.52         0.48         0.13         0.22         2.7           CK         NML.00860         0.53         0.59         0.39         0.32         2.8         39	SPRR2A <sup>a,b</sup>	NM_005988	0.40	0.37	0.21	0.13	
CLCA4         NM_012128         0.42         0.28         0.22         0.14         23           PLA3G2A <sup>4</sup> NM_0005177         -         -         0.23         0.35         0.14         11           PLA3G2A <sup>4</sup> NM_000513         -         0.23         0.35         0.14         41           VAV3*         NM_002613         -         -         0.16         0.17         28.38           CCL2*         NM_002613         -         -         0.18         0.17         1           LNCR         AL389981         0.60         0.49         0.22         0.18         0.17         1           LNCR         AL389981         0.60         0.49         0.22         0.18         0.17         1           LNCR         AL389981         0.60         0.49         0.22         0.18         0.17         1 <td>S100A9<sup>a,b</sup></td> <td>NM_002965</td> <td>-</td> <td>0.27</td> <td>0.40</td> <td>0.13</td> <td>10</td>	S100A9 <sup>a,b</sup>	NM_002965	-	0.27	0.40	0.13	10
CLECSF2         NM_005127         -         -         0.26         0.14         11           PLA3C2A*         NM_00300         -         0.23         0.35         0.14         41           VAV3*         NM_00103         -         -         0.27         0.15         3, 5           CC12*         NM_002982         -         -         0.16         0.17         28, 38           GTA4*         NM_00213         -         -         0.18         0.17         28, 38           D1*A*         NM_002165         -         0.50         0.41         0.18         1           D1*A*         NM_002165         -         0.52         0.49         0.20         0.27         0.26           D1*A*         NM_002135         -         0.52         0.49         0.20         0.21         0.27           D1*A*         NM_00433         -         0.47         0.23         0.22         2.7           D1*CR2*         NM_00860         0.52         0.48         0.13         0.22         2.7           D1*CR2*         NM_00730         -         0.47         0.23         0.23         15.38           D1*CR2*         NM_00733         -<	CLCA4	NM_012128	0.42	0.28	0.22	0.14	23
PLA3C2A <sup>a</sup> NM.000300         -         0.23         0.35         0.14         41           VAV3 <sup>a</sup> NM.006113         -         -         0.27         0.15         2, 10, 11, 19           CCL2 <sup>a</sup> NM.002055         -         -         -         0.15         2, 10, 11, 19           CSTA <sup>ab</sup> NM.002165         -         0.50         0.41         0.18         0.17         1           L/NCR         AL39981         0.60         0.49         0.32         0.18         -         -         0.16         0.17         1         -         -         0.16         0.17         1         -         -         0.16         0.17         1         -         -         0.17         0.15         0.16         0.17         1         -         -         0.19         0.21         CA         -         0.19         0.22         -         -         0.17         0.13         0.22         2.2         -         CA         -         0.19         0.22         -         -         0.19         0.22         7         -         -         0.19         0.22         -         -         CA         -         0.19         0.23         0	CLECSF2	NM_005127	-	-	0.26	0.14	11
VAV3*         NM_006113         -         -         0.15         3, 5           GL2*         NM_002982         -         -         0.15         2, 10, 11, 19           GJA1*         NM_002982         -         -         0.16         0.17         28, 38           GJA1*         NM_00213         -         -         0.18         0.17         1           L/NCR         AL389981         0.60         0.49         0.32         0.18         1           L/NCR         AL389981         0.60         0.49         0.32         0.18         1           L/NCR         AL389981         0.60         0.42         0.20         1         1           UFM4*         ML006418         2.28         0.65         0.44         0.19         0.22         22           NCF2*         NM_000860         0.52         0.48         0.13         0.22         27           GPC1*         NM_003716         -         -         0.13         0.22         27           GPC1*         NM_003716         -         -         0.16         0.33         0.23         15, 38           GGR         NM_001534         -         -         0.41	PLA2G2A <sup>a</sup>	NM_000300	-	0.23	0.35	0.14	41
CCL2*         NM_002982         -         -         -         0.15         2, 10, 11, 19           CSTA*b         NM_005213         -         -         0.18         0.17         1           L/NCR         AL389981         0.60         0.49         0.32         0.18         1           L/NCR         AL389981         0.60         0.49         0.32         0.18         1           L/NCR         AL389981         0.60         0.49         0.32         0.18         1           DLPM*         ML002165         -         0.52         0.49         0.20         1         27           KRT23         NM_005315         0.58         0.29         0.57         0.20         1         27           CPC2*         NM_00033         -         0.47         0.23         0.21         27           GPRATA*         NM_003716         -         -         0.39         0.22         7           GPRMB         NM_001005340         -         -         0.38         0.23         15.38           GIB6         NM_001244         -         0.59         0.39         0.23         15.38           GIB6         NM_001247         -	VAV3 <sup>a</sup>	NM_006113	-	-	0.27	0.15	3, 5
GAA <sup>1a</sup> NM_000165         -         1.85         0.16         0.17         1           LNCR         AL389981         0.60         0.49         0.32         0.18           UNCR         AL389981         0.60         0.49         0.32         0.18           OLFM4 <sup>3</sup> NL002165          0.50         0.41         0.19           D1P <sup>JA</sup> NL002167         -         0.52         0.49         0.20           NCF2 <sup>3</sup> NL00418         2.28         0.65         0.44         0.19           NCF2 <sup>3</sup> NL00453         -         0.47         0.23         0.21         27           NCF2 <sup>4</sup> NL000860         0.52         0.48         0.13         0.22         22           CA <sup>2</sup> NL001534         -         -         0.23         0.22         7           GPNMB         NL00105340         -         -         0.38         0.23         15.38           GJB6         NL001544         -         -         0.34         0.24         2.5           GJB6         NL002475         0.58         0.45         0.42         0.26         8.3.9           ZIC <sup>2</sup> N	CCL2 <sup>a</sup>	NM_002982	-	-	-	0.15	2, 10, 11, 19
CSTA <sup>bb</sup> NL005213         -         -         0.18         0.17         1           LNCR         AL39981         0.60         0.49         0.32         0.18         1           ID1 <sup>bh</sup> NL002165          0.50         0.41         0.18           ID1 <sup>bh</sup> NL002165          0.52         0.49         0.20           KRT23         NL015515         0.58         0.29         0.57         0.20           KRT23         NL000433         -         0.47         0.23         0.21         27           HPCD <sup>b</sup> NL000860         0.52         0.48         0.13         0.22         27           CA2 <sup>a</sup> NL000860         0.52         0.48         0.13         0.22         27           GPR174*         NL000581         -         -         0.38         0.23         -           GPRMB         NL0010540         -         -         0.39         0.23         -           GJB6         NL001729         0.53         0.45         0.42         0.23         -           GJB6         NL0012577         0.52         0.58         0.27         0.25         0.56         0.25 <td>GJA1<sup>a</sup></td> <td>NM_000165</td> <td>-</td> <td>1.85</td> <td>0.16</td> <td>0.17</td> <td>28, 38</td>	GJA1 <sup>a</sup>	NM_000165	-	1.85	0.16	0.17	28, 38
LINCR         AL38981         0.60         0.49         0.32         0.18           LINCR         AL389981         0.60         0.41         0.18           OLEM44         NL006418         2.28         0.65         0.44         0.19           BIC innescript         AF402776          0.52         0.49         0.20           NCF2*         NL00433          0.47         0.23         0.21         27           PCDP         NL000860         0.52         0.48         0.13         0.22         22           CA2*         NL003716          -         0.39         0.22         7           GPRNB         NL0015340          -         0.39         0.23         5.38           GJB6         NL001724         -         -         0.39         0.23         5.38           GJB6         NL001724         -         -         0.41         0.23         28.39           CIC2*         NNL00172         0.53         0.45         0.42         0.24         4.25           VAX2         NL010124         -         -         0.33         0.25         0           OVGL2*         NL0015777<	CSTA <sup>a,b</sup>	NM_005213	-	-	0.18	0.17	1
ID1 <sup>a,b</sup> NM.002165         -         0.50         0.41         0.18           DCFM4*         NM.006418         2.28         0.65         0.44         0.19           BTC moscripr         AF402776         -         0.52         0.49         0.20           KRT23         NM.0015515         0.58         0.29         0.57         0.20           KRT24         NM.000860         0.52         0.48         0.13         0.22         22           CA2*         NM.003531         -         0.59         0.39         0.22         7           GPR174*         NM.0012533         -         0.65         0.39         0.23         15.38           GPR14*         NM.0012340         -         -         0.38         0.23         15.38           GB6         NM.001247         -         -         0.41         0.23         28.39           CIC2*         NM.001247         -         -         0.41         0.23         28.39           CIC2*         NM.001247         -         -         0.54         0.42         0.42           VAX2         NM.012476         -         -         0.53         0.56         0.25	LINCR	AL389981	0.60	0.49	0.32	0.18	
OLFM4         NM.00618         2.28         0.65         0.44         0.19           BC transcript         A F402776          0.52         0.49         0.20           KRT23         NM.015151         0.58         0.29         0.57         0.20           NCF2 <sup>9</sup> NM.000433          0.47         0.23         0.21         27           PRCDP         NM.000581           0.33         0.22         27           GRNAW         NM.003716           0.38         0.23         7           GPN144         NM.005340           0.41         0.32         28, 39           ADM <sup>4</sup> NM.00124           0.41         0.23         28, 39           ZIC2 <sup>a</sup> NM.00124           0.41         0.23         28, 39           ZIC2 <sup>a</sup> NM.007129         0.53         0.45         0.42         0.23         28, 39           ZIC2 <sup>a</sup> NM.00125777         0.52         0.58         0.42         0.25         0.54         0.24           VA22         NL012476         -         -         0.33	ID1 <sup>a,b</sup>	NM_002165	-	0.50	0.41	0.18	
BIC transcript       AF402776       -       0.52       0.49       0.20         NCF2 <sup>a</sup> NM_007515       0.58       0.29       0.57       0.20         NCF2 <sup>a</sup> NM_000860       0.52       0.48       0.13       0.22       22         DCKDK <sup>a</sup> NM_000861       -       -       0.19       0.22       7         CA2 <sup>a</sup> NM_003716       -       -       0.39       0.22       7         GPR174 <sup>a</sup> NM_001534       -       -       0.38       0.23       15, 38         GPNB       NM_001544       -       -       0.39       0.23       15, 38         GB6       NL001544       -       -       0.41       0.23       28, 39         ZIC2 <sup>a</sup> NM_007129       0.53       0.45       0.42       0.23       23         VAX2       NM_012476       -       -       0.54       0.23       25         SCAMP1       NM_00225777       0.52       0.58       0.27       0.25       25         SCAMP1       NM_002120       -       0.55       0.56       0.25       27         VCG <sup>ab</sup> NM_002120       -       0.58       0.43       0	OLFM4 <sup>a</sup>	NM_006418	2.28	0.65	0.44	0.19	
KRT23         NM_015515         0.58         0.29         0.57         0.20           NCF2*         NM_000433          0.47         0.23         0.21         27           HPGD <sup>4</sup> NM_000860         0.52         0.48         0.13         0.22         22           CA2*         NM_000581         -         -         0.19         0.22         7           GPRIAF         NM_005340         -         -         0.39         0.22         7           GPNMB         NM_0015340         -         -         0.39         0.23         15, 38           GIB6         NL007124         -         -         0.45         0.42         0.23           VAX2         NM_01729         0.53         0.45         0.42         0.23         42, 39           UGCGL1 <sup>4</sup> NM_0025777         0.52         0.58         0.27         0.25         0.58         0.27         0.25           VAX2         NM_01025777         0.52         0.58         0.42         0.26         8, 31, 33, 35           KRT4 <sup>4</sup> NM_002467         -         0.45         0.42         0.26         8, 31, 33, 35           KRT4 <sup>4</sup> NM_002508	BIC transcript	AF402776	-	0.52	0.49	0.20	
NCF2 <sup>3</sup> NM_000433        0.47       0.23       0.21       27         HPCD <sup>3</sup> NM_000500       0.52       0.48       0.13       0.22       22         BCKDK <sup>4</sup> NM_003716       -       -       0.23       0.22       7         GPR174 <sup>4</sup> NM_003530       -       0.59       0.39       0.22       7         GPNMB       NM_001005340       -       -       0.38       0.23       7         GPNMB       NM_0010584       -       0.65       0.39       0.23       15, 38         GB6       NM_00783       -       -       0.41       0.23       28, 39         ZIC2 <sup>a</sup> NM_007129       0.53       0.45       0.42       0.23       23         VAX2       NM_0102476       -       -       0.54       0.23       25         VGCGL <sup>1</sup> NM_0025777       0.52       0.58       0.27       0.25       0.56       0.25         MYC <sup>a,b</sup> NM_00272       0.53       0.39       0.45       0.42       0.26       8, 31, 33, 35         MYC <sup>a,b</sup> NM_00270       -       0.55       0.56       0.25       0.57       0.54       0.26	KRT23	NM_015515	0.58	0.29	0.57	0.20	
HPCD <sup>b</sup> NML00860       0.52       0.48       0.13       0.22       22         CA2 <sup>a</sup> NML003716       -       -       0.19       0.22       7         CA2 <sup>a</sup> NML003716       -       -       0.39       0.22       7         GPR174 <sup>a</sup> NML00105340       -       -       0.38       0.23       7         MPED2       NML001584       -       0.65       0.39       0.23       15, 38         GB6       NML007129       0.53       0.45       0.42       0.23       28, 39         ZIC2 <sup>a</sup> NML012476       -       -       0.54       0.23       28, 39         VAX2       NML012476       -       -       0.54       0.24       4, 25         UGCGL1 <sup>a</sup> NML00125777       0.52       0.58       0.27       0.25       0.33       0.45       0.42       0.26       8, 31, 33, 35         SCAMP1       NML002467       -       0.55       0.56       0.25       0.27       0.25       0.26       8, 31, 33, 35       SKR14 <sup>a</sup> NML002467       -       0.45       0.26       8, 31, 33, 35       SKR14 <sup>a</sup> NML002467       -       0.38       0.27       25	NCF2 <sup>a</sup>	NM_000433	-	0.47	0.23	0.21	27
BCKDK <sup>a</sup> NM_003716         -         -         0.19         0.22           GPR174 <sup>a</sup> NM_0032553         -         0.59         0.39         0.22         7           GPR174 <sup>a</sup> NM_0032553         -         0.59         0.39         0.23         27           GPRNB         NM_001005340         -         -         0.38         0.23         5           ADM         NM_001124         -         -         0.39         0.23         15, 38           GIB6         NM_00783         -         -         0.41         0.23         28, 39           ZIC2 <sup>a</sup> NM_001247         0.53         0.45         0.42         0.23         28, 39           ZIC2 <sup>a</sup> NM_002425         0.58         0.46         0.24         0.25         25           SCAMP1         NM_002427         0.52         0.58         0.27         0.25         25           VC2 <sup>a</sup> NM_002167         -         0.45         0.42         0.26         8, 31, 33, 35           KRT4 <sup>a</sup> NM_002272         0.53         0.39         0.45         0.26         8           ND <sup>a</sup> NM_002508         -         -         0	HPGD <sup>a</sup>	NM_000860	0.52	0.48	0.13	0.22	22
CA2 <sup>a</sup> NM_003716         -         -         0.23         0.22         27           GPR174 <sup>a</sup> NM_0035353         -         0.59         0.38         0.23         7           GPNMB         NM_00105340         -         -         0.65         0.39         0.23         1         5.38           GJB6         NM_001124         -         0.65         0.41         0.23         28, 39           ZIC2 <sup>a</sup> NM_007129         0.53         0.45         0.42         0.23           MMP10 <sup>b,b</sup> NM_002425         0.58         0.46         0.24         0.23           VAX2         NM_002425         0.58         0.46         0.24         0.24         4, 25           UGCGL1 <sup>a</sup> NM_002425         0.58         0.46         0.24         0.25         0.58           CVAX2         NM_002466         -         -         0.033         0.25         0.50         0.56         0.25           SCAMP1         NM_002467         -         0.55         0.56         0.26         0.25         5         0.26         0.26         0.27         37, 38, 39         0.45         0.26         0.5         0.26         0.27 <td< td=""><td>BCKDK<sup>a</sup></td><td>NM_005881</td><td>-</td><td>-</td><td>0.19</td><td>0.22</td><td></td></td<>	BCKDK <sup>a</sup>	NM_005881	-	-	0.19	0.22	
GPR174 <sup>a</sup> NML032553         -         0.59         0.39         0.22         7           MPPED2         NML00105340         -         -         0.38         0.23           MPPED2         NML001584         -         0.65         0.39         0.23         15, 38           ADM <sup>a</sup> NML007129         0.53         0.45         0.41         0.23         23           ZIC2 <sup>a</sup> NML007129         0.53         0.45         0.42         0.23         5           VAX2         NML0012476         -         -         0.54         0.23         5           VAX2         NML00125777         0.52         0.58         0.27         0.25         5           VOL2 <sup>a</sup> NML002577         0.52         0.58         0.27         0.25         5           VOL2 <sup>a</sup> NML002467         -         0.45         0.42         0.26         8, 31, 33, 35           KRT4 <sup>a</sup> NML002730         -         -         0.38         0.27         25           FAT2 <sup>a</sup> NML00147         -         0.58         0.43         0.27         25           SHANK2         NML002451         -         0.39         0.28<	CA2 <sup>a</sup>	NM_003716	-	-	0.23	0.22	27
GPNMB         NML00105340         -         -         0.63         0.23           MPPED2         NML001584         -         0.65         0.39         0.23         15, 38           GIB6         NML001124         -         -         0.41         0.23         28, 39           ZIC2 <sup>a</sup> NML007129         0.53         0.45         0.42         0.23         28, 39           VAX2         NML012476         -         -         0.54         0.23         4, 25           UGCGL1 <sup>a</sup> NML00125777         0.52         0.58         0.46         0.24         0.24         4, 25           UGCGL1 <sup>a</sup> NML001025777         0.52         0.58         0.27         0.25         0.58         0.47         0.26         8, 31, 33, 35         KRT4 <sup>a</sup> NML002477         -         0.45         0.26         0.26         0.26         0.26         0.26         0.26         0.26         0.27         37, 38, 39         0.27         25         5.7         5.6         0.28         0.27         37, 38, 39         0.27         37, 38, 39         0.27         37, 38, 39         0.27         37, 38, 39         0.27         37, 38, 39         0.28         0.29         0.28	GPR174 <sup>a</sup>	NM_032553	-	0.59	0.39	0.22	7
MPED2         NM_001584         -         0.65         0.39         0.23           ADM <sup>4</sup> NM_001124         -         -         0.41         0.23         15, 38           GJB6         NM_007129         0.53         0.45         0.42         0.23         28, 39           ZIC2 <sup>a</sup> NM_001296         -         -         0.54         0.23         28, 39           VAX2         NM_0012476         -         -         0.54         0.24         0.24         4, 25           UGCGL1 <sup>a</sup> NM_00125777         0.52         0.58         0.46         0.24         0.25         -           OVOL2 <sup>a</sup> NM_002467         -         -         0.33         0.25         -           OVOL2 <sup>a</sup> NM_002467         -         0.45         0.42         0.26         8, 31, 33, 35           KRT4 <sup>a</sup> NM_002467         -         0.45         0.42         0.26         8, 31, 33, 35           NID <sup>a</sup> NM_002467         -         0.45         0.42         0.26         8, 31, 33, 35           RAT4 <sup>a</sup> NM_002467         -         0.58         0.43         0.27         25           FAT2 <sup>a</sup> N	GPNMB	NM_001005340	-	-	0.38	0.23	
ADM*         NM_0001124         -         -         0.39         0.23         15, 38           GIB6         NM_006783         -         -         0.41         0.23         28, 39           ZIC2 <sup>a</sup> NM_007129         0.53         0.45         0.42         0.23           VAX2         NM_012476         -         -         0.54         0.23           MMP10a <sup>b</sup> NM_002425         0.58         0.46         0.24         0.24         4, 25           UGCCL1 <sup>a</sup> NM_00125777         0.52         0.58         0.27         0.25           SCAMP1         NM_002467         -         0.45         0.42         0.26         8, 31, 33, 35           KRT4 <sup>a</sup> NM_002467         -         0.45         0.42         0.26         8, 31, 33, 35           KRT4 <sup>a</sup> NM_00272         0.53         0.39         0.45         0.26         8, 31, 33, 35           KRT4 <sup>a</sup> NM_002730         -         -         0.38         0.27         37, 38, 39           PRKACA         NM_004310         -         -         0.39         0.28         0,27           SI00A12         NM_1005521         -         -         0.33	MPPED2	NM_001584	-	0.65	0.39	0.23	
GJB6         NM_006/83         -         -         0.41         0.23         28,39           ZIC2 <sup>a</sup> NM_007129         0.53         0.45         0.42         0.23           MMP10 <sup>a,b</sup> NM_002425         0.58         0.46         0.24         0.24         4, 25           UGCGL1 <sup>a</sup> NM_00125777         0.52         0.58         0.46         0.24         0.25           SCAMP1         NM_00125777         0.52         0.55         0.56         0.25           VYC <sup>a,b</sup> NM_001220         -         0.45         0.42         0.26         8, 31, 33, 35           VRC <sup>a,b</sup> NM_002467         -         0.58         0.43         0.27         25           FAT2 <sup>a</sup> NM_002508         -         -         0.38         0.27         25           FAT2 <sup>a</sup> NM_00147         -         0.58         0.43         0.27         25           SI00A12         NM_00230         -         -         0.39         0.28         10, 27           SI00A12         NM_005621         -         -         0.36         0.29         -           SERPINB5 <sup>a,b</sup> NM_002639         -         -         0.31	ADM <sup>a</sup>	NM_001124	_	_	0.39	0.23	15, 38
ZIC2"         NML00/129         0.53         0.42         0.42         0.42           VAX2         NML012476         -         -         0.54         0.23           VAX2         NML002425         0.58         0.46         0.24         0.24         4, 25           UGCGL1 <sup>a</sup> NML00125777         0.52         0.58         0.27         0.25           SCAMP1         NML004866         -         -         -         0.33         0.25           VYCu <sup>b</sup> NML002120         -         0.55         0.56         0.25           MYCu <sup>b,b</sup> NML002467         -         0.45         0.42         0.26         8, 31, 33, 35           KRT4 <sup>a</sup> NML00272         0.53         0.39         0.45         0.26         -           PRKACA         NML002730         -         -         0.38         0.27         37, 38, 39           RHOH <sup>a</sup> NML004310         -         -         0.32         0.29         -           S100A12         NML002483         -         0.60         -         0.25         0.29         -           SERPINB5 <sup>a,b</sup> NML002639         -         -         0.55         0.29	GJB6	NM_006783	-	-	0.41	0.23	28, 39
VAX2       NML012476       -       -       0.54       0.23         MMP10abb       NML002425       0.58       0.46       0.24       0.24         UGCGL1 <sup>a</sup> NML001025777       0.52       0.58       0.27       0.25         SCAMP1       NML001025777       0.52       0.55       0.56       0.25         OVOL2 <sup>a</sup> NML01220       -       0.45       0.42       0.26       8, 31, 33, 35         MYC <sup>a,b</sup> NML002467       -       0.45       0.42       0.26       8, 31, 33, 35         KRT4 <sup>a</sup> NML00272       0.53       0.39       0.45       0.26       8, 31, 33, 35         NID <sup>a</sup> NML001477       -       0.58       0.43       0.27       25         FAT2 <sup>a</sup> NML001477       -       0.58       0.43       0.27       37, 38, 39         RHOF <sup>m</sup> NML002730       -       -       0.39       0.28       10, 27         S100A12       NML03561       -       -       0.32       0.29       29         SHANK2       NML133266       -       -       0.31       0.30       1, 14         PTPR2 <sup>i</sup> <sup>a</sup> NML002483       -       -       0.55 <td>ZIC2"</td> <td>NM_007129</td> <td>0.53</td> <td>0.45</td> <td>0.42</td> <td>0.23</td> <td></td>	ZIC2"	NM_007129	0.53	0.45	0.42	0.23	
MMP10 <sup></sup> NML002425         0.58         0.46         0.24         0.24         0.24         4, 25           UGCGL1 <sup>a</sup> NML00125777         0.52         0.58         0.27         0.25           SCAMP1         NML00125777         0.52         0.58         0.27         0.25           OVOL2 <sup>a</sup> NML021220         -         0.45         0.42         0.26         8,31,33,35           KRT4 <sup>a</sup> NML002467         -         0.45         0.42         0.26         8,31,33,35           KRT4 <sup>a</sup> NML002508         -         -         0.38         0.27         25           FAT2 <sup>a</sup> NML001447         -         0.58         0.43         0.27         37,38,39           RHOH <sup>a</sup> NML00508         -         -         0.43         0.27         37,38,39           S100A12         NML004310         -         -         0.32         0.28         10,27           SHANK2         NML00433         -         -         0.43         0.42         0.29           VEHA4         NML002483         -         0.60         -         0.29         2           SEPINB5 <sup>a,b</sup> NML002483         -	VAX2	NM_012476	-	-	0.54	0.23	4.05
CCCCCL1 <sup>a</sup> NM_L001023777         0.32         0.38         0.27         0.28           SCAMP1         NM_L004866         -         -         0.33         0.25           VYC <sup>a,b</sup> NM_002467         -         0.55         0.56         0.25           MYC <sup>a,b</sup> NM_002272         0.53         0.39         0.45         0.26           NID <sup>a</sup> NM_002508         -         -         0.38         0.27         25           FAT2 <sup>a</sup> NM_001447         -         0.58         0.43         0.27         25           PRKACA         NM_002730         -         -         0.43         0.27         37, 38, 39           RHOH <sup>a</sup> NM_004310         -         -         0.39         0.28         0.29           StANK2         NM_133266         -         -         0.32         0.29         -           StANK2         NM_002483         -         0.60         -         0.29         -           SterNB5 <sup>a,b</sup> NM_002438         -         0.60         -         0.29         -           SterNP1NB <sup>5,a,b</sup> NM_002851         -         -         0.31         0.30         28	MMP10 <sup>4,0</sup>	NM_002425	0.58	0.46	0.24	0.24	4, 25
SCAMP1         NML004866         -         -         -         0.53         0.25           OVOL2 <sup>a</sup> NML021220         -         0.55         0.56         0.26         8, 31, 33, 35           KRT4 <sup>a</sup> NML002467         -         0.45         0.42         0.26         8, 31, 33, 35           KRT4 <sup>a</sup> NML002508         -         -         0.38         0.27         25           FAT2 <sup>a</sup> NML001447         -         0.58         0.43         0.27         37, 38, 39           RHOH <sup>a</sup> NML004310         -         -         0.39         0.28         37, 38, 39           S100A12         NML005621         -         -         0.66         0.28         10, 27           SHANK2         NML002483         -         -         0.32         0.29         -           CEACAM6 <sup>a</sup> NML002483         -         -         0.55         0.29         -           SERPINB5 <sup>a,b</sup> NML002851         -         -         0.31         0.30         1, 14           PTPRZ1 <sup>a</sup> NML002851         -         -         0.43         0.30         28           SBF2         NML030962         -	UGCGLI"	NM_001025777	0.52	0.58	0.27	0.25	
OV0L2       NML0212120       -       0.33       0.36       0.25         MYCa,b       NML002467       -       0.45       0.42       0.26       8, 31, 33, 35         KRT4 <sup>a</sup> NML002272       0.53       0.39       0.45       0.26       8, 31, 33, 35         NID <sup>a</sup> NML002508       -       -       0.38       0.27       25         FAT2 <sup>a</sup> NML001447       -       0.58       0.43       0.27       37, 38, 39         RHOH <sup>a</sup> NM_004310       -       -       0.39       0.28       10, 27         S100A12       NM_005621       -       -       0.32       0.29       10, 27         SHANK2       NM_13266       -       -       0.32       0.29       10, 27         SHANK2       NM_002483       -       0.66       0.29       10, 27         SHANK2       NM_002483       -       0.60       -       0.29         Verta       -       0.60       -       0.29       11, 14         SERPINB5 <sup>a,b</sup> NM_002639       -       -       0.31       0.30       28         SBF2       NM_002639       -       -       0.31       0.30       28 </td <td>OVOL 2ª</td> <td>NM 021220</td> <td>-</td> <td>-</td> <td>0.55</td> <td>0.25</td> <td></td>	OVOL 2ª	NM 021220	-	-	0.55	0.25	
M1C 0-4       NML002407       0.53       0.45       0.42       0.26       5, 31, 35, 35         KRT4 <sup>a</sup> NM_002272       0.53       0.39       0.45       0.26         M1D <sup>a</sup> ML002508       -       -       0.38       0.27       25         FAT2 <sup>a</sup> NM_001447       -       0.58       0.43       0.27       37, 38, 39         PRKACA       NM_002730       -       -       0.39       0.28       0.27       37, 38, 39         RHOH <sup>a</sup> NM_004310       -       -       0.39       0.28       0.29       <	MVCa.b	NM 002467	_	0.33	0.30	0.25	0 21 22 25
KR14       NML002272       0.33       0.39       0.43       0.20         NID <sup>a</sup> NML002508       -       -       0.38       0.27       25         FAT2 <sup>a</sup> NML001447       -       0.58       0.43       0.27       37, 38, 39         PRKACA       NML002300       -       -       0.39       0.28       37, 38, 39         RHOH <sup>a</sup> NML005621       -       -       0.666       0.28       10, 27         SHANK2       NML133266       -       -       0.666       0.28       10, 27         SHANK2       NML002483       -       0.43       0.42       0.29       -         None       CAA6762       -       -       0.55       0.29       -         SERPINB5 <sup>a,b</sup> NML002639       -       -       0.31       0.30       1, 14         PTPRZ1 <sup>a</sup> NML002851       -       -       0.38       0.30       28         SBF2       NML030962       -       -       0.57       0.44       0.30         RASSF6       NML177532       -       0.57       0.48       0.30       28, 39         PRN <sup>a</sup> NML000311       -       -       0.50		NM 002272	-	0.45	0.42	0.26	6, 51, 55, 55
FAT2 <sup>a</sup> NM_001447       -       0.58       0.43       0.27       23         FAT2 <sup>a</sup> NM_002730       -       -       0.43       0.27       37, 38, 39         PRKACA       NM_004310       -       -       0.43       0.28       10, 27         S100A12       NM_005621       -       -       0.66       0.28       10, 27         SHANK2       NM_133266       -       -       0.32       0.29       10, 27         CEACAM6 <sup>a</sup> NM_002483       -       0.43       0.42       0.29       10, 27         None       CAA6762       -       -       0.55       0.29       11, 14         PTPR21 <sup>a</sup> NM_002639       -       -       0.31       0.30       1, 14         PTPR21 <sup>a</sup> NM_002851       -       -       0.31       0.30       28         SBF2       NM_030962       -       -       0.44       0.30       28         SBF2       NM_030962       -       -       0.44       0.30       28         SBF2       NM_030962       -       -       0.44       0.30       7         RASSF6       NM_177532       -       0.57	NID <sup>a</sup>	NM_002508	0.55	0.39	0.45	0.20	25
PR12       NML001447       -       0.38       0.43       0.27       37, 38, 39         PRKACA       NM_002730       -       -       0.39       0.28       37         RHOH <sup>a</sup> NM_004310       -       -       0.39       0.28       10, 27         S100A12       NM_005621       -       -       0.66       0.28       10, 27         SHANK2       NM_13266       -       -       0.32       0.29       -         CEACAM6 <sup>a</sup> NM_002483       -       0.60       -       0.29       -         None       CAA6762       -       -       0.55       0.29       -         EPHA4       NM_004438       -       0.60       -       0.31       0.30       1, 14         PTPRZ1 <sup>a</sup> NM_002851       -       -       0.31       0.30       28         SBF2       NM_03962       -       -       0.41       0.30       -         RASSF6       NM_177532       -       0.57       0.44       0.30       -         GJB2 <sup>a</sup> NM_00404       -       -       0.50       0.30       28, 39         IFNGR1 <sup>a</sup> NM_000416       -       -	NID EAT2 <sup>a</sup>	NM 001447	-	- 0.58	0.30	0.27	23
RHACA       NML002130       -       -       0.43       0.27       57, 58, 39         RHOH <sup>a</sup> NML004310       -       -       0.39       0.28         S100A12       NML005621       -       -       0.666       0.28       10, 27         SHANK2       NML133266       -       -       0.32       0.29       -         CEACAM6 <sup>a</sup> NML002483       -       0.43       0.42       0.29         None       CAA6762       -       -       0.55       0.29         EPHA4       NML004438       -       0.600       -       0.29         SERPINB5 <sup>a,b</sup> NML002639       -       -       0.31       0.30         CLDN8 <sup>a</sup> NML002851       -       -       0.31       0.30         SBF2       NML030962       -       -       0.41       0.30         RASSF6       NML177532       -       0.57       0.44       0.30         PRNP <sup>a</sup> NML000311       -       -       0.48       0.30         GJB2 <sup>a</sup> NML00404       -       -       0.50       0.30       28, 39         IFNGR1 <sup>a</sup> NML000416       -       -       0.50 <td></td> <td>NM_002720</td> <td>-</td> <td>0.36</td> <td>0.43</td> <td>0.27</td> <td>27 28 20</td>		NM_002720	-	0.36	0.43	0.27	27 28 20
RHOH       INICLOUGTION       Image: Constraint of the second sec	RHOHa	NM_004310	_		0.45	0.27	57, 50, 59
SHOAL2       NML1000211       -       -       0.00       0.20       10,27         SHANK2       NML1002483       -       -       0.32       0.29         CEACAM6 <sup>a</sup> NML002483       -       0.43       0.42       0.29         None       CAA6762       -       -       0.55       0.29         EPHA4       NML004438       -       0.600       -       0.29         SERPINB5 <sup>a,b</sup> NML002639       -       -       0.31       0.30         PTPRZ1 <sup>a</sup> NML002851       -       -       0.31       0.30         CLDN8 <sup>a</sup> NML177532       -       0.57       0.44       0.30         PRNP <sup>a</sup> NML000311       -       -       0.50       0.30       28,39         IFNGR1 <sup>a</sup> NML000416       -       -       0.34       0.31       31	S100412	NM_005621			0.65	0.28	10.27
CEACAM6 <sup>a</sup> NM_002483       -       0.43       0.42       0.29         None       CAA6762       -       -       0.55       0.29         EPHA4       NM_00438       -       0.600       -       0.29         SERPINB5 <sup>a,b</sup> NM_002639       -       -       0.28       0.30       1, 14         PTPRZ1 <sup>a</sup> NM_002851       -       -       0.31       0.30       28         SBF2       NM_030962       -       -       0.41       0.30       28         SBF2       NM_00311       -       -       0.44       0.30       -         GJB2 <sup>a</sup> NM_00404       -       -       0.48       0.30       28, 39         IFNGR1 <sup>a</sup> NM_000416       -       -       0.34       0.31       30	SHANK2	NM 133266	_		0.00	0.20	10, 27
None       CAA6762       -       -       0.55       0.29         EPHA4       NM_004438       -       0.600       -       0.29         SERPINB5 <sup>a,b</sup> NM_002639       -       -       0.28       0.300       1, 14         PTPRZ1 <sup>a</sup> NM_002851       -       -       0.31       0.30       28         SBF2       NM_030962       -       -       0.41       0.30       28         SBF2       NM_0030962       -       -       0.44       0.30       28         GJB2 <sup>a</sup> NM_000311       -       -       0.48       0.30       28, 39         IFNGR1 <sup>a</sup> NM_000416       -       -       0.34       0.31       28, 39	CEACAM6 <sup>a</sup>	NM 002483		0.43	0.32	0.29	
Ford       Charlow Control of the second secon	None	CAA6762		-	0.55	0.29	
Entrin       Initial of 100       Initial of 100       Initial of 100       Initial of 100         SERPINB5a.b       NM_002639       -       -       0.31       0.30       1, 14         PTPRZ1 <sup>a</sup> NM_002851       -       -       0.31       0.30       28         CLDN8 <sup>a</sup> NM_19328       0.58       0.43       0.38       0.30       28         SBF2       NM_030962       -       -       0.41       0.30       -         RASSF6       NM_177532       -       0.57       0.44       0.30       -         PRNP <sup>a</sup> NM_000311       -       -       0.48       0.30       28, 39         IFNGR1 <sup>a</sup> NM_000416       -       -       0.34       0.31       -	EPHA4	NM 004438	_	0.60	-	0.29	
Difference       -       -       0.30       0.10       0.11       0.10         PTPRZ1 <sup>a</sup> NM_002851       -       -       0.31       0.30       28         CLDN8 <sup>a</sup> NM_019328       0.58       0.43       0.38       0.30       28         SBF2       NM_030962       -       -       0.41       0.30       28         RASSF6       NM_177532       -       0.57       0.44       0.30         PRNP <sup>a</sup> NM_000311       -       -       0.48       0.30         GJB2 <sup>a</sup> NM_00404       -       -       0.50       0.30       28, 39         IFNGR1 <sup>a</sup> NM_000416       -       -       0.34       0.31	SERPINB5 <sup>a,b</sup>	NM 002639	_	-	0.28	0.30	1 14
CLDN8 <sup>a</sup> NM_199328       0.58       0.43       0.38       0.30       28         SBF2       NM_030962       -       -       0.41       0.30       28         RASSF6       NM_177532       -       0.57       0.44       0.30         PRNP <sup>a</sup> NM_000311       -       -       0.48       0.30         GJB2 <sup>a</sup> NM_004004       -       -       0.50       0.30       28, 39         IFNGR1 <sup>a</sup> NM_000416       -       -       0.34       0.31	PTPRZ1 <sup>a</sup>	NM 002851	_	_	0.31	0.30	1, 17
SBF2     NM_030962     -     -     0.41     0.30       RASSF6     NM_00311     -     0.57     0.44     0.30       GJB2 <sup>a</sup> NM_00404     -     -     0.50     0.30     28, 39       IFNGR1 <sup>a</sup> NM_000416     -     -     0.34     0.31	CLDN8 <sup>a</sup>	NM 199328	0.58	0.43	0.38	0.30	28
RASSF6     NM_177532     -     0.57     0.44     0.30       PRNP <sup>a</sup> NM_000311     -     -     0.48     0.30       GJB2 <sup>a</sup> NM_004004     -     -     0.50     0.30     28, 39       IFNGR1 <sup>a</sup> NM_000416     -     -     0.34     0.31	SBF2	NM_030962	-	-	0.41	0.30	20
PRNP <sup>a</sup> NM_000311         -         -         0.48         0.30         28, 39         J           GJB2 <sup>a</sup> NM_00404         -         -         0.34         0.31         28, 39	RASSF6	NM_177532	_	0.57	0.44	0.30	
GJB2 <sup>a</sup> NM_004004     -     -     0.50     0.30     28, 39       IFNGR1 <sup>a</sup> NM_000416     -     -     0.34     0.31	PRNP <sup>a</sup>	NM_000311	_	_	0.48	0.30	
IFNGR1 <sup>a</sup> NM_000416 0.34 0.31	GJB2 <sup>a</sup>	NM_004004	_	_	0.50	0.30	28, 39
	IFNGR1 <sup>a</sup>	NM_000416	_	_	0.34	0.31	

Table 1 (continued)

HUGO gene name	NCBI acc. no.	NCBI acc. no. Fold induction/repression				
		GLI1 24 h	GLI1 72 h	GLI2 24 h	GLI2 72 h	
IKBKE <sup>a</sup>	NM 014002	_	_	0.48	0.31	
None <sup>a</sup>	AP001695	_	_	0.48	0.31	
HIST1H2AM	NM_003514	-	0.59	_	0.31	16, 20, 24, 29
ITGA6 <sup>a</sup>	NM_000210	_	_	0.29	0.32	
DST	NM_001723	_	_	0.46	0.32	
TMEM45A <sup>a</sup>	NM 018004	_	_	0.42	0.33	
CSRP2 <sup>a</sup>	NM_001321	_	_	0.32	0.34	8.17
DSG1 <sup>a</sup>	NM 001942	_	_	0.32	0.34	28
ATP1B3P1 <sup>a</sup>	AF005898	_	_	0.38	0.34	20
ALDH3A1 <sup>a</sup>	NM 000691	_	_	0.50	0.34	27
ACE2	NM 021804	_		_	0.34	27
MAF <sup>a</sup>	NM_001031804	_	-	0.31	0.35	26.29
ENSG00000146394a	AF116669	_	_	0.34	0.35	20, 27
ZNF230a	NM 006300	_		0.34	0.35	
SAMD0 <sup>a</sup>	NM_017654		0.66	0.41	0.35	
DI Y1 <sup>a</sup>	NM 178120	-	0.00	0.41	0.35	
	NM_001670	-	-	0.41	0.35	30
	NM_002886	-	-	0.40	0.35	14 27
VADS2I	NM_020442	-	0.00	0.49	0.35	14, 57
VAR52L	NM 002142	-	-	0.49	0.35	10
MADK6ª	NM_002748	_	-	0.31	0.35	27
MALIN	NM 020760	-	-	-	0.35	57
INFL UEV1ab	NM_001002052	-		-	0.35	
	NM_002659	-	- 0.47	0.38	0.36	
VDD <sup>a</sup>	NM_002658	0.02	0.47	0.45	0.30	10 22 40
	NM_002245	-	-	0.45	0.30	19, 55, 40
	NM_001624	-	-	0.44	0.36	25
	NM_005502	_		-	0.30	21 41
ABCAT	NM_003087	-	-	0.37	0.37	21, 41
SNCG	NM_002862	-	0.40	0.43	0.37	
PIGL TMOD2	NM_002863	-	-	0.43	0.37	6
TMOD3	NM_014547	-	-	0.51	0.37	0
MALATI"	AF203815	_	-	0.51	0.37	2.07
RAPIGAI	NM_002885	-	-	0.64	0.37	3, 27
DEFB1"	NM_005218	-	0.63	-	0.37	24
IGFBR2	NM_001024847	-		-	0.37	34
LIB4K2	NM_019839	-	-	0.55	0.38	7, 13
ALDH6A1	NM_005589	-	0.38	0.56	0.38	
SPINKS	NM_006846	-	-	0.58	0.38	1, 11
TIMP3	NM_000362	-	-	0.62	0.38	1, 4, 25
HCCS	NM_005333	-	0.50	0.64	0.38	1 21
CDKN2B	NM_004936	-	-	-	0.38	1, 31
CNTNI	NM_001843	-	-	-	0.38	
Coort51	NM_138408	-	-	0.45	0.39	
PERPa	NM_022121	-	-	0.56	0.39	
TncRNA"	AF001892	-	-	0.58	0.39	
AKR1C4	NM_001818	-	-	-	0.39	23
KIAA1815	NM_024896	-	-	-	0.39	
CDKN1A <sup>a,b</sup>	NM_000389	0.60	0.60	0.29	0.40	1, 31
ETFA <sup>a</sup>	NM_000126	-	-	0.34	0.40	
MCM7 <sup>a</sup>	NM_005916	0.60	0.58	0.39	0.40	26, 29, 31, 32
DLX3 <sup>a,b</sup>	NM_005220	-	0.62	0.52	0.40	
FZD6	NM_003506	-	_	-	0.40	
UBAP2	NM_018449	-	-	-	0.40	
FBLN5	NM_006329	_	-	-	0.41	25
MAP3K8 <sup>a</sup>	NM_005204	_	_	-	0.41	27
RAB38 <sup>a</sup>	NM_022337	-	-	0.31	0.42	
KIAA1404	NM_021035	-	0.59	0.47	0.42	
MAOA <sup>a</sup>	NM_000240	-	-	0.50	0.42	41
TncRNA	AF001892	_	-	0.52	0.42	
ALG8	NM_001007027	-	-	0.52	0.42	

(continued on next page)

# Table 1 (continued)

HUGO gene name	NCBI acc. no.	Fold induction/	Pathway ID			
		GLI1 24 h	GLI1 72 h	GLI2 24 h	GLI2 72 h	
MEIS1	NM_002398	_	-	0.52	0.42	
SERPINB13	NM_012397	-	_	0.59	0.42	1
CYB5R3	NM_000398	-	0.65	0.63	0.42	15
BMP7 <sup>a</sup>	NM_001719	-	0.66	-	0.42	2
S100A7 <sup>a,b</sup>	NM_002963	3.06	2.14	_	0.42	
RNASE3 <sup>a</sup>	NM_002935	-	-	-	0.42	
PEX13	NM_002618	-	-	0.46	0.43	
APCDD1	NM_153000	-	0.64	0.47	0.43	
FUBP1	NM_003902	-	0.64	0.55	0.43	
TM/SF3	NM_016551	-	0.40	0.63	0.43	
HLA-DKA <sub>a</sub>	NM_019111 NM_002041	-	-	-	0.43	
SL C24A2	NM 020680	_	_	0.40	0.44	
SLC24A5	NM 000228	-	_	0.42	0.44	25
	NM 016357	0.00	-	0.50	0.44	20
CHRNB1	NM_000747		0.58	0.55	0.44	50
COL17A1	NM 000494	_	-		0.44	28
GNG13	NM_016541	_	_	_	0.44	37. 38. 39
UGT1	NM_000463	_	_	_	0.44	01,00,00
GABRE	NM_004961	_	_	0.44	0.45	
ZBTB39	NM_014830	_	_	0.48	0.45	
KRT16	NM_005557	_	_	0.54	0.45	8
IF	NM_000204	_	_	0.58	0.45	11
KCNK9	NM_016601	-	_	0.62	0.45	
DGKA	NM_001345	-	_	0.63	0.45	5
DHRS3	NM_004753	-	0.42	-	0.45	22
HIST2H2BC	AI016731	-	0.54	-	0.45	
CD44	NM_000610	-	-	-	0.45	
IQGAP2 <sup>a</sup>	NM_006633	-	-	-	0.45	1, 3, 6, 30, 36
OLR1	NM_002543	-	_	-	0.45	
SQLE <sup>a</sup>	NM_003129	-	-	-	0.45	15, 41
NAB1 <sup>a,b</sup>	NM_005966	-	-	0.39	0.46	
BMP2	NM_001200	-	-	0.45	0.46	2
AKR1C1 <sup>a</sup>	NM_001353	-	_	0.52	0.46	
ABCA9	NM_080283	-	-	-	0.46	10
F/ MVO1D	NM_000131	_	_	0.41	0.47	40
MIOID MAZa	NM 002282	- 1.55	- 0.50	0.44	0.47	0, 50
None	CAB4649	1.55	0.39	0.59	0.47	
SPTBN4	NM 020971	_	_	0.66	0.47	6 30
BCAS1	NM_003657	_	0.58	0.00	0.47	15
UGCG <sup>a</sup>	NM_003358	_	0.64	_	0.47	6, 25, 28
DST	NM_001723	_	_	_	0.47	0, 20, 20
None	AP00049	_	_	_	0.47	
RORC	NM_001001523	_	_	_	0.47	7
MGST2	NM_002413	0.66	0.58	0.46	0.48	3, 11, 15, 22
MSX2 <sup>a</sup>	NM_002449	-	-	0.47	0.48	
CLSTN3	NM_014718	-	0.66	0.53	0.48	
RBMS2	NM_002898	-	-	0.53	0.48	18
<i>RICS</i> <sup>a</sup>	NM_014715	-	-	0.54	0.48	
AHNAK	NM_001620	-	0.62	0.57	0.48	
LRP1 <sup>a</sup>	NM_002332	-	0.52	0.61	0.48	8, 21, 24, 41
TIAI	AA485255	-	-	-	0.48	
ZNF133	NM_003434	_	-	-	0.48	
SLC38A2	NM_01100	-	-	0.51	0.49	2
BMP1 NET1	NM_005862	_	-	0.53	0.49	2
NETT SCN1D	NM_001027	-	-	0.57	0.49	1/
CYCL1	NM_001511	_	_	0.58	0.49	2 3 8 10 10
CRYAR	NM_001885	_	-	0.02	0.49	2, 5, 6, 10, 19
CRIAD	1401001005	—	1.0	_	0.49	1

Table 1 (continued)

HUGO gene name	ene name NCBI acc. no. Fold induction/repression					Pathway ID
		GLI1 24 h	GLI1 72 h	GLI2 24 h	GLI2 72 h	
CAP350	NM_014810	_	_	-	0.49	
CDK2	NM_001798	_	_	-	0.49	9, 31, 32
KRT15	NM_002275	_	_	-	0.49	- , ,
МСР	NM_002389	_	_	-	0.49	11
OAS2 <sup>a</sup>	NM_001032731	_	_	-	0.49	
PCDH7	NM_002589	_	_	-	0.49	
PDCD4	NM_014456	_	_	-	0.49	
SRD5A1	NM_001047	_	-	0.41	0.50	
CEBPB <sup>a</sup>	NM_005194	_	_	0.49	0.50	10, 37, 40
TNFRSF18	NM_004195	_	_	0.59	0.50	
TOB1 <sup>a</sup>	NM_005749	_	_	0.41	0.51	40
GABRR1	NM_002042	_	_	0.47	0.53	10
TXN <sup>a</sup>	NM_003329	_	_	0.39	0.54	8.14
SMPDL3A	NM_006714	_	_	0.45	0.54	0,11
IGERP6	NM_002178		0.38	-	0.54	17 38
GALNT5	NM_014568	_	0.49	_	0.54	17,50
ATP1R1	NM_001001787	_	1.72	0.32	0.51	
HEFA	NM_000410		-	0.32	0.55	21
S100Pa	NM_005980		0 19	0.40	0.55	21
FOSL 2	NM_005253		0.17	0.40	0.55	
GALNT3	NM_004482	-	_	0.49	0.55	
NMU	NM_006681	-	- 0.53	0.49	0.50	
	NM_001012621	-	0.53	0.52	0.57	
IL52 <sup>2</sup>	NM_001012631	_	0.55	0.50	0.57	
FBAW /	NM_000123	-	-	0.39	0.58	
CDIDD	NM_000123	-	-	0.45	0.59	0.12
GPIBB	NM_000407	-	-	0.47	0.59	9, 12
None	AF312913	-	-	0.45	0.61	
SCFDI	NM_016106	-	-	0.45	0.61	10
KLKBI	NM_000892	-	0.53	0.47	0.61	10
SCNNIA	NM_001038	0.60	0.36	0.65	0.61	26
MAP3K4	NM_005922	-	-	0.45	0.62	36
CSNK1A1	NM_001025105	_	-	0.50	0.65	
CDA	NM_001785	-	0.48	0.63	0.65	
CISD <sup>a</sup>	NM_001909	-	0.48	-	0.65	
ZNF384	NM_133476	-	-	0.48	0.66	
CSNK1A1	NM_001025105	-	-	0.49	0.66	
RRM1	NM_001033	-	2.15	-	1.51	41
RSAFD1	NM_018264	-	2.34	-	1.52	
ITGB1 <sup>a</sup>	NM_002211	2.43	1.89	1.56	1.59	
DEK	NM_003472	1.77	2.13	-	1.63	
CYC1	NM_001916	-	_	2.12	1.64	
AREG <sup>a</sup>	NM_001657	1.87	2.13	-	1.65	2, 8
EML4	NM_019063	-	-	2.45	1.66	
RIPK1	NM_003804	1.72	2.15	-	1.66	13, 35
SLC1A4	NM_003038	2.52	1.81	2.50	1.68	23
ARL6IP	NM_015161	_	1.52	0.46	1.74	
RASA4	NM_006989	-	-	2.00	1.74	3
EB-1	NM_020140	1.85	2.46	-	1.81	
MYLK	NM_005965	2.40	2.88	2.39	1.82	
ECT2	NM_018098	-	2.66	-	1.84	
TGFBI	NM_000358	2.05	2.90	-	1.86	8, 25
PSMB9	NM_002800	1.55	2.17	1.87	1.89	40
PPP1CB <sup>a</sup>	NM_002709	1.82	2.62	-	1.94	9
FXYD3 <sup>a,b</sup>	NM_005971	-	-	3.53	1.95	23
MPHOSPH1 <sup>a</sup>	NM_016195	-	2.14	-	1.95	
TEAD1 <sup>a</sup>	NM_021961	-	2.08	-	2.01	
MS4A6A	NM_022349	1.57	-	-	2.01	
JUN	NM_002228	-	-	-	2.01	26, 33, 34, 35, 38
PITX1	NM_002653	-	-	-	2.01	
LMO4	NM_006769	-	_	1.55	2.02	
PLD3	NM_001031696	2.06	1.83	-	2.02	7

(continued on next page)

Table	1	(continued)
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GLII 24 h         GLII 25 h         GLII 27 h         GLII 27 h           ELOVI.6         NM.0204090         -         -         -         2.03           HTHPD2         NM.060650         -         191         -         2.03         41           LILESD         NM.000855         -         161         -         2.04         15           NMNS         NM.000651         163         -         -         2.06         15           BARD1         NM.00105316         -         -         2.02         2.09         2.5,29,31,32           SEMA3B         NM.001005316         -         -         2.02         2.02         2.0,29,31,32           STR54         NM.0016326         -         1.07         -         2.11         3.7,38           STR54         NM.001526         -         1.80         -         2.14         -           CKMT1         NG.002086         -         1.80         -         2.14         -           CARS <sup>1</sup> NM.002088         -         -         2.16         9           ADMECAA         NM.002178         -         -         2.16         9           ADMECAA         NM.002179 <t< th=""><th>HUGO gene name</th><th>NCBI acc. no.</th><th colspan="4">Fold induction/repression</th><th colspan="2">Pathway ID</th></t<>	HUGO gene name	NCBI acc. no.	Fold induction/repression				Pathway ID	
ELOVL6         NML02090         -         -         -         2.02           MTHFD2         NML006816         -         -         2.03         12           GTF2IRD         NML005855         -         1.61         -         2.04         15           NANS         NML018946         1.53         -         -         2.06         15           SEMA3B         NML00051         1.54         -         -         2.06         15           SEMA3B         NML0005914         -         -         2.06         200         2.6, 29, 31, 32           SEMA3B         NML0005914         -         -         2.10         37, 38         37, 38           ZAV7264         NML00316         -         -         2.11         -         1.01         -         2.14         -         -         2.14         -         -         2.14         -         -         2.16         -         -         2.16         -         -         2.16         -         -         2.16         -         -         2.16         -         -         2.16         -         -         2.16         -         -         2.16         -         -         -         <			GLI1 24 h	GLI1 72 h	GLI2 24 h	GLI2 72 h		
MTHEP2NML006362.0341LIRBSNML005852.0312GTT2IRD1NML005851.632.0415BARD1NML0016511.632.0615BARD1NML001059142.065SEMA38NML010059142.062.092.6, 29, 31, 32EDG2NML001062.1137, 38ZAP254NML0016602.11-STK6NML005602.11-TMEM28NML015662.16-CAS297NML003082.16-TMEM28NML012182.16-COA397NML003082.16-COA397NML012182.16-SOX2NML01282.16-SOX2NML01282.16-SOX2NML01272.16-SOX2NML01272.183.26, 3.2CK53NML012472.23CMG4NML003742.24-SOX2NML0103742.24-SOX2NML003752.24<	ELOVL6	NM_024090	_	_	_	2.02		
LLLRBSNALL068402.0412NANSNAL0159461.542.065SRAD1NAL01095142.065FMNXAL3751852.065SEMA3BNAL01095142.076.09, 31, 32CE02NAL01095142.1037, 38ZNF264NAL005002.11-TMEM3NAL015862.12-TMEM3NAL015862.12-TMEM3NAL015862.13-CALS79NAL005082.14-TMEA3NAL015862.16-CALS79NAL012381.522.169CANS74NAL012381.522.16-CDK57NAL012381.522.16-CDK57NAL012381.522.16-SO2NAL012381.522.16-SO3NAL012381.522.16-SO3NAL0102382.16SO4NAL0102382.16SO3NAL0102372.16-SO3NAL0102372.23-CNS2	MTHFD2	NM_006636	_	1.91	_	2.03	41	
CHT2IRD1NML005685-1.61-2.04JNANSNML0094651.542.06ISBARD1NML00059142.06SCSEMA3BNML001059142.022.092.6, 29, 31, 32EDG2NML0046562.022.092.6, 29, 31, 32EDG2NML004012.11-STK6NML005602.11-TMEM28NML015662.12-TMEM28NML015662.14-TMEM28NML012191.793.20-2.16-TMEM28NML012191.793.20-2.16-TMEM28NML012191.793.20-2.16-TMEM28NML012192.16-TMEN79NML012192.16-SOX2NML01282.16-SOX2NML001792.483.8, 3.2-CK33NML002172.462.188RTC3NML002172.16CM24NML002172.16CK32NML0012212.13-CK32NML001242.24-CK44	LILRB5	NM_006840	-	_	-	2.03	12	
NANSNAL0189461.542.0415BARD1NML00104551.542.06FNNXML3751852.022.09MCM2NML001059142.1037, 38ZNF264NML0014172.1037, 38ZNF264NML005002.11-TMEM3NML01586-1.60-2.12-MCM2NML015862.14TMEM3NML015862.14-CMT1NG.0051562.14-CMT2NML013812.16-CMT3NML012191.522.169APOBECANML012881.522.169CMT4NML01282.169SO2NML01281.522.169SO3NML01282.169SO3NML01282.1616.20SO3NML01442.188RFC3NML016272.18SO3NML019271.802.18SO3NML019272.18SO3NML019272.24CNS4NML0192462.24<	GTF2IRD1	NM_005685	-	1.61	-	2.04		
BARD1NML000H651.542.06FENNXML0010059141.552.07SEMA3BNML0010059141.552.07EDG2NML0014012.1037,38ZNF264NML0039072.111.70STK6NML0030002.111.71STK6NML015662.141.71CKNT1NG.0051562.141.71LGALSPNML012382.169CKNT1NG.0031562.169CKNTNML01281.522.169CKNTNML002882.169CKS*NML01281.522.169CKS*NML01282.188, 2.0, 32CDS2NML0017902.482.188CKS2NML01712.183, 2.0, 32CKS2NML0017212.183, 2.0, 32CKS2NML0018272.22-CKS4NML0018122.152.23-CKS4NML0017972.162.21-CKS4NML0017972.162.21-CKS4NML0017972.152.23-CKS5NML001797	NANS	NM_018946	1.63	_	_	2.04	15	
FMNXML.3751852.06SEMA3BNL.001059142.022.092.6, 39, 31, 32MCN2NML.0045262.022.092.6, 39, 31, 32ZNF264NML.0034172.013.7, 38STK6NML.0034072.111TMEM28NML.015662.121MRA57NML.015662.121CKMT1NG.0051562.141CKMT1NG.003072.161CRA757NML.0023782.161CRA757NML.0023782.161CRA757NML.0012581.522.161CRA754NML.0023782.161SOX2NML.0017691.682.188CR53NML.0024172.1616, 201CR54NML.0024172.183, 26, 322CK52NML.0014242.183, 26, 321CK53NML.014272.122.18CK52NML.014282.162.32-CK54NML.0015122.162.32-CK54NML.0015422.122.16CK54NML.001542 <td>BARD1</td> <td>NM_000465</td> <td>1.54</td> <td>-</td> <td>-</td> <td>2.06</td> <td></td>	BARD1	NM_000465	1.54	-	-	2.06		
SEMA3B         NAL.001005914         -         -         1.55         207           EDG2         NAL.001401         -         -         2.10         37, 38           ZNE264         NAL.003407         -         -         2.11         37, 38           ZNE364         NAL.003000         -         -         2.11         -           STK6         NAL.003000         -         -         2.11         -           STK5         NAL.003005         -         -         2.14         -           CKNT1         NG.003156         -         -         2.16         -           CKNT1         NG.003080         -         -         2.16         -           CKX3         NM.00238         -         -         2.16         -           CXC3         NM.003839         -         -         -         2.16         -           CXS2         NM.00128         1.52         -         -         2.16         -         -           CDS3         NM.001799         -         -         2.16         -         -         -         2.16         -         -         -         2.16         -         -         -	FMN	XM_375185	-	_	-	2.06		
MCM2NML.0043262.022.092.6, 29, 31, 32ZNF264NML.0034172.11ZNF264NML.0036002.11TMEM28NML.01566-N2.12WRA8*NML.01566-1.80-2.12CKNT1NG.0051562.14CKNT1NG.0051562.14CKNT1NG.0030392.16DYRNSF1LANML.002381.522.16CYC3*NML.0012581.522.16CYC3*NML.0012581.522.16SOX2NML.001769-1.681.512.17SOX2NML.001769-1.681.512.17MKI67*NML.0024172.188RFC3NML.0024172.188RFC3NML.002472.22-CKS2NML.0012422.22-GTA4NML.002372.242.17KIK5*NML.001422.242.4.37CKS2NML.0015122.162.23CKS4NML.0014272.242.4.37CKS4NML.0015122.242.4.37CKS4NML.0015122.242.4.37CKS4NML.00236 <td< td=""><td>SEMA3B</td><td>NM_001005914</td><td>_</td><td>_</td><td>1.55</td><td>2.07</td><td></td></td<>	SEMA3B	NM_001005914	_	_	1.55	2.07		
EDC2NML0014012.1037, 38STR56NML0054072.11STR56NML0156662.11MRA82NML0125191.793.20-2.14LGALS94NML00251562.14LGALS94NML002308-1.71-2.16VERG2NML002308-1.71-2.16VERG2NML002381.522.16CDC34NML002381.522.16SO22NML00179-1.681.512.17CDS4NML00179-1.681.512.17CDS4NML001792.483.26.32CDS2NML001472.18EMF24NML001472.16CDS4NML001472.21CDS4NML0015122.22CDS4NML001512-3.09-2.21CDS4NML001512-1.59-2.23CDS4NML0015222.152.23CDS4NML00152-1.59-2.34CDS1NML00152-1.59-2.34CDS1NML00152-1.59-2.34CDS1NML002462-1.59-2.34CDS1NML002372.34 </td <td>MCM2</td> <td>NM_004526</td> <td>-</td> <td>-</td> <td>2.02</td> <td>2.09</td> <td>26, 29, 31, 32</td>	MCM2	NM_004526	-	-	2.02	2.09	26, 29, 31, 32	
ZNE264NML0034171.702.11TMEM28NML01566-1.80-2.12MRAS2NML012191.793.20-2.14CKNT1NG.0051562.14LGALS9'NML003082.14LRIG2NML0148132.16TNFRSFILMNML003082.16CDK3'NML01281.522.16SOX2NML017962.665CD2NML001797-1.681.512.17SOX2NML0017972.482.18RFG3NML002172.482.18CKS2NML014271.80-2.362.21CSX4NML003172.362.21CS44NML003722.22-CS44NML003722.22-CS44NML003722.23-CS74NML0032422.24VEGFNML002372.23-FNANML002372.25-CS74NML002362.24CS84NML002362.24ZS74NML002372.24CS74NML002362.24CS74NML00236<	EDG2	NM_001401	-	-	-	2.10	37, 38	
STK6NML0056062.11MRAS*NML0125191.793.20-2.14CKNT1NC.0051562.14LGALS9*NML0023082.14LGALS9*NML003082.16CDK3*NML002381.522.16OCK3*NML002581.522.16POBEC3ANML002781.62-2.169APOBEC3ANML01790-1.681.512.17KI67***NML00179-1.681.512.17KI67***NML00179-1.682.188RFC3NML00147-1.960.612.209CKS2NML014271.80-2.12-2.12CD84NML00317-1.60-2.21-CS7NML001512-1.60-2.21-CD84NML003572.26CD84NML003572.152.33-CD84NML0024602.162.34-CD74NML0024602.152.34-PNNNML0024602.162.34-PNNNML0024602.171.11,13CD74NML0024602.371.21,13CD75NML002361 </td <td>ZNF264</td> <td>NM_003417</td> <td>-</td> <td>1.70</td> <td>-</td> <td>2.11</td> <td></td>	ZNF264	NM_003417	-	1.70	-	2.11		
TMEM28NM.01508-1.80-2.12MRAS*NM.012191.793.20-2.14CKMTING.0051562.14LKIG2NM.0418132.15LKIG2NM.0038392.16TNRRSF11ANM.0038392.16CDK3*NM.1015881.522.16SOX2NM.001602.16CDPNM.0017692.16SOX2NM.001769-1.682.17MKIG*A*NM.0017692.482.18SOX2NM.001424-1.682.183.26,32CKS2NM.0014271.80-2.482.18CKS2NM.0014271.80-3.262.21CD94NM.00371-1.60-2.22MEOX1*NM.003722.23-CKS2NM.0015122.162.32FYNNM.002372.162.32FVNNM.002372.2424,37RrSL*NG.009032.453.87-2.24FYNNM.002372.362.32FVNNM.002382.271.3RrSL*NM.002372.362.32FVNNM.002382.362.32FVNNM.00238- <t< td=""><td>STK6</td><td>NM_003600</td><td>-</td><td>-</td><td>-</td><td>2.11</td><td></td></t<>	STK6	NM_003600	-	-	-	2.11		
MRAS*NM0122191.793.20-2.14CKMTING.0051562.14LGALS9*NM002382.15TNRSF1IANM0038302.16PCDG20NM0012881.522.16SOX2NM0012881.522.16SOX2NM0017692.16SOX2NM.0017692.16SOX2NM.0017692.18SOX2NM.0017692.482.18SRTC3NM.002472.482.18SCK52NM.0012422.209KLK5*NM.0018272.22-CD84NM.001827-3.09-2.22VEGFNM.00146281.661.821.632.33VEGFNM.00146281.661.821.632.33NCBP1NM.0020372.242.437RFS14'NM.002036-2.152.33-SRG2NM.001012271-1.99-2.24RFC4NM.0020381.612.36-2.34SRG2NM.0010122711.911.67-2.33RG2NM.0010122711.67-2.333.16CF14NM.00233-2.3421.5RG2NM.00133<	TMEM28	NM_015686	-	1.80	-	2.12		
CKMTI         NG_000156         -         -         -         2.14           LRIG2         NM_014813         -         -         -         2.15           LRIG2         NM_010383         -         -         2.16         9           DYRRSF1LA         NM_00383         -         -         -         2.16         9           CDK3 <sup>A</sup> NM_0145699         -         -         -         2.16         16.20           CD9         NM_001769         -         -         -         2.16         16.20           CD9         NM_00147         -         -         1.68         2.18         8           RTG3         NM_001424         -         -         -         2.48         2.18         8           CKS2         NM_001427         -         -         -         2.22         1.55         2.21         1.55         2.21         1.55         2.21         1.55         2.23         1.55         1.63         2.23         1.55         1.63         2.23         1.55         1.57         1.55         1.57         1.55         1.51         1.51         2.35         2.44         3.7           CDSA         NM_00124628 <td>MRAS<sup>a</sup></td> <td>NM_012219</td> <td>1.79</td> <td>3.20</td> <td>-</td> <td>2.14</td> <td></td>	MRAS <sup>a</sup>	NM_012219	1.79	3.20	-	2.14		
LGALS9*NML.002382.14LKRC2NL.00148132.15TNPRSF11ANML.0038902.169CDG3*NML.0012581.522.169APOBEC3ANML.0012582.169CDQ3NML.0012682.1616.20CD9NML.0017692.188CR167**/NML.0024172.482.188RTC3NML.001272.183.26.32CKS2NML.001273.262.21-CD84NML.001874-1.60-2.22-CD84NML.0018742.152.33-CD84NML.0012722.242.4.37FVNNML.0020372.152.33-NCEP1NML.0020372.242.3.3-RFC4NML.002037-1.67-2.242.3.3RC52NML.001012271-1.96-2.271.12.13RTS3NML.002331.612.36-2.301.6.2CTNNA3NML.002362.271.12.133.8.99EZ12NML.00246-1.67-2.333.8.99CTNNA3NML.002332.353.1 <tr< td=""><td>CKMT1</td><td>NG_005156</td><td>-</td><td>-</td><td>-</td><td>2.14</td><td></td></tr<>	CKMT1	NG_005156	-	-	-	2.14		
LRIG2NM.00148132.15TNRRSF11AML.003839-1.71-2.169CDK3°NM.00128S1.522.169APOBEC3ANM.001662.1616.20SOX2NM.0017691.681.512.17MK167 <sup>10</sup> NM.0024171.682.188EMP2°NM.0024172.482.188RFC3NM.0024172.163.26, 32CKS2NM.0029152.183.26, 32CKS2NM.001827-1.960.612.209CKS4NM.00247-1.60-2.21-CSTA4NM.002472.22-CKS4NM.00124272.23-FYNNM.0024862.152.33-VEGFNM.0024862.2424, 37RFC4NM.0029162.2424, 37RFC4NM.0029162.232.6CTNA3NM.0029231.562.3015, 20CFGF2NM.0024862.2424, 37RFC4NM.002931.612.362.32-CTNA3NM.002931.612.362.32-CTNA3NM.00293 <td>LGALS9<sup>a</sup></td> <td>NM_002308</td> <td>-</td> <td>-</td> <td>-</td> <td>2.14</td> <td></td>	LGALS9 <sup>a</sup>	NM_002308	-	-	-	2.14		
TNFRSF1A       NM.00389       -       1.71       -       2.16         CDK3*       NM.001258       1.52       -       -       2.16         APOBEC3A       NM.145699       -       -       2.16       1.62         CDS       NM.001709       -       1.68       1.51       2.17         MK167 <sup>th</sup> NM.002417       -       -       2.48       2.18       8         EMP2*       NM.001424       -       -       2.48       2.18       8       .52         CKS2       NM.001427       1.96       0.61       2.20       9       .52       .55       .52       .52       .55	LRIG2	NM_014813	-	_	_	2.15		
CDK3**NM.0012581.522.169APOBEC3ANM.0031062.1616.20SOX2NM.0031061.681.512.17MK167*b*NM.0024171.682.188EMP2*NM.0012422.482.188ENC3NM.0029152.162.009KK5*b*NM.0029152.162.019CKS2NM.00127-1.960.612.2099KK5*b*NM.012471.80-3.262.212.022.022.022.022.022.022.02	TNFRSF11A	NM_003839	-	1.71	-	2.16		
APOBEC3A         NML45699         -         -         -         2.16           SOX2         NML001769         -         -         -         2.16         16.20           CD9         NML001769         -         1.68         1.51         2.17           EMP2 <sup>3</sup> NML001241         -         -         1.68         2.18         8           RFC3         NML002915         -         -         2.48         2.18         3.26, 32           CKS2         NML001827         -         1.96         0.61         2.20         9           CKS4         NML001827         -         1.60         -         2.21         -           CD84         NML0018427         1.80         -         2.36         2.21         -           VEGK1         NML001937         -         1.61         2.36         2.37         -           VEGF         NML00104628         1.66         1.82         1.63         2.23         -           STS1 <sup>4</sup> NML001271         -         1.59         -         2.24         24, 37           RFC4         NML001271         -         1.99         -         2.26         2.32	CDK3 <sup>a</sup>	NM_001258	1.52	-	-	2.16	9	
SOX2         NL.003106         -         -         -         2.16         16.20           CD9         NL.001769         -         1.68         1.51         2.17           MK167 <sup>3h</sup> NL.002417         -         -         1.68         2.18         8           EMP23         NL.001247         -         -         -         2.18         3, 26, 32           CKS2         NL.001247         1.80         -         3.26         2.21         5           CD84         NL.00374         -         1.60         -         2.21         5           GSTA4         NL.00157.2         -         -         2.15         2.23         5           CD84         NL.001024628         1.66         1.82         1.63         2.23         5           FVN         NL0002037         -         -         2.15         2.23         5           SCR14         NL002036         -         1.59         -         2.24         24, 37           RF54         NL0010122711         -         1.96         -         2.27         1.12         13           RG52         NL002039         1.56         -         -         2.29	APOBEC3A	NM_145699	-	-	-	2.16		
CD9NM_001769-1.681.512.17KM507 <sup>10</sup> NM_001441.682.18EMP2 <sup>4</sup> NM_001441.682.188RFG3NM_0029152.183.26.32CKS2NM_001827-1.960.612.209KLK5 <sup>ab</sup> NM_012471.80-3.262.21CD84NM_003872.222.152.23MEOX1 <sup>a</sup> NM_004527.22.232.242.4, 37VECFNM_0012681.661.821.632.232.337VECFNM_0020372.242.4, 372.122.13RFS1 <sup>a</sup> NG.000032.453.87-2.242.4, 37RFS4NG.000032.453.87-2.271.12, 13GTNA3NM_0012271-1.96-2.2626.32BIC5 <sup>a</sup> NM_0012271-1.96-2.271.12, 13CTS3NM_0037981.612.36-2.232.16M23NM_0037981.612.36-2.322.16BIC5 <sup>a</sup> NM_0017182.331.622.32CTNA3NM_0024632.322.322.12MX2NM_0017182.3422.12MX2NM_0017182.3422.12MX2 <th< td=""><td>SOX2</td><td>NM_003106</td><td>-</td><td>-</td><td>-</td><td>2.16</td><td>16, 20</td></th<>	SOX2	NM_003106	-	-	-	2.16	16, 20	
MK167 <sup>3AB</sup> NM.002147         -         -         1.68         2.18           RFC3         NM.002145         -         -         2.48         3, 26, 32           CKS2         NM.001287         1.80         -         3.26         221           CD84         NM.0012427         -         -         2.22         -           MEOX1 <sup>14</sup> NM.0012427         -         -         -         2.22           MEOX1 <sup>14</sup> NM.0012427         -         -         -         2.23           VEGF         NM.00237         -         2.15         2.23         -           STSL3         NG.000903         2.45         3.87         -         2.24         2.4, 37           RFC4         NM.001271         -         1.96         -         2.27         1.12, 13           GS2         NM.003798         1.61         2.36         2.32         -	CD9	NM_001769	-	1.68	1.51	2.17		
EMP2*         NM_001424         -         -         2.48         2.18         8           RFC3         NM_001877         -         1.96         0.61         2.20         9           KLK5*b         NM_001827         1.80         -         3.26.32         2.21         -           CD84         NM_003874         -         1.60         -         2.21         -           GSTA4         NM_001512         -         3.09         -         2.22         -           VEGF         NM_00124628         1.66         1.82         1.63         2.23         -           VEGF         NM_00124628         1.66         1.82         1.63         2.24         24.37           RPS1         NM_002462         -         1.59         -         2.24         24.37           RPS4         NG.00003         2.45         3.87         -         2.24         24.37           RPS4         NM_00101271         -         1.96         -         2.26         26.32           RGS2         NM_001456         -         -         2.23         3.8.39         -           RGS2         NM_002463         -         -         2.30         16.2	MKI67 <sup>a,b</sup>	NM_002417	-	-	1.68	2.18		
RFC3       NML002915       -       -       -       -       2.18       3,26,32         CKS2       NML001827       -       1.60       -       2.20       9         KLKS <sup>hb</sup> NML001827       1.80       -       3.26       2.21       -         CD84       NML008374       -       1.60       -       2.21       -         GSTA4       NML001512       -       3.09       -       2.22       -         MEOX1 <sup>a</sup> NML0016327.2       -       -       -       2.22       -         VEGF       NML00102468       1.66       1.82       1.63       2.23       -         VEGF       NML002037       -       -       2.15       2.24       2.4, 37         RFC4       NML0010271       -       1.99       -       2.26       2.6, 32         BIRC5 <sup>a</sup> NML0010271       -       1.96       -       2.27       1, 13         CTNA3       NML00455       -       -       2.30       1.62, 20       3.8, 39         EZH2       NML00456       -       -       2.30       1.62, 20       3.31, 40         CSF2       NML000411       -       -	EMP2 <sup>a</sup>	NM_001424	-	-	2.48	2.18	8	
CKS2       NML01827       -       1.96       0.61       2.20       9         KLS5 <sup>th</sup> NML003874       -       1.60       -       2.21         CD84       NML003874       -       1.60       -       2.21         GSTA4       NML001512       -       -       2.22       -         WEOK1*       NML001272       -       -       -       2.23         VEGF       NML00124628       1.66       1.82       1.63       2.33         FYN       NML0024628       1.66       1.82       1.63       2.33         RCS1       NML002466       -       1.59       -       2.26       26, 32         BIRC5*       NML001012711       -       1.96       -       2.27       1, 12, 13         CTNNA3       NML002956       -       1.67       -       2.39       3.38, 39         EZH2       NML004456       -       1.67       -       2.30       16, 202         MX2       NML00456       -       -       2.75       2.32       2.40       2         EXO1*       NML002956       1.91       1.84       -       2.32       2.40       2         MX2	RFC3	NM_002915	-	-	-	2.18	3, 26, 32	
KLKS <sup>AD</sup> NM.012427       1.80       -       3.26       2.21         CD84       NM.003874       -       1.60       -       2.21         GSTA4       NM.001512       -       3.09       -       2.22         MEOX1 <sup>a</sup> NM.004527.2       -       -       -       2.22         VEGF       NM.0024628       1.66       1.82       1.63       2.23         VCBP1       NM.0024628       1.66       1.82       1.63       2.23         VCBP1       NM.002466       -       1.59       2.24       2.4       3.7         RFC4       NM.002916       -       1.99       -       2.26       2.5       3.8         RFC4       NM.0012271       -       1.96       -       2.27       1.1       1.3         CTNNA3       NM.0012271       -       1.66       -       2.30       1.6 2.02         FGR2       NM.001415       -       -       -       2.30       1.6 2.02         FGR2       NM.001718       -       2.03       1.66       2.32       -         MX2       NM.003686       1.91       1.84       -       2.34       2       -	CKS2	NM_001827	-	1.96	0.61	2.20	9	
CD84NM_003874 $ 1.60$ $ 2.21$ MEOX14NM_001512 $ 309$ $ 2.22$ MEOX14NM_004527.2 $  2.22$ VEGFNM_001024628 $1.66$ $1.82$ $1.63$ $2.23$ NCBP1NM_002486 $ 1.59$ $ 2.24$ $24.37$ RFS1NG_000903 $2.45$ $3.87$ $ 2.24$ $24.37$ RFC4NM_002916 $ 1.99$ $ 2.26$ $26.32$ BIRC53NM_001012271 $ 1.966$ $ 2.27$ $1,12,13$ CTNNA3NM_003798 $1.61$ $2.36$ $ 2.23$ $1.56$ GS2NM_00141 $ 2.36$ $16.20$ $16.20$ FGFR2NM_0004456 $ 1.67$ $ 2.30$ $16.20$ FGFR2NM_0004453 $  2.75$ $2.32$ $-$ EX01aNM_003866 $1.91$ $1.84$ $ 2.32$ $-$ EX01aNM_003866 $1.91$ $1.84$ $ 2.33$ $2.12$ WEE1NM_00758 $  2.23$ $2.40$ $1.5$ Nore $26061$ $   2.46$ $-$ Nore $26061$ $   2.46$ $-$ Nore $26061$ $   2.46$ $-$ Nore $26061$ $   2.52$ $1.58$ Nore $26061$ $-$ </td <td>KLK5<sup>a,b</sup></td> <td>NM_012427</td> <td>1.80</td> <td>-</td> <td>3.26</td> <td>2.21</td> <td></td>	KLK5 <sup>a,b</sup>	NM_012427	1.80	-	3.26	2.21		
GSTA4         NM_001512         -         3.09         -         2.22           WEOX1 <sup>a</sup> NM_001024628         1.66         1.82         1.63         2.23           VEGF         NM_002037         -         -         2.15         2.23           FYN         NM_002486         -         1.59         -         2.24         24, 37           RPSL <sup>1</sup> NG_000903         2.45         3.87         -         2.24         24, 32           RFC4         NM_00112271         -         1.99         -         2.27         1.12, 13           CTNNA3         NM_0003798         1.61         2.36         -         2.29         3.38, 39           EZH2         NM_0004456         -         1.67         -         2.30         1.62           FGFR2         NM_0004456         -         -         2.75         2.32           MX2         NM_0003866         1.91         1.84         -         2.32           BMP6         NM_000758         -         1.73         2.35         31           CSF2         NM_00012333         -         -         1.79         2.40         2,8           ANXA3         NM_00012333	CD84	NM_003874	-	1.60	-	2.21		
MEOXI <sup>1</sup> NM_0004527.2         -         -         -         -         2.22           VEGF         NM_00124628         1.66         1.82         1.63         2.23           NCBP1         NM_002486         -         1.59         -         2.24         24, 37           RFS1L <sup>a</sup> NG_000903         2.45         3.87         -         2.26         26, 32           BIRC5 <sup>a</sup> NM_001012271         -         1.96         -         2.27         1, 12, 13           CTNNA3         NM_00398         1.61         2.36         -         2.27         1, 3           RG52         NM_0004456         -         1.67         -         2.30         16, 20           CTNNA3         NM_000453         -         2.36         2.32         16           PGFR2         NM_000463         -         -         2.30         16, 20           TGGR2         NM_0002463         -         -         2.32         20           MX2         NM_000366         1.91         1.84         -         2.32         2.12           MDK4         NM_00011233         -         -         2.34         2         2.12	GSTA4	NM_001512	-	3.09	-	2.22		
VEGFNML.00246281.661.821.632.23NCBP1NML.0024862.152.23NCBP1NML.002486-1.59-2.24RFSC4NML.002916-1.99-2.2626, 32BIRC5 <sup>a</sup> NML.00112271-1.96-2.271, 12, 13CTNNA3NML.0037981.612.36-2.293, 88, 39EZH2NML.0024331.562.3016, 20FGFR2NML.002463-1.67-2.3016, 20FGFR2NML.0036661.911.84-2.32-EXO1 <sup>a</sup> NML.0038661.911.84-2.32-BMP6NML.0017181.732.3531CSF2NML.000758-1.51-2.402, 8ANXA3NML.005139-1.51-2.402, 8ANXA3NML.0023401.652.41-TTKNML.003318-1.660.632.43-ZFYVE20NML.0023401.652.401, 5SERPINA1NML.002242.5211IGFBP5NML.002242.5211IGFBP5NML.005992.5213ARCNML.0051932.54-1IGFBP5NML.006151.672	MEOX1 <sup>a</sup>	NM_004527.2	-	-	-	2.22		
FYN       NL002037       -       -       -       -       2.15       2.23         RNCBP1       NL002486       -       1.59       -       2.24       24, 37         RPS5L <sup>a</sup> NG_000903       2.45       3.87       -       2.24       2.24         RFC4       NL002916       -       1.99       -       2.26       26, 32         BIRC5 <sup>a</sup> NL00101271       -       1.96       -       2.27       1, 2, 13         CTNNA3       NL003798       1.61       2.36       -       2.29       3, 38, 39         EZH2       NL000456       -       1.67       -       2.30       16, 20         FGFR2       NL000141       -       2.03       1.66       2.32          MX2       NL00366       1.91       1.84       -       2.32          EXO1 <sup>a</sup> NL00378       -       -       1.73       2.35       31         CSF2       NL000758       -       -       2.40       2, 8         NDK <sup>a</sup> NL0001339       -       -       2.40       2, 8         Nore       Z60461       -       -       2.40       1, 5 <t< td=""><td>VEGF</td><td>NM_001024628</td><td>1.66</td><td>1.82</td><td>1.63</td><td>2.23</td><td></td></t<>	VEGF	NM_001024628	1.66	1.82	1.63	2.23		
$\begin{array}{c c c c c c c c c c c c c c c c c c c $	FYN	NM_002037	-	-	2.15	2.23		
RPS1 <sup>-1</sup> NC_000905       2.45       3.87       -       2.24         RFC4       NNL_002916       -       1.99       -       2.26       26, 32         BIRC5 <sup>3</sup> NML_00112271       -       1.96       -       2.27       1, 12, 13         CTNNA3       NML_002916       1.61       2.36       -       2.27       13         RGS2       NML_00243       1.56       -       -       2.30       16, 20         FGFR2       NML_004456       -       1.67       -       2.30       16, 20         KX2       NML_003686       1.91       1.84       -       2.32       2         EXO1 <sup>a</sup> NML_003686       1.91       1.84       -       2.33       2         WEE1       NML_003380       -       -       1.73       2.35       31         CSF2       NML_00112333       -       -       2.23       2.40       2, 8         ANXA3       NML_005139       -       -       2.23       2.40       2, 8         ANXA3       NML_00318       -       -       2.24       2       1.5         ZFYVE20       NML_003318       -       -       2.41 <td< td=""><td>NCBPI</td><td>NM_002486</td><td>-</td><td>1.59</td><td>-</td><td>2.24</td><td>24, 37</td></td<>	NCBPI	NM_002486	-	1.59	-	2.24	24, 37	
RFC4       NML002916       -       1.99       -       2.26       26, 32         BRC53       NML00112271       -       1.96       -       2.27       1, 12, 13         CTNNA3       NML003798       1.61       2.36       -       2.29       3, 38, 39         EZH2       NML004456       -       1.67       -       2.30       16, 20         FGFR2       NML00141       -       2.03       1.66       2.32         EXO1 <sup>a</sup> NML002463       -       -       2.32       -         EXO1 <sup>a</sup> NML003798       1.91       1.84       -       2.32       -         EXO1 <sup>a</sup> NML003390       -       -       1.73       2.35       31         CSF2       NML000758       -       -       1.73       2.35       31         CSF2       NML00112333       -       -       2.40       2, 8         ANXA3       NML005139       -       -       2.40       1, 5         None       Z60461       -       -       2.41       -         TTK       NML002318       -       -       2.41       -         SERPINA1       NML00244       -	RPS5L"	NG_000903	2.45	3.87	-	2.24	26.22	
BIRCS*NML001012271-1,96-2,271,12,15CTNNA3NML0037981.612,36-2,2713RGS2NML0029231.562.293,38,39EZH2NML00141-2,031.662.32FGFR2NML0024632.752.32EXO1aNML0036861.911.84-2.32BMP6NML0017182.3331CSF2NML000758-1.79-2.372,12MDKaNML0010123332.232.402,8ANXA3NML001123332.232.402,8ANXA3NML001123332.41-TTKNML00318-1.660.632.43-ZFYVE20NML022401.652.46-HMRa*NML00295-2.12-2.51-IGFBP5NML000592.521IGFBP5NML000592.5217,38ARCNML001532.54-NCAM1NML006151.672.38-2.54-NCAM1NML0031951.532.531.942.57-IEF3*NML0031951.532.531.942.57-	RFC4	NM_002916	-	1.99	_	2.26	26, 32	
CTINNAS       NML003/98       1.51       2.36       -       2.27       1.5         RGS2       NML002923       1.56       -       -       2.29       3,38,39         EZH2       NML000141       -       1.67       -       2.30       16,20         FGFR2       NML002463       -       -       2.75       2.32          EXO1 <sup>a</sup> NML003866       1.91       1.84       -       2.34       2         BMP6       NML003390       -       -       1.73       2.35       31         CSF2       NML000758       -       1.79       -       2.40       2, 8         ANXA3       NML005139       -       1.51       -       2.40       2, 8         None       Z60461       -       -       -       2.40       1, 5         None       Z60461       -       -       -       2.40       1, 5         None       Z60461       -       -       -       2.40       1, 4         KRT18       NML002340       1.65       -       -       2.40       14         IGFBP5       NML00255       -       2.12       -       2.52       1, 38	BIRC5"	NM_001012271	-	1.96	-	2.27	1, 12, 13	
NNS.2       NML.002923       1.50       -       -       -       2.29       5, 36, 39         FGFR2       NML.001416       -       1.67       -       2.30       16, 20         FGFR2       NML.002463       -       -       2.03       1.66       2.32         EXO1 <sup>a</sup> NML.003686       1.91       1.84       -       2.32         BMP6       NML.003390       -       -       -       2.35       31         CSF2       NML.000758       -       -       2.23       2.40       2, 8         ANXA3       NML00012333       -       -       2.23       2.40       2, 8         ANXA3       NML000318       -       -       2.23       2.40       2, 8         ANXA3       NML00318       -       -       -       2.40       1, 5         None       Z60461       -       -       -       2.40       1, 5         VERD       NML002240       1.65       -       -       2.46       -         HMMR <sup>a</sup> NML00224       -       -       2.51       -       -       -       2.51       -       -       -       2.51       -       -	DCS2	NML003798	1.01	2.30	_	2.27	13	
E212NML004456-1.67-2.5016, 20FGFR2NML00141-2.031.662.32MX2NML0024632.752.32EX01aNML0036861.911.84-2.32BMP6NML0017182.332.16CSF2NML0007581.732.3531CSF2NML0007582.232.402.8ANXA3NML0051392.232.402.8ANXA3NML0033182.41TTKNML0033182.41TTKNML0022401.652.46HMMRaNML002242.46HMMRaNML00295-2.12-2.521GFBP5NML0005992.5217, 38RRCNML0151932.531PRKYaXML497470-1.84-2.54NCAM1NML006151.672.38-2.54AP3B2NML0045162.262.56TCEA2aNML0031951.532.531.942.57	KG52	NML002923	1.50	-	-	2.29	5, 58, 59 16, 20	
$\begin{array}{cccccccccccccccccccccccccccccccccccc$	EZED2	NM_000141	-	2.02	-	2.30	10, 20	
MAZNML002403 $  2.73$ $2.52$ EXO1aNML0036861.911.84 $ 2.32$ EXO1aNML001718 $  2.34$ $2$ WEE1NML003390 $  1.73$ $2.35$ $31$ CSF2NML000758 $ 1.79$ $ 2.37$ $2, 12$ MDKaNML00112333 $  2.23$ $2.40$ $2, 8$ ANXA3NML005139 $ 1.51$ $ 2.40$ $1, 5$ NoneZ60461 $   2.41$ TTKNML00318 $ 1.66$ $0.63$ $2.43$ ZFYVE20NML022340 $1.65$ $  2.46$ HMMRaNML00224 $   2.51$ SERPINA1NML000295 $ 2.12$ $ 2.52$ $1$ IGFBP5NML000599 $   2.53$ $-$ ARCNML015193 $   2.53$ $-$ PKYaXML497470 $ 1.84$ $ 2.54$ NCAM1NML000615 $1.67$ $2.38$ $ 2.54$ AP3B2NML004516 $   2.266$ $2.56$ TCEA2aNML004516 $   2.57$	FUFK2 MV2	NM_002463	-	2.03	2.75	2.32		
EXC1INLC0030001.911.94 $  2.32$ BMP6NM_001718 $2.34$ 2WEE1NM_0033901.73 $2.35$ $31$ CSF2NM_000758-1.79- $2.37$ $2, 12$ MDK <sup>a</sup> NM_00112333 $2.23$ $2.40$ $2, 8$ ANXA3NM_005139-1.51- $2.40$ $1, 5$ NoneZ60461 $2.41$ TTKNM_003318-1.66 $0.63$ $2.43$ ZFYVE20NM_0223401.65 $2.46$ HMMR <sup>a</sup> NM_002242.51 $4$ KRT18NM_0002952.521IGFBP5NM_000599 $2.52$ $17, 38$ ARCNM_015193 $2.53$ $1.67$ $2.38$ - $2.54$ PKKY <sup>a</sup> XM_497470- $1.67$ $2.38$ - $2.54$ $1.44$ $1.53$ $2.53$ $1.94$ $2.57$ TCEA2 <sup>a</sup> NM_0045161.53 $2.53$ $1.94$ $2.57$ $1.57$ $1.57$ $1.57$ $1.57$ $1.57$ $1.57$ $1.57$ $1.57$	MA2 EXO1 <sup>a</sup>	NM_002686	-	- 1.84	2.15	2.32		
DM10       MML001118       -       -       -       -       -       -       2.57       2.157       2         WEE1       NML003390       -       -       1.79       -       2.35       31         CSF2       NML000758       -       1.79       -       2.37       2,12         MDK <sup>a</sup> NML00112333       -       -       2.23       2.40       2,8         ANXA3       NML005139       -       1.51       -       2.40       1,5         None       Z60461       -       -       -       2.41         TTK       NML002318       -       1.66       0.63       2.43         ZFYVE20       NML012484       -       -       -       2.40       14         KRT18       NML000224       -       -       -       2.51       -         SERPINA1       NML000295       -       -       -       2.52       1         IGFBP5       NML000599       -       -       -       2.53       -         ARC       NML015193       -       -       -       2.53       -         PRKY <sup>a</sup> XML497470       -       1.84       -       <	BMP6	NM_001718	1.91	1.04	_	2.32	2	
CSF2       NML000758       -       1.79       -       2.37       2, 12         MDK <sup>a</sup> NML00112333       -       -       2.23       2.40       2, 8         ANXA3       NML005139       -       1.51       -       2.40       1, 5         None       Z60461       -       -       -       2.40       1, 5         TTK       NML003318       -       1.66       0.63       2.43         ZFYVE20       NML002340       1.65       -       -       2.46         HMMR <sup>a</sup> NML00224       -       -       2.51       14         KRT18       NML00295       -       2.12       -       2.52       1         IGFBP5       NML000599       -       -       -       2.52       17, 38         ARC       NML015193       -       -       -       2.53       17, 38         ARC       NML00515       1.67       2.38       -       2.54       14         NCAM1       NML00615       1.67       2.38       -       2.54       14         AP3B2       NML00615       1.53       2.53       1.94       2.57         TCEA2 <sup>a</sup> NML004516<	WFF1	NM_003390			1 73	2.34	2	
MDK <sup>a</sup> NM_001012333       -       -       2.23       2.40       2, 8         ANXA3       NM_005139       -       1.51       -       2.40       1, 5         None       Z60461       -       -       -       2.41       1, 5         TTK       NM_003318       -       1.66       0.63       2.43         ZFYVE20       NM_022340       1.65       -       -       2.46         HMMR <sup>a</sup> NM_00224       -       -       2.51       14         KRT18       NM_000295       -       2.12       -       2.52       1         IGFBP5       NM_000599       -       -       -       2.52       17, 38         ARC       NM_015193       -       -       -       2.53       17, 38         PRKY <sup>a</sup> XM_497470       -       1.84       -       2.54       14         NCAM1       NM_000615       1.67       2.38       -       2.54       14         AP3B2       NM_004644       -       -       2.26       2.56       153       1.94       2.57         TCEA2 <sup>a</sup> NM_003195       1.53       2.53       1.94       2.57       153 </td <td>CSF2</td> <td>NM 000758</td> <td>_</td> <td>1 79</td> <td>-</td> <td>2.37</td> <td>2 12</td>	CSF2	NM 000758	_	1 79	-	2.37	2 12	
ANXA3       NML005139       -       1.51       -       2.40       1, 5         None       Z60461       -       -       2.41       1         TTK       NM_003318       -       1.66       0.63       2.43         ZFYVE20       NM_022340       1.65       -       -       2.46         HMMR <sup>a</sup> NM_012484       -       -       2.49       14         KRT18       NM_000224       -       -       2.52       1         SERPINA1       NM_000295       -       2.12       -       2.52       1         IGFBP5       NM_000599       -       -       -       2.52       17, 38         ARC       NM_015193       -       -       -       2.53       17, 38         PRKY <sup>a</sup> XM_497470       -       1.84       -       2.54       -         NCAM1       NM_00615       1.67       2.38       -       2.54       -         TCEA2 <sup>a</sup> NM_003195       1.53       2.53       1.94       2.57       -         ILF3 <sup>a</sup> NM_004516       -       -       -       2.57       -       -	MDK <sup>a</sup>	NM_001012333	_	-	2.23	2.40	2,12	
None       Z60461       -       -       2.41         TTK       NM_003318       -       1.66       0.63       2.43         ZFYVE20       NM_022340       1.65       -       -       2.46         HMMR <sup>a</sup> NM_012484       -       -       2.49       14         KRT18       NM_000224       -       -       2.51       2.52       1         IGFBP5       NM_000295       -       2.12       -       2.52       1         IGFBP5       NM_00599       -       -       2.52       17, 38         ARC       NM_015193       -       -       2.53       77, 38         PRKY <sup>a</sup> XM_497470       -       1.84       -       2.54         NCAM1       NM_00615       1.67       2.38       -       2.54         AP3B2       NM_004644       -       -       2.26       2.56         TCEA2 <sup>a</sup> NM_003195       1.53       2.53       1.94       2.57         ILF3 <sup>a</sup> NM_004516       -       -       -       2.57	ANXA3	NM_005139		1 51	_	2.40	2, 0	
TTK       NM_003318       -       1.66       0.63       2.43         ZFYVE20       NM_022340       1.65       -       -       2.46         HMMR <sup>a</sup> NM_012484       -       -       2.49       14         KRT18       NM_000224       -       -       2.51         SERPINA1       NM_000295       -       2.12       -       2.52       1         IGFBP5       NM_000599       -       -       -       2.52       17, 38         ARC       NM_015193       -       -       -       2.54         NCAM11       NM_00615       1.67       2.38       -       2.54         AP3B2       NM_004644       -       -       2.26       2.56         TCEA2 <sup>a</sup> NM_003195       1.53       2.53       1.94       2.57         ILF3 <sup>a</sup> NM_004516       -       -       -       2.57	None	Z60461	_	_	_	2.41	1,5	
ZFY VE20       NM_022340       1.65       -       -       2.46         HMMR <sup>a</sup> NM_012484       -       -       2.49       14         KRT18       NM_000224       -       -       2.51         SERPINA1       NM_000295       -       2.12       -       2.52       1         IGFBP5       NM_000599       -       -       -       2.53       7, 38         PRKY <sup>a</sup> XM_497470       -       1.84       -       2.54         NCAM1       NM_00615       1.67       2.38       -       2.54         AP3B2       NM_004644       -       -       2.26       2.56         TCEA2 <sup>a</sup> NM_003195       1.53       2.53       1.94       2.57         ILF3 <sup>a</sup> NM_004516       -       -       -       2.57	ттк	NM 003318	_	1.66	0.63	2.43		
HMMR <sup>a</sup> NM_012484       -       -       -       2.49       14         KRT18       NM_000224       -       -       -       2.51       5         SERPINA1       NM_000295       -       2.12       -       2.52       1         IGFBP5       NM_000599       -       -       -       2.52       17, 38         ARC       NM_015193       -       -       -       2.53       5         PRKY <sup>a</sup> XM_497470       -       1.84       -       2.54         NCAM1       NM_00615       1.67       2.38       -       2.54         AP3B2       NM_004644       -       -       2.26       2.56         TCEA2 <sup>a</sup> NM_003195       1.53       2.53       1.94       2.57         ILF3 <sup>a</sup> NM_004516       -       -       -       2.57	ZFYVE20	NM_022340	1.65	_	-	2.46		
KRT18       NM_000224       -       -       2.51         SERPINA1       NM_000295       -       2.12       -       2.52       1         IGFBP5       NM_000599       -       -       -       2.52       17, 38         ARC       NM_015193       -       -       -       2.53         PRKY <sup>a</sup> XM_497470       -       1.84       -       2.54         NCAM1       NM_00615       1.67       2.38       -       2.54         AP3B2       NM_004644       -       -       2.26       2.56         TCEA2 <sup>a</sup> NM_003195       1.53       2.53       1.94       2.57         ILF3 <sup>a</sup> NM_004516       -       -       -       2.57	HMMR <sup>a</sup>	NM_012484	_	_	_	2.49	14	
SERPINA1       NM_000295       -       2.12       -       2.52       1         IGFBP5       NM_000599       -       -       -       2.52       17, 38         ARC       NM_015193       -       -       -       2.53         PRKY <sup>a</sup> XM_497470       -       1.84       -       2.54         NCAM1       NM_00615       1.67       2.38       -       2.54         AP3B2       NM_004644       -       -       2.26       2.56         TCEA2 <sup>a</sup> NM_003195       1.53       2.53       1.94       2.57         ILF3 <sup>a</sup> NM_004516       -       -       -       2.57	KRT18	NM 000224	_	_	_	2.51		
IGFBP5     NM_000599     -     -     2.52     17, 38       ARC     NM_015193     -     -     -     2.53       PRKY <sup>a</sup> XM_497470     -     1.84     -     2.54       NCAM1     NM_000615     1.67     2.38     -     2.54       AP3B2     NM_004644     -     -     2.26     2.56       TCEA2 <sup>a</sup> NM_003195     1.53     2.53     1.94     2.57       ILF3 <sup>a</sup> NM_004516     -     -     -     2.57	SERPINA1	NM_000295	_	2.12	_	2.52	1	
ARC       NM_015193       -       -       2.53         PRKY <sup>a</sup> XM_497470       -       1.84       -       2.54         NCAM1       NM_000615       1.67       2.38       -       2.54         AP3B2       NM_004644       -       -       2.26       2.56         TCEA2 <sup>a</sup> NM_003195       1.53       2.53       1.94       2.57         ILF3 <sup>a</sup> NM_004516       -       -       -       2.57	IGFBP5	NM_000599	_	_	_	2.52	17.38	
PRKY <sup>a</sup> XM_497470         -         1.84         -         2.54           NCAM1         NM_00615         1.67         2.38         -         2.54           AP3B2         NM_004644         -         -         2.26         2.56           TCEA2 <sup>a</sup> NM_003195         1.53         2.53         1.94         2.57           ILF3 <sup>a</sup> NM_004516         -         -         -         2.57	ARC	NM_015193	_	_	_	2.53		
NCAM1         NM_000615         1.67         2.38         -         2.54           AP3B2         NM_004644         -         -         2.26         2.56           TCEA2 <sup>a</sup> NM_003195         1.53         2.53         1.94         2.57           ILF3 <sup>a</sup> NM_004516         -         -         -         2.57	PRKY <sup>a</sup>	XM_497470	_	1.84	_	2.54		
AP3B2       NM_004644       -       -       2.26       2.56         TCEA $2^a$ NM_003195       1.53       2.53       1.94       2.57         ILF $3^a$ NM_004516       -       -       -       2.57	NCAM1	NM_000615	1.67	2.38	_	2.54		
TCEA2 <sup>a</sup> NM_003195         1.53         2.53         1.94         2.57           ILF3 <sup>a</sup> NM_004516         -         -         -         2.57	AP3B2	NM_004644	_	_	2.26	2.56		
ILF3 <sup>a</sup> NM_004516 2.57	TCEA2 <sup>a</sup>	NM_003195	1.53	2.53	1.94	2.57		
	ILF3 <sup>a</sup>	NM_004516	_	_	_	2.57		

Table 1	(continued)
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HUGO gene name	NCBI acc. no.	Fold induction/	Pathway ID			
		GLI1 24 h	GLI1 72 h	GLI2 24 h	GLI2 72 h	
ADD3 <sup>a</sup>	NM_001121	_	_	_	2.58	
MAD2L1 <sup>a</sup>	NM_002358	1.58	1.90	_	2.59	26
RARRES3 <sup>a,b</sup>	NM_004585	1.50	2.04	2.37	2.63	
BAP1	NM_004656	_	_	_	2.64	
GPR161	NM_007369	_	_	-	2.68	7
UBE2H	NM_003344	_	1.77	_	2.69	
AURKB	NM_004217	_	1.67	_	2.71	
BRCA1	NM_007294	_	1.87	_	2.71	13
SLC7A8	NM_012244	-	2.46	1.50	2.73	
PSAT1	NM_021154	_	1.76	1.76	2.73	
APC <sup>a</sup>	NM_000038	-	1.77	-	2.74	33
COL5A2 <sup>a</sup>	NM_000393	-	-	-	2.77	25
LITAF <sup>a</sup>	NM_004862	-	1.58	2.97	2.78	
CKS1B <sup>a,b</sup>	NM_001826	-	2.09	-	2.78	9
CAMK1 <sup>a</sup>	NM_003656	1.97	3.07	-	2.78	39
LRRN6A	NM_032808	-	2.70	-	2.79	
OAT <sup>a</sup>	NM_000274	-	-	1.92	2.80	
KIF11	NM_004523	-	2.25	-	2.82	
SEPT11 <sup>a</sup>	NM_018243	-	-	2.05	2.84	
G1P2 <sup>a</sup>	NM_005101	_	1.82	2.16	2.84	
PCNA <sup>a</sup>	NM_002592	2.07	2.34	-	2.87	8, 26, 31, 32
UBE2T	NM_014176	-	2.25	0.48	2.89	
LGALS1 <sup>a,b</sup>	NM_002305	-	-	2.12	2.93	3, 13
LMNB1	NM_005573	-	1.86	-	3.06	
FZD7	NM_003507	-	1.73	-	3.10	12, 33
GPR160	NM_014373	-	-	1.64	3.15	
SERPINB2 <sup>a</sup>	NM_002575	-	-	-	3.15	1, 40
Clorf183	NM_198926	-	1.74	-	3.16	
EP300	NM_001429	_	_	-	3.16	34
CDKN3 <sup>a</sup>	NM_005192	-	2.33	0.58	3.17	
CISL <sup>a,0</sup>	NM_001912	2.35	7.52	1.59	3.30	
ILIR2ª	NM_004633	-	-	-	3.30	
FUS2	U/316/	1.59	2.71	-	3.44	
FENI"	NM_004111	1.66	1.69	2.06	3.47	2 20 20
KGS19"	NM_002775	1.62	1.57	2.08	3.54	3, 38, 39
CL12	NM_005270	5.42	5.45	2.79	3.07	17
GLIZ TOP2 A <sup>a</sup>	NM_001067	_	- 2.00	2.57	3.80	
CCNR1 <sup>b</sup>	NM_031066	-	1.08	-	3.05	0.21
CD40a	NM_001250	-	1.90	0.01	3.00	9, 51 10, 11, 13, 40
KDT8	NM_002273	_	_	_	3.90	10, 11, 15, 40
CCNB2	NM_004701	-	2.00	-	3.98 4.06	0
CDC20 <sup>a</sup>	NM_001255		2.39	_	4.00	8 9 12
KLK10 <sup>a,b</sup>	NM_002776	_	-	2.58	4.12	0, 9, 12
LARS2	NM_015340	_	_	_	4 14	18
ASPM <sup>a</sup>	NM_018136	_	2.76	_	4.15	10
CDC45L <sup>a,b</sup>	NM_003504	_	2.41	_	4.24	31. 32
DHRS9 <sup>a</sup>	NM_005771	2.80	2.11	2.62	4.26	01,02
CDC2 <sup>a,b</sup>	NM_001786	_	2.91	_	4.37	9
CENPF	NM_016343	_	1.97	_	4.41	26
CENPA <sup>a</sup>	NM_001809	_	2.81	_	4.60	16, 20, 24, 26, 29
PTCH <sup>a,b</sup>	NM_000264	2.68	3.35	2.81	4.65	8
ANLN <sup>a</sup>	NM_018685		2.53	_	4.67	-
DLG7 <sup>a</sup>	NM_014750	_	3.39	_	4.88	
UBE2C	NM_007019	_	1.77	_	4.94	9
TGM3 <sup>a</sup>	NM_003245	3.00	6.24	2.09	4.96	
HRH1 <sup>a</sup>	NM_000861	2.39	3.66	3.98	5.00	7,10
PLCL1 <sup>a</sup>	NM_006226	1.66	2.70	2.09	5.19	24
SIGLEC6	NM_001245	_	_	4.50	5.34	
EDN1 <sup>a</sup>	NM_001955	1.95	2.90	2.70	5.94	

(continued on next page)

Table 1 (continued	)
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HUGO gene name NCBI acc. no. Fold induction/repression						Pathway ID
		GLI1 24 h	GLI1 72 h	GLI2 24 h	GLI2 72 h	
BCL2 <sup>a,b</sup>	NM_000633	_	1.67	1.77	6.41	11, 13, 35
KIF23 <sup>a</sup>	NM_138555	_	2.94	0.49	6.46	9
IL6 <sup>a</sup>	NM_000600	_	3.50	-	7.20	2, 8, 11, 12, 38
SDC2	NM_002998	_	-	-	7.45	
FGF19 <sup>a</sup>	NM_005117	1.97	4.92	1.93	7.77	
CPZ <sup>a</sup>	NM_001014447	_	4.38	-	7.82	
DOC1 <sup>a</sup>	NM_014890	1.69	4.41	2.09	8.49	30
TNC <sup>a,b</sup>	NM_002160	4.73	35.45	3.31	9.69	25
FOXE1 <sup>a,b</sup>	NM_004473	2.62	4.97	5.55	10.38	
KLK6 <sup>a,b</sup>	NM_001012964	2.88	6.79	2.70	10.45	
CCL17 <sup>a</sup>	NM_002987	1.66	2.55	2.13	11.14	2, 10, 19
FST <sup>a,o</sup>	NM_006350	1.69	2.03	3.46	16.35	34
BAMBI	NM_012342	-	-	0.36	-	
LOC440416	XM_498659	-		0.38	-	
IGFIR	NM_000875	_	-	0.38	-	20
ACTRIO	NM_018477	—	-	0.39	_	30
ANXAI SL COZA I	NM_000700	—	1.79	0.40	-	1, 5, 10, 12, 14, 24
SLC2/AI	NM_198580	-	-	0.40	-	7
EIF2AK3"	NM_004836	0.62	-	0.41	_	18
GPK120	NML020455	-	-	0.41	-	
PCBD1	NM_002022	-	-	0.41	-	7
S115 COX6C	NM 004274	_	-	0.42	-	/ 41
PL A2C1P	NM 000028	—	-	0.45	—	41
SMC6L1	NM 024624	_	-	0.44	-	
	NM 020056		0.59	0.44	_	
CHMP5	NM_016410		0.59	0.45	_	
CCNG2	NM_004354	_	_	0.45	_	9 31
PRDX3	NM_006793	_	_	0.45	_	9, 51
BPGM	NM_001724	_	_	0.46	_	
DUSP14	NM_007026	_	_	0.46	_	40
RPLP2	NM_001004	_	_	0.46	_	7.18
SUPT7L	NM_014860	_	-	0.46	_	.,
ERO1L	NM_014584	_	-	0.47	_	
ITGAE	NM_002208	_	-	0.47	_	
LAPTM5	NM_006762	_	-	0.47	_	
PDK1	NM_002610	_	-	0.47	_	41
XRCC1	NM_006297	-	-	0.47	-	
ZNF354B	NM_058230	_	-	0.47	_	
HSD11B2	NM_000196	0.65	0.63	0.48	_	15
AP1G1	NM_001030007	-	-	0.48	_	21
FBN1	NM_000138	_	-	0.48	-	25
PTD004	NM_013341	_	-	0.48	_	
SEPT3	NM_019106	_	-	0.48	_	9
SLMAP	NM_007159	-	-	0.48	-	
MERTK	NM_006343	0.59	0.46	0.49	_	12
EPX	NM_000502	-	-	0.49	-	
RGNEF	XM_371755	_	-	0.49	-	
GLRX2	NM_016066	_	-	0.49	-	13
KCMF1	NM_020122	-	-	0.49	-	
NDE1	NM_017668	-	-	0.49	-	
OGT	NM_181672	_	-	0.49	_	27
RITI	NM_006912	_	-	0.49	-	10
UBE2B	NM_005537	-	-	0.49	-	40
ZDHHC13	NM_019028	_	-	0.49	_	
DUSP2	NM_006824	-	-	0.50	-	
EDNAIDP2	NIVI_000824	-	-	0.50	_	
NIF9 I IMP 1	NIVI_022542	-	-	0.50	_	14 26
NDUER2	NM_004546	_	_	0.50	_	14, 50 41
NDUFB2	11111_004540	-	-	0.50	-	71

HUGO gene name	NCBI acc. no.	Fold induction/	Pathway ID			
		GLI1 24 h	GLI1 72 h	GLI2 24 h	GLI2 72 h	
TCP1	NM_030752	_	-	0.50	_	7, 27
SLC28A1	NM_004213	0.49	0.42	1.91	_	
IQGAP1	NM_003870	-	-	2.02	_	1, 3, 30, 36
SFRP1 <sup>a</sup>	NM_003012	2.17	2.33	2.04	_	
CD24	NM_013230	-	-	2.07	_	11
DAZAP2	NM_014764	-	0.63	2.09	-	40
CREG	NM_003851	-	-	2.10	_	8
COX6B	NM_001863	_	_	2.15	_	41
PLA2G4C	NM_003706	-	_	2.17	_	5, 10, 22, 27
EEF1G	NM_001404	0.52	0.44	2.21	_	18, 37
DHRSX	NM_145177	-	-	2.33	-	
SLC7A5	NM_003486	_	_	2.36	_	
HMGA2	NM_001015886	_	_	2.49	_	16, 20, 26, 29
KRTHB3	NM_002282	2.17	0.62	3.23	_	
KRT6L <sup>a</sup>	NM_175834	-	-	3.99	_	
KRT2A	NM_000423	-	0.45	6.17	-	
ASS	NM_000050	0.61	0.28	_	_	
IGFBP3 <sup>a</sup>	NM_000598	-	0.38	-	-	17, 38
MMP12 <sup>a</sup>	NM_002426	-	0.42	-	_	4, 14, 25
CALR	NM_004343	0.64	0.43	_	_	39
RPL13A	NM_012423	-	0.43	_	_	7
ZNF496	NM_032752	0.54	0.45	-	-	
FAM14A	NM_032036	-	0.49	_	_	
UACA	NM_001008224	-	2.04	-	_	
ECHDC1 <sup>a</sup>	NM_018479	_	2.11	_	-	7
GAS1	NM_002048	_	2.12	_	_	
MGC27165	AF067420	_	2.12	_	_	
LCE2B <sup>a,b</sup>	NM_014357	1.81	2.13	_	_	
MOSPD3	NM_023948	1.70	2.14	_	_	
INHBB <sup>a</sup>	NM_002193	1.65	2.27	_	_	2
<b>BDNF</b> <sup>a</sup>	NM_001709	1.81	3.30	-	-	
C3AR1	NM_004054	0.45	_	_	_	7, 10, 14, 19
GPX7	NM_015696	2.02	_	_	_	
SMC2L1	NM_006444	2.08	-	-	_	16
VGLL4	NM_014667	2.20	_	_	_	

Genes differentially expressed are sorted by fold induction/repression values of the GLI2 $\Delta$ N 72-h time point. Gene names represent approved gene symbols according to the HUGO Gene Nomenclature Committee (http://www.gene.ucl.ac.uk/nomenclature). Genes without a HUGO gene name are written in italic. Genes named "None" represent Incyte EST sequences, which do not show any significant match with annotated nucleotide sequences in the GenBank/GenPept databases. Pathway ID numbers refer to Fig. 4. White background, induced gene; gray background, repressed gene; light face, gene significant at fold-change  $\geq 1.5$ ; bold face, gene significant at fold-change  $\geq 2.0$ ; –, no significant value.

<sup>a</sup> Resequenced EST clone.

<sup>b</sup> Verified by QRT-PCR.

Table 1 (continued)

and differentiation-opposing effects of the two oncogenic transcription factors. The identity of differentially expressed genes reflects the activity of signaling pathways previously implicated in keratinocyte and hair follicle differentiation. The data support the view that GLI transcription factors have overlapping yet distinct activities. There are clear quantitative differences in the effects of the two transcription factors on a small number of positively regulated genes such as TNC, FST, and BCL2 (Figs. 5B and 5C). The activated form of GLI2, GLI2 $\Delta$ N, effects massive target gene repression, whereas only weak repression is seen with GLI1 expression. Phosphorylation of GLI2 by PKA without evidence for proteolytic processing favors the interpretation that no Ci/GLI3-like product is responsible for the repression of most GLI2 target genes. These results suggest that  $GLI2\Delta N$  may specifically activate the transcription of a repressor, which would then act



Fig. 2. Changes in gene expression after induction of GLI1 or GLI2 $\Delta$ N by tetracycline in HaCaT keratinocytes. Venn diagram of the array data comparing the inducing and repressing activities of GLI1 and GLI2 $\Delta$ N. Genes changing  $\geq$ 2.0-fold in response to GLI1 or expression after 24 and 72 h were included. The total number of genes induced or repressed by each transcription factor is indicated below.



Fig. 3. GL11 and GL12 $\Delta$ N are phosphorylated in the presence of forskolin, but not proteolytically processed. (A) Immunoprecipitation (IP) showing phosphorylation of GL11 and GL12 $\Delta$ N by protein kinase A (PKA) upon forskolin (FSK) treatment. GL11 and GL12 $\Delta$ N were immunoprecipitated from FSK-treated cells expressing GL11 (GL11 HaCaT) or GL12 $\Delta$ N (GL12 $\Delta$ N HaCaT) using GL1-specific antibodies (G1-C18, G2-N20) or normal goat IgG. Phosphorylated GLIs were visualized with a primary antibody recognizing phosphorylated PKA sites (PKA substrate Ab) (top) and anti GL1 antibodies (bottom). (B) No lower molecular bands of GL11 or GL12 $\Delta$ N protein were observed in GL11 HaCaT or GL12 $\Delta$ N HaCaT cells upon FSK treatment. Total lysates of tetracycline-induced cells grown for 48 h in the presence of FSK and controls were analyzed by Western blot using specific antibodies recognizing GL11 and GL12. Nonspecific signals are marked by asterisks.

on target genes. Alternatively or additionally, other modifications of GLI2 or interactions with other GLI molecules [22] or unrelated further factors may result in gain of repressive activity. A more comprehensive picture of the mechanism of the overlaps and specificities of the GLI proteins will emerge from the clarification of these issues.

#### Material and methods

# Cell cultures

HaCaT cells were cultured in Dulbecco's modified Eagle medium (pH 7.2, high glucose; Invitrogen Life Technologies) supplemented with 10% fetal calf serum (Invitrogen Life Technologies), 100  $\mu$ g/ml streptomycin, and 62.5  $\mu$ g/ml



Fig. 4. Functional clustering of up- and downregulated genes. Clustering of array data was carried out using the Pathway explorer software (https://www. pathwayexplorer.genome.tugraz.at/). Grouping of genes refers to the GenMapp pathway or functional group classification. 196 of 456 differentially expressed genes were mapped to 41 pathways or functional groups (see Table 1); for the remaining genes no match was found. Most of the 196 genes gave matches in more than one pathway (total of 345 hits). Groups with fewer than 4 members are pooled in "others." The number of hits found in each group is shown in parentheses. Numbers in front of each gene group denote the pathway ID as shown in Table 1.



Fig. 5. Expression patterns of representative GL11 and GL12 $\Delta$ N target genes. Induction of target genes was measured by QRT-PCR. Fold change refers to the ratios of RNA from cells induced with tetracycline for the times indicated to uninduced cells. (A) Genes with similar expression patterns in response to GL11 and GL12 $\Delta$ N overexpression. (B) Genes preferentially induced by GL11. (C) Genes preferentially induced by GL12 $\Delta$ N. (D) Genes preferentially repressed by GL12 $\Delta$ N.

penicillin (Sigma–Aldrich) at 37°C, 5% CO<sub>2</sub>. For PKA activation, forskolin (in EtOH) (Sigma–Aldrich) was added to a final concentration of 10  $\mu$ M. Controls were treated with EtOH only.

Double stable inducible HaCaT lines expressing either human GL11 (GL11 HaCaT) or GL12 $\Delta$ N tagged with a 6×HIS epitope (GL12 $\Delta$ N HaCaT) [43] were grown in the presence of 25 µg/ml zeocin (Invitrogen Life Technology) and 8 µg/ml Blasticidin-S (ICN-Biomedica). Transgene expression was induced by adding 1 µg/ml tetracycline (Tet) (Invitrogen Life Technologies) to the medium.

# Preparation of <sup>33</sup>P-labeled cDNA

Total RNA was extracted with TRI reagent (Molecular Research Center) according to the manufacturer's instructions followed by LiCl precipitation. To eliminate differences between clonal cell lines, RNA from four independently isolated lines expressing either GLI1 or GLI2 $\Delta$ N was pooled for cDNA array analysis. cDNA labeling was carried out as described previously [75]. In brief, 15 µg pooled total RNA was reverse transcribed with Superscript II (Invitrogen Life Technologies) in the presence of 70 µCi [ $\alpha$ -<sup>33</sup>P]dCTP (3000 Ci/mmol;

Table 2 Roles of GL11 and GL12  $\Delta N$  in proliferation and differentiation

Gene	GLI1 HaCaT			GLI2∆N HaCaT			
name	12 h+Tet fI/R (±SD)	24 h+Tet fI/R (±SD)	72 h+Tet fI/R (±SD)	12 h+Tet fI/R (±SD)	24 h+Tet fI/R (±SD)	72 h+Tet fI/R (±SD)	
CCNA2	0.97 (±0.044)	0.86 (±0.101)	7.49 (±0.127)	0.98 (±0.039)	1.46 (±0.166)	5.63 (±0.437)	
CDC2	1.10 (±0.133)	1.07 (±0.151)	6.07 (±0.515)	1.06 (±0.039)	1.18 (±0.137)	5.59 (±0.271)	
CDC45L	1.17 (±0.277)	2.64 (±0.068)	13.39 (±0.808)	0.85 (±0.093)	2.39 (±0.398)	14.39 (±0.747)	
E2F1	1.17 (±0.071)	3.45 (±0.179)	4.96 (±0.069)	0.64 (±0.013)	3.99 (±0.097)	9.85 (±0.102)	
CCNB1	1.27 (±0.313)	1.24 (±0.215)	4.84 (±0.625)	1.03 (±0.046)	0.85 (±0.103)	4.84 (±0.351)	
CKS1B	0.93 (±0.030)	1.35 (±0.082)	3.54 (±0.878)	1.04 (±0.054)	1.26 (±0.087)	4.96 (±0.394)	
CCNE	0.86 (±0.085)	1.80 (±0.069)	1.49 (±0.288)	0.82 (±0.010)	1.74 (±0.024)	4.11 (±0.107)	
CDKN1A	0.99 (±0.072	0.52 (±0.028)	0.71 (±0.039	0.56 (±0.010)	0.32 (±0.020	0.38 (±0.054	
KRT1	1.27 (±0.048)	0.81 (±0.050)	0.67 (±0.286)	1.00 (±0.323)	0.15 (±0.006)	0.04 (±0.019)	
KRT10	0.83 (±0.079)	0.55 (±0.030)	0.45 (±0.088)	0.98 (±0.267)	0.09 (±0.001)	0.01 (±0.005)	
IVL	0.80 (±0.041)	0.56 (±0.018)	0.32 (±0.025)	1.21 (±0.623)	0.25 (±0.041)	0.04 (±0.002)	
PI3	0.83 (±0.041)	0.37 (±0.013)	0.25 (±0.044)	1.25 (±0.222)	0.20 (±0.024)	0.10 (±0.027)	
SPRR2A	0.82 (±0.206)	0.49 (±0.068)	0.34 (±0.177)	1.15 (±0.837)	0.18 (±0.005)	0.05 (±0.003)	

Ratios and SD were calculated from the average of four real-time RT-PCR measurements.

Amersham Biosciences). Labeled cDNA was purified with GFX DNA purification columns (Amersham Biosciences) and equal counts of labeled cDNA were added to each hybridization.

#### High-density DNA filter array production and hybridization

The Human Drug Discovery clone set (10,000 sequence-verified ESTs) and a selection of 2000 sequence-verified EST clones from the human UniGem version 2.0 library were obtained from Incyte Genomics. Both sets were amplified by PCR, spotted, and hybridized separately with labeled cDNA. PCR amplification, array production, and hybridization were done as described previously [60,75]. Arrays were exposed for 4 days and scanned with a BAS-1800II (Fuji) phosphorimager. Array images were analyzed using the AIDA Metrix suite (Raytest). Data from two independent hybridizations were collected at each time point. Data were normalized by total signal intensity and the statistical significance was analyzed using the SAM software package [48]. Only genes showing at least a 2-fold change in expression were called significant. For genes reaching this threshold at one time point, further points were analyzed also at 1.5-fold change.

The data discussed in this publication have been deposited in the NCBI Gene Expression Omnibus (GEO; http://www.ncbi.nlm.nih.gov/geo/) and are accessible through GEO Series Accession No. GSE 1434.

# **QRT-PCR** analysis

RNA prepared as described above was further purified with the High Pure RNA isolation kit (Roche) to remove any genomic contamination. cDNA was synthesized from 4  $\mu$ g purified total RNA with Superscript II (Invitrogen) using oligo(dT) primers, according to the manufacturer's instructions. QRT-PCR analysis was performed on a Rotorgene 2000 (Corbett Research) using iQTM SYBR Green Supermix (Bio-Rad). Primer sequences not published previously [43,60] are shown in Table 3 (supplementary material). Large ribosomal protein P0 (RPLP0) was used as a reference in all QRT-PCR analyses [76].

### Immunoprecipitation and Western blot analysis

GL11 HaCaT and GL12 $\Delta$ N HaCaT cells were lysed 24 h after Tet induction in RIPA buffer (150 mM NaCl, 0.1% SDS, 10 mM Tris–HCl, pH 7.4, 1% Triton X-100, 1% sodium deoxycholate, 1 mM PMSF, 1 mM protease inhibitor mix (Sigma–Aldrich)) at 4°C. Lysates were cleared by centrifugation (15 min, 13,000 rpm, 4°C) and incubated overnight with the appropriate antibody at 4°C. After incubation with protein G–Sepharose (Amersham Biosciences) for 2 h at 4°C, the Sepharose was washed four times with RIPA buffer and proteins were eluted in hot lysis buffer (125 mM Tris (pH 6.8), 5% glycerol, 2% SDS, 1%  $\beta$ mercaptoethanol, 0.006% bromophenol blue) and resolved by SDS–PAGE. SDS–PAGE and Western blotting were performed according to standard protocols. Primary and secondary antibodies used were goat polyclonal anti-GL12 (GL12 N20; Santa Cruz), goat polyclonal anti-GL11 (GL11 C18; Santa Cruz), rabbit anti-phospho-(Ser/Thr) PKA substrate antibody (Cell Signaling Technologies), anti-rabbit IgG–HRP (Santa Cruz), and rabbit anti-goat IgG– HRP (Chemicon).

#### Luciferase reporter assay

HaCaT cells were grown in 12-well plates to 80% confluence and transfected in triplicate with GLI1, GLI2 $\Delta$ N [43], GLI2 [34], and *Renilla* luciferase (pRL-SV40 (Promega)) expression plasmids and pGL3 luciferase reporter plasmids as indicated in Fig. 1B. Cells were harvested 48 h after transfection and luciferase activity was measured with a Lucy II luminometer (Anthos) using the dualluciferase reporter assay system (Promega) according to the manufacturer's instructions. Data were normalized for *Renilla* luciferase activity.

# Acknowledgments

We thank S. Siller for excellent technical assistance and Dr. Maximilian Muenke for providing the full-length GLI2 expression construct. This work was supported by FWF Project P14227, GEN-AU Project "Ultra-sensitive Proteomics and Genomics," the University of Salzburg program "Biosciences and Health," and a predoctoral fellowship of the Austrian Academy of Science to V.S.

# Appendix A. Supplementary data

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ygeno.2005.12.003.

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