# Involvement of TGF- $\beta$ Receptor– and Integrin-Mediated Signaling Pathways in the Pathogenesis of Granular Corneal Dystrophy II

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**PURPOSE.** The purpose of this study was to elucidate the pathophysiological process in primary cultured corneal fibroblasts (PCFs) from normal subjects and granular corneal dystrophy (GCD) II patients, by using cDNA microarrays.

**METHODS.** PCFs were isolated from the corneas of normal subjects and GCD II patients who were heterozygous and homozygous for the *TGFBI* R124H mutation. RNA was isolated from each sample, and gene expression profiles were analyzed with a cDNA microarray consisting of approximately 29,000 genes. Cell adhesion assays were performed to confirm the functionality of the detected gene expression profiles.

**RESULTS.** Twofold differences were detected in the expression of 555 genes between wild-type and homozygous GCD II PCFs. Of these, 319 genes were upregulated, and 236 genes were downregulated in the homozygous GCD II PCFs. The most abundant and consistent changes were observed in gene families encoding signal transduction pathways involving the TGF-\u03b3 receptor- and integrin-mediated signaling, cell differentiation and proliferation, immune responses, cell adhesion, extracellular matrix (ECM) proteolytic enzymes, cell cycle, cytoskeletal organization, mitochondrial energy metabolism, collagen catabolism, response to wounding, response to oxidative stress, and the ubiquitin-mediated proteasomal degradation pathway. Cell adhesion assays demonstrated that heterozygous and homozygous GCD II PCFs strongly attached to collagen-I, collagen-IV, fibronectin, and laminin, compared with wild-type cells.

Conclusions. Alterations in the TGF- $\beta$  receptor- and integrinmediated signaling pathway may play a key role in GCD II pathophysiology. If the novel factors identified in this study are involved in GCD II pathogenesis, they could assist in designing further studies to elucidate specific mechanisms of this disease. (Invest Ophthalmol Vis Sci. 2010;51:1832-1847) DOI: 10.1167/iovs.09-4149

**G** ranular corneal dystrophy II (GCD II) is a disorder characterized by age-dependent progressive accumulation of protein deposits in the corneal epithelia and stroma, followed by disruption of corneal transparency. GCD II is an autosomal dominant disorder caused by a point mutation (R124H) in the transforming growth factor- $\beta$ -induced gene (*TGFBI*) on chromosome 5, region q31.<sup>1,2</sup> *TGFBI* encodes a highly conserved 683 amino acid protein (TGFBIp) that contains a secretary signal sequence and an Arg-Gly-Asp (RGD) motif that serves as a ligand recognition site for integrins.<sup>1</sup> TGFBIp is a component of extracellular matrix (ECM) that mediates cell adhesion and migration by interacting with integrins.<sup>3–5</sup> More recently, it has been shown that loss of TGFBIp induces cell proliferation and spontaneous tumor development in *TGFBI*-knockout mice.<sup>6</sup>

Thirty-eight different mutations in *TGFBI* are involved in corneal dystrophies. Remarkably, different mutations cause unique corneal dystrophy phenotypes, such as R124H in GCD II (also called Avellino corneal dystrophy), R124C in lattice corneal dystrophy type I, R555W in granular corneal dystrophy type I, and R555Q in Thiel-Behnke corneal dystrophy.<sup>7</sup>

The cornea is an avascular tissue located in the anterior part of the eye and consists of five layers of tissue that serve as a barrier to infection. The principal cell types of the cornea include corneal epithelial cells in the outer region, keratocytes in the middle region, and endothelial cells in the inner region. Keratocytes, also known as corneal fibroblasts, have a dendritic morphology and produce keratan sulfate proteoglycans that are necessary for the maintenance of the corneal structure and physiology, particularly for the maintenance of corneal transparency.<sup>8,9</sup> These cells are also responsible for the synthesis of collagen fibrils and the ECM and for stromal repair after injury or infection.

TGFBIp plays a significant role in the health of the cornea. For example, increased production of TGFBIp by corneal fibroblasts has been detected in areas of corneal injury,<sup>10</sup> and ablation of the corneal stroma by laser in situ keratomileusis (LASIK) in GCD II patients accelerates TGFBIp deposition.<sup>11,12</sup> Overexpression of mutant TGFBI induces apoptotic cell death in human corneal epithelial cells,13 and age-dependent retinal degeneration has been observed in transgenic mice that express a mutant form of the human *TGFBI*.<sup>14</sup> More recently, we have reported that PCFs are most susceptible to oxidative stress.<sup>15</sup> However, the pathophysiological process underlying GCD II has yet to be fully elucidated. To understand the pathophysiology of GCD II, we used cDNA microarray analysis to identify differential gene expression profiles between homozygous GCD II and wild-type PCFs. We also tested the ability of these cells to adhere to various ECM proteins to confirm the functional relevance of the gene expression results.

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Pair	Normal Cornea Sex/Age	Mean Age	Heterozygous Sex/Age	Mean Age	Homozygous Sex/Age	Mean Age	Use of Samples
1	F/20		F/37		F/13		Microarray RT-PCR Western blot Cell-adhesion assay
2	M/10	25.3	F/20	35.3	M/10	16.6	Microarray RT-PCR Cell-adhesion assay
3	M/45		F/49		F/27		Microarray Cell-adhesion assay

TABLE 1. Pairs of GCD II and Normal Samples

# **MATERIALS AND METHODS**

# Isolation and Culture of Primary Corneal Fibroblasts

Wild-type (n = 3), heterozygous (n = 3), and homozygous (n = 3)primary human corneal fibroblasts were prepared by using a published method.15 Donor confidentiality was maintained according to the Declaration of Helsinki, and the protocol was approved by Severance Hospital IRB Committee (CR04124), Yonsei University. GCD II was diagnosed by DNA sequencing analysis of TGFBI mutations. Age, sex, and diagnosis in the GCD II cases are shown in Table 1. After removal of the corneal button for penetrating keratoplasty, the remaining corneal rims were harvested for culture of the normal corneal fibroblast. The medical records of the donors from the eye bank of Yonsei University Severance Hospital did not show any genetic or systemic metabolic disease. The fibroblasts grown from the pieces of corneal rims were treated as normal ones. Genetic normality of the BIGH3 gene in normal primary corneal fibroblasts was determined by DNA sequencing analysis. Table 1 presents information regarding the corneal fibroblasts used in these studies. For cDNA microarray analysis, six samples (normal sample pairs 1, 2, and 3; and homozygous sample pairs 1, 2, and 3) were analyzed, excluding the heterozygous sample. For RT-PCR studies, the samples were prepared by pooling total RNA from two samples (Table 1, pairs 1 and 2). The sample pairs 1 and 2 were used for Western blot analysis. For the cell adhesion assay, nine samples (normal, heterozygous, and homozygous sample pairs 1, 2, and 3) were analyzed.

## **RNA Extraction and Gene Expression Profiling**

Transcriptional profiles were evaluated in three independent cell preparations, by using a cDNA microarray (GeneChip Human Gene 1.0 ST Array, GeneChip; Affymetrix, Santa Clara, CA) containing approximately 29,000 genes. To determine a variation and average changes (*x*-fold) in the expression of different genes in each sample and to compare these samples, we analyzed six samples (normal sample pairs 1, 2 and 3, and homozygous samples pair 1, 2, and 3) for new microarray analysis without total RNA pooling. Total RNA was extracted from the PCFs (TRIzol; Invitrogen, Carlsbad, CA) followed by purification (RNeasy kit; Qiagen, Valencia, CA) to remove residual DNA. The concentration of total RNA was determined by UV spectrophotometry (ND-1000 UV-Vis Spectrophotometer; Nanodrop Technologies, Wilmington, DE). Two quality controls were used for each RNA sample: (1) an A<sub>260</sub>/A<sub>280</sub> ratio between 1.7 and 2.3; and (2) an electropherogram showing two distinct ribosomal peaks corresponding to either 18S and 28S for eukaryotic RNA bands at a ratio of 28S/18S of >0.5 with minimal or no degradation. The arrays were scanned (GeneChip Scanner 3000 7G; Affymetrix), raw signal intensities were normalized (GeneChip Operating Software [GCOS] algorithm; Affymetrix), and the data were analyzed (Gene Chip DNA Analysis Software [GDAS], ver. 2.0 according to the Affymetrix GeneChip Expression Analysis Technical Manual; http://www.affymetrix.com). We detected a twofold change in differential gene expression between the normal and homozygous samples. For statistical data analysis, we used a two-tailed unpaired Student's *t*-test (P < 0.05), to assess significant differences between the two cell types.

## **Reverse Transcription–Polymerase** Chain Reaction

Two micrograms of total RNA was reverse transcribed into cDNA (Superscript II reverse transcriptase; Invitrogen, Carlsbad, CA) and an Oligo (dT) primer (Invitrogen). The cDNA was amplified by using primers derived from the sequence of the selected differentially expressed genes, and  $\beta$ -actin expression was used as the control. Amplification products were visualized by electrophoresis in 1.2% agarose gels containing ethidium bromide. Specific RT-PCR primer sets and annealing temperatures are listed in Table 2.

## Preparation of Cell Lysates and Western Blot Analysis

Cell lysates were prepared in radio immunoprecipitation assay (RIPA) buffer (pH 7.4; containing a Complete Mini Protease Inhibitor Tablet; Roche Diagnostics, Indianapolis, IN). Crude cell lysates were centrifuged at 10,000g for 10 minutes at 4°C, to remove nuclear fragments and tissue debris. A portion of the supernatant was used to determine the total protein concentration with a bicinchoninic acid protein assay (BCA; Kit; Pierce, Rockford, IL), and equal amounts of each sample were analyzed by Western blot, as described previously.<sup>15</sup> The following antibodies were used: anti-integrin  $\alpha_2$  (1:1000; Chemicon, Te-

TABLE 2. PCR Primer Pairs

Genes	Accession Number	Forward Primers	<b>Reverse Primers</b>	Product Size (bp)	Annealing Temp. (°C)
FMOD	NM_002023	5'-GGAAGAGGGGGATCTTTGGAC-3'	5'-CCACCACTCATGCTTTTCCT-3'	199	60
SOD-2	NM_001024466	5'-CGTCACCGAGGAGAAGTACC-3'	5'-CTGATTTGGACAAGCAGCAA-3'	196	59
TGF-B1	NM_000660	5'-GGGACTATCCACCTGCAAGA-3'	5'-CCTCCTTGGCGTAGTAGTCG-3'	239	60
TGF-β2	NM_001135599	5'-CCGGAGGTGATTTCCATCTA-3'	5'-CTCCATTGCTGAGACGTCAA-3'	287	58
TGF-β3	NM_003239	5'-GAGTCAGAGCCCAGCAAAAC-3'	5'-AGAAGGAGGGAGGAAAACCA-3'	246	58
TGFB1	NM_000358	5'-GTGTGTGCTGTGCAGAAGGT-3'	5'-TTGAGAGTGGTAGGGCTGCT-3'	172	58
β-Actin	NM_001101	5'-GGACTTCGAGCAAGAGATGG-3'	5'-AGCACTGTGTTGGCGTACAG-3'	234	58

mecula, CA); anti-TGF- $\beta$  receptors I, II, and III (1:200, 1:200, and 1:100, respectively; Santa Cruz Biotechnology, Santa Cruz, CA); and antifibronectin (1  $\mu$ g/mL; Calbiochem, San Diego, CA). Horseradish peroxidase (HRP)-conjugated anti-mouse IgG or anti-rabbit IgG at 1:5000 were used as secondary antibodies (GE Healthcare, Piscataway, NJ). Immunoblots were developed using enhanced chemiluminescence (ECL) as described by the manufacturer (Pierce, Rockford, IL). Each immunoreactive protein band was image scanned, and optical densities were quantified (ImageJ software, version 1.37; developed by Wayne Rasband, National Institutes of Health, Bethesda, MD; available at http://rsb.info.nih.gov/ij/index.html) and were corrected by background subtraction and normalized to the intensity of the corresponding  $\beta$ -actin protein bands.

## **Cell-ECM Adhesion Profile Assays**

Cell adhesion assays were performed using the ECM cell adhesion array kit (Cytomatrix; Chemicon International) according to the manufacturer's instructions. Nine samples (three samples for each of normal, heterozygous, and homozygous corneal fibroblast) were analyzed, and each experiment was repeated three times.

## **Statistical Analysis**

Results were evaluated for significance (P < 0.05) with one-way ANOVA followed by Newman-Keuls multiple comparison tests. Results are expressed as the mean  $\pm$  SD (Prism ver. 4.0; Graph Pad Software Inc, San Diego, CA).

# RESULTS

# Gene Expression Profiles in Wild-Type and Homozygous GCD II PCFs

The GeneChip Human Gene 1.0 ST Array (Affymetrix) is a whole-transcript analysis chip composed of approximately 29,000 genes. To identify specific genes involved in the pathogenesis of GCD II, we compared the gene expression profiles between primary cultured wild-type and homozygous GCD II corneal fibroblasts. We detected twofold differences in the expression of 555 genes between these two cell types. Of these, 319 of these genes were upregulated and 236 were downregulated in the homozygous GCD II PCFs compared with wild-type (Table 3). Characterization of these genes into ontology groups suggests that GCD II-specific changes largely relate to changes in signal transduction (17%), cell cycle (13%), immune response (13%), cell adhesion (9%), cell differentiation (9%), cytoskeleton (9%), cell proliferation (6%), extracellular space (6%), cell-cell signaling (5%), response to wounding (5%), mitochondrion (2%), ubiquitin cycle (2%), endopeptidase activity (2%), TGF- $\beta$  receptor signaling pathway (1%), integrin-mediated signaling pathway (1%), collagen (1%), and response to oxidative stress (1%) (Fig. 1). Specific genes that were markedly upregulated were IFI44L (43.5-fold, P <0.0017777), IF16 (17.0-fold, P < 0.0002129), SFRP4 (16.5-fold, P < 0.0000311), PDEPDC6 (15.2-fold, P < 0.0000081), JARID1D C3 (15.2-fold, P < 0.0000078), OAS2 (12.9-fold, P < 0.0006065), XAF1 (14.1-fold, P < 0.0005192), STEA2P (10.2fold, *P* < 0.0000087), and *CLDN1* (10.2-fold, *P* < 0.0002109) (Table 4). The most downregulated genes were DDX3Y (-59.9-fold, P < 0.0002855), FBN2 (-47.8-fold, P < 0.0002855)0.0000903), RPS4Y1 (-27.2-fold, P < 0.0000016), EIF1AY (-19.5-fold, P < 0.0014353), RELN (-17.4-fold, P < 0.0014353)0.0001692), USP9Y (-16.3-fold, P < 0.0000009), KRT34 (-12.1-fold, P < 0.0000017), NLGN4Y (-11.8-fold, P < 0.0000017)0.0001143), UTY (-11.2-fold, P < 0.0000027), CYorf15B (-11.1-fold, P < 0.0000012), and CDH6 (-10.2-fold, P < 0.0000012)0.0000005) (Table 5). We next confirmed the differential expression of genes identified by the microarray using RT-PCR. We tested the expression patterns of 10 representative genes in wild-type and homozygous GCD II PCFs and found that their relative expression levels were similar to those identified by the microarray (Figs. 2A, 2B). For example, expression of *FMOD* and *SOD2* was increased in homozygous GCD II PCFs as opposed to that in wild-type cells. Expression of *TGFB1*, *TGFB1*, *TGFB2*, and *TGFB3* was the same in heterozygous GCD II, homozygous GCD II, and wild-type PCFs.

## **Differential Expression of ECM-Associated Genes**

To confirm the ECM affinity data, we next tested the expression of proteins involved in ECM remodeling by Western blot (Figs. 2C, 2D), as we expected that expression levels between wild-type, heterozygous, and homozygous GCD II PCFs would be different. We first investigated the expression patterns of collagen metabolism-related matrix metalloprotease (MMP)-1 and -2, because microarray assay profiles have shown a different expression of MMP-1 and -2. The protein levels of MMP-1 and -2 increased in heterozygous and homozygous GCD II compared with wild-type PCFs (Figs. 2C, 2D). Expression level of integrin  $\alpha_2$ , which is involved in collagen metabolism and cell adhesion, was also increased in heterozygous and homozygous GCD II PCFs. Furthermore, significantly increased protein levels of TGF-B receptors I, II, and III were observed in heterozygous and homozygous GCD II PCFs (Figs. 2C, 2D). These results suggest that the disturbance of ECM metabolism, especially collagen metabolism, is a major factor leading to TGFBIp deposition in corneal ECM of GCD II.

# Increased Affinities for ECM Substrates of GCD II PCFs

We detected altered expression of several ECM component genes (Table 3) in wild-type versus GCD II PCFs. As such, we hypothesized that the adhesive properties of GCD II PCFs may be different from those of wild-type PCFs. To test this, we investigated ECM adhesive properties of GCD II PCFs using an adhesion assay (Cytomatrix; Chemicon International), as described in Materials and Methods. The heterozygous and homozygous GCD II PCFs were more adhesive to collagen-I, collagen-IV, fibronectin, and lamine, than were the wild-type cells (Fig. 3).

# DISCUSSION

In this study, cDNA microarray technology was used to compare the gene expression profiles of homozygous GCD II PCFs to that of wild-type cells, in an attempt to better understand a potential mechanism of GCD II disease. We detected at least a twofold change in expression of 555 genes and confirmed the relative expression levels of a select number of genes by RT-PCR and Western blot analysis. Finally, differences in the cell adhesion properties between GCD II and wild-type PCFs were detected, suggesting that disturbances in ECM-cell adhesion may play an important role in this disease.

# Expression Levels of Genes Involved in the TGF- $\beta$ Signaling Pathway

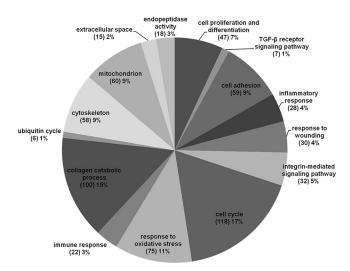
The TGF- $\beta$  signaling pathway has been implicated as a regulator in numerous cellular and physiological processes including ECM homeostasis.<sup>16</sup> The expression of TGF- $\beta$  in corneal fibroblast cultures also suggests that it plays a role in regulating ECM metabolism through the TGF- $\beta$  signaling pathway.<sup>17-19</sup> TGF- $\beta$ initiates signaling through a complex made up of TGF- $\beta$  receptor (T $\beta$ R) I and T $\beta$ RII<sup>20</sup> and signals to the nucleus through the Smads protein.<sup>21</sup> Our results show that T $\beta$ RI, -II, and -III were upregulated in heterozygous and homozygous GCD II PCFs

# TABLE 3. GO Analysis of Genes Up- and Downregulated in GCD II CFBs

		Ge	nes	
GO ID	GO Category	Up	Down	n
GO:0007165	Signal transduction	SFRP4, C3, GRP, TLR3 CXCL5, CXCL6, AHR, DTNA, CCL26, TNFAIP6, F2RL2, TAS2R43, GDF15, LPHN2, TNFRSF10A, TLR4, ANGPT1, TGFBR3, PTGER4, RASSF2, TLR1, ANK2, CLIC2, TNC, MAPK10, PBEF1, RAPH1, IRAK3	ARHGAP118, FGL2, PTGER2 ARHGAP11A, CAMK4, GPSM2, IGFBP5, CXCL12, TRHDE	37
GO:0007267	Cell-cell signaling	IL8, MME, STC1, CXCL5, CXCL6, CCL2, CCL26, TNFAIP6, GDF15, EFNA5 LIF, PBEF1	INHBA, CXCL12, DLG7, TRHDE	15
GO:0007229	Integrin-mediated signaling pathway	ITGB3	ITGA8	2
GO:0005615	Extracellular space	SFRP4, SCG2, GRP, APOL1, IGFBP2, IL8, STC1, CXCL5, CXCL1, CXCL6, CCL2, CFH, CCL26, AKRIB1, CFHR1, MMP3, SULF2, APOD, CXCL2, LGALS3BP, CSF1, GDF15, GREM2, CLU, EFNA5, PLA2R1, WFDC1, LIF, PAPPA, TNFAIP2	BRCA2, GREM1, PSG7, CXCL12, MMP1, PSG5, RELN	37
GO:0030574 O:0001306	Collagen catabolism Response to oxidative stress	MMP3 SOD2, OSGIN2	MMP1	2 2
GO:0007179	Transforming growth factor-beta receptor signaling pathway	GDF15, TGFBR3		2
GO:0007155	Cell adhesion	CLDN1, PCDHB3, CCL2 TNFAIP6, LGALS3BP, ROBO1, CNTNAP2, ITGB3, COL8A1, SRPX, ADAM23, RASSF2, HMCN1, TNC, LAMC2, CASK, THBS3, PCDHB13, NFASC	AEBP1, PCDH18, TROAP, DSG2, HAPLN1, CDH18, CXCL12, NLGN1, EDIL3, CDH6, NLGN4Y, RELN	31
GO:0007156	Homophilic cell adhesion	PCDHB3, ROBO1, PCDHB2 PCDHB4, PCDHB13	PCDH18, CDH10, DSG2, CDH18, CDH6	10
GO:0030155	Regulation of cell adhesion	ICAM1, IL8, LAMA3		3
GO:0006955	Immune response	IF16, OAS2, OAS1, IF127, IFIT3, HLA-DPA1, IL8, CXCL5, CXCL1, CXCL6, DPP4, CCL26, IGJ, IF130, CXCL2, PSMB9, ILIR1, TAP1, PTGER4, HLA-DPB1, MR1, LIF, HLA-E, HLA- C, MICA, IRF1, HLA-E, HLA-C, IFIT5, IFITM3, HLA-B, PSMB8, MICA, HLA-B, HLA-DPB1	EXO1, CXCL12, GBP3	37
GO:0006954	Inflammatory response	C3, SCG2, II.8, TLR3, CXCL5 CXCL1, CXCL6, CCL2, CCL26, TNFAIP6, CXCL2, ILIR1, AOX1, TLR4, EPHX2, TLR1	CXCL12	17
GO:0006958	Complement activation, classic pathway	C3, CIS, SERPING1, CF1, CLU		5
GO:0006956	Complement activation, classic pathway	CFHR1, CFB		2
GO:0002474	Antigen processing and presentation of peptide antigen via MHC class I	HLA-E, HLA-C, MICA, HLA-B, MICA,		5
GO:0019885	Antigen processing and presentation of endogenous	ARTS-1	LRAP	2
GO:0030154	Cell differentiation	SFRP4, FRZB, CSF1, TTLL7, DUSP6, EFNA5, FRK, PAPPA, DCLK1	SEMA3D, BEX1, CENPF, STMN1, ITGA8, PEG10	15
GO:0008283 GO:0008285	Cell proliferation Negative regulation of cell proliferation	CREG1 IL8, CXCL1, RARRES3, FRK, GPNMB	KIF2C, KIF15, TPX2	8 5
GO:0005856	Cytoskeleton	FRMD4B, PLEKHH2, FLG, EPB4IL5, MAP9, RAPH1	PKP2, DSG2, SHROOM3, ACTC1	10
GO:0005739	Mitochondrion	IFIG, OAS2, OAS1, SOD2, AK3L1, ACSL5, PDK3, DMGDH, LACTB, BDH2, BNIP3, SQRDL	KIAA0101	13
GO:0007049	Cell cycle	PDPN, RASSF2, MAP9, MAPK13	SGOL2, FANC1, CDC2, CLSPN, Cl4orf106, UBE2C, C1T, SMC4, RACGAP1, UHRF1, CKS2, CCNF, CDCA8, NCAPD2, WEE1, FBXO5, CENPE, ERCC6L, KIFC1, ESC02, KIF23, SGOLI, KIFC1, CDCA3, PRC1, NDC80, NUSAP1, BUBIB, PLK1, CDCA2, NCAPG, FAM64A, SPC25, CCNB2, CEP55, CDC20, ASPM, ANLN, FOXM1, SPAG5, NUF2, DLG7 (conth	46 nues)

TABLE 3 (continued). GO Analysis of Genes Up- and Downregulated in GCD II CFBs

			Genes	
GO ID	GO Category	Up	Down	n
GO:0051318	G <sub>1</sub> phase	PRUNE2, PRUNE2		2
GO:0007601	Visual perception	GLRB, HMCN1	GJA7	3
GO:0004252	Serine-type endopeptidase activity	CFB, CORIN, PRSS23, CF1	RELN	5
GO:0004867	Serine-type endopeptidase inhibitor activity	SERPING1, SERPIN11, WFDC1	SERPINB7	4
GO:0004190	Aspartic-type endopeptidase activity		PEG10	1
GO:0004222	Metalloendopeptidase activity	ADAM23		1
GO:0030574	Collagen catabolic process	MMP3	MMP1	2
GO:0030199	Collagen fibrit organization	COLI4A1		1
GO:0005581	Collagen	COL14A1		1
GO:0004232	Interstitial collagenase activity		MMP1	1
GO:0007181	Transforming growth factor beta receptor complex assembly	FMOD		1
GO:0007179	Transforming growth factor-beta receptor signaling pathway	GDF15, TGFBR3		2
GO:0030512	Negative regulation of transforming growth factor beta receptor signaling pathway		PEG10	1
GO:0006512	Ubiquitin cycle	FBX032, FBX016, FBXL2	UBE2C, UHRF1, FBX05, CDCA3, CDC20, USP9Y	9
GO:0004842	Ubiquitin-protein ligase activity	FBXL2	UBE2C	2
GO:0009611	Response to wounding	F2RL2, GAP43		2
GO:0006979	Response to oxidative stress	SOD2, PRNP		2
GO:0004364	Glutathione S- transferase activity	GSTM1		1



**FIGURE 1.** Gene ontological classification of differentially regulated genes in homozygous GCD II PCFs. Genes that were differentially expressed at a minimum of twofold were included in the analysis. Numbers in parentheses represent the number of genes.

compared with wild-type. Moreover, we identified different gene expression levels of the T $\beta$ R complex assembly gene (*FMOD*; 3.2-fold increased, P < 0.0000113) in homozygous GCD II PCFs compared with wild-type PCFs (Table 4). This suggests that TGFBIp expression may occur more rapidly in GCD II than in wild-type PCFs under various physiological conditions and could result in accelerated TGFBIp deposition and ultimate GCD II disease. Also, because overexpression of misfolded or mutant proteins could induce protein aggregation or deposition, increased T $\beta$ R expressions may play an important role in exacerbating GCD II pathogenesis. This idea is supported by previous studies in which GCD II was aggravated by TGF- $\beta$  after LASIK surgery.<sup>11,12,22</sup> However, the specific mechanism(s) regarding the increase in T $\beta$ R expression in GCD II corneal fibroblasts remains unknown.

## Differential Expression of Proteolytic Enzymes Involved in ECM Metabolism

T $\beta$ R-mediated signaling stimulates matrix deposition by promoting the expression of components of the ECM such as collagen and suppresses and/or activates proteolytic enzymes such as MMPs, which also degrade collagen.<sup>23,24</sup> Previous studies have shown that expression of abnormal proteoglycan filaments and disruption in collagen organization were present

# TABLE 4. Upregulated Homozygous GCD II-Related Genes

No.	Gene Accession	Gene Symbol	Gene Description	Change	Р
1	NM_006820	IFI44L	Interferon-induced protein 44-like	43.5	0.0017777
2	NM_022872	IFI6	Interferon, alpha-inducible protein 6	17.1	0.0002129
3	NM_003014	SFRP4	Secreted frizzled-related protein 4	16.5	0.0000311
4	NM_022783	DEPDC6	DEP domain containing 6	15.2	0.0000081
5	NM_000064	C3	Complement component 3	15.2	0.0000078
6	NM_002535	OAS2	2'-5'-Oligoadenylate synthetase 2, 69/71kDa	12.9	0.0006065
7	NM_017523	XAF1	XIAP associated factor-1	11.4	0.0005192
8	NM_152999	STEAP2	Six transmembrane epithelial antigen of the prostate 2	10.2	0.0000087
9	NM_021101	CLDN1	Claudin I	10.2	0.0002109
10	NM_016816	OAS1	2',5'-Oligoadenylate synthetase 1, 40/46kDa	9.7	0.0035803
11	ENST00000260184	FLJ20035	Hypothetical protein FLJ20035 (FLJ20035), mRNA	9.7	0.0013714
12	NM_005532	IFI27	Interferon, alpha-inducible protein 27	9.1	0.0003262
13	NM_003469	SCG2	Secretogranin II (chromogranin C)	8.4	0.0000092
14	NM_002091	GRP	Gastrin-releasing peptide	8.3	0.0000031
15	NM_001031683	IFIT3	Interferon-induced protein with tetratricopeptide repeats 3	7.6	0.0061816
16	uc002feh.1	CHST6	Carbohydrate (N-acetylglucosamine 6-O) sulfotransferase 6	7.6	0.0000052
17	NM_139072	DNER	Delta/notch-like EGF repeat containing	7.5	0.0000055
18	NM_080284	ABCA6	ATP-binding cassette, sub-family A (ABC1), member 6	7.3	0.0000006
19	NM_203349	SHC4	SHC (Src homology 2 domain containing) family, member 4	7	0.0000941
20	NM_020299	AKRIBI0	Aldo-keto reductase family 1, member B10 (aldose reductase)	6.9	0.0000183
21	NM_007168	ABCA8	ATP-binding cassette, sub-family A (ABC1), member 8	6.7	0.0001116
22	NM_006417	IFI44	Interferon-induced protein 44	6.7	0.002165
23	NM_033554	HLA-DPA1	Major histocompatibility complex, class II, DP alpha 1	6.6	0.0000318
24	NM_024574	C4orf31	Chromosome 4 open reading frame 31	6.6	0.0000578
25	NM_145343	APOL1	Apolipoprotein L, 1	6.6	0.0001028
26	NM_033554	HLA-DPA1	Major histocompatibility complex, class II, DP alpha 1	6.5	0.0002743
27	NM_033554	HLA-DPA1	Major histocompatibility complex, class II, DP alpha 1	6.5	0.0002743
28	NR_003198	SNORD114-6	Small nucleolar RNA, C/D box 114-6	6.5	0.0000037
29	NM_000597	IGFBP2	Insulin-like growth factor binding protein 2, 36kDa	6.2	0.0005975
30	NM_004163	RAB27B	RAB27B, member RAS oncogene family	6.1	0.0001163
32	NM_000201	ICAM1	Intercellular adhesion molecule I (CD54), human rhinovirus receptor	6	0.0000264
33	NM_000584	IL8	Interleukin 8	5.9	0.0001314
34	NM_021110	COL14A1	Collagen, type XIV, alpha I (undulin)	5.5	0.0000128
35	NM_001024465	SOD2	Superoxide dismutase 2, mitochondrial	5.5	0.0004007
38	NM_003265	TLR3	Toll-like receptor 3	5.3	0.0012359
39	NM_152703	SAMD9L	Sterile alpha motif domain containing 9-like	5.1	0.0005941
40	NM_007288	MME	Membrane metallo-endopeptidase	4.8	0.0000029
41	NM_005907	MAN1A1	Mannosidase, alpha, class IA, member 1	4.7	0.0000526
42	NM_003155	STC1	Stanniocalcin 1	4.7	0.0003264
43	NM_022154	SLC39A8	Solute carrier family 39 (zinc transporter), member 8	4.7	0.0034818
44	NM_139248	LIPH	Lipase, member H	4.6	0.0000636
45	NM_001002264	EPSTI1	Epithelial stromal interaction I (breast)	4.6	0.0019874
46	BC022571	PRUNE2	Prune homolog 2 (Drosophila)	4.5	0.0006296
47	NM_002994	CXCL5	Chemokine (C-X-C motif) ligand 5	4.5	0.001963
48	NM_001511	CXCL1	Chemokine (C-X-C motif) ligand I (melanoma growth stimulating activity, alpha)	4.5	0.006012
49	NM_002538	OCLN	Occludin	4.4	0.00084
50	NM_018937	PCDHB3	Protocadherin beta 3	4.4	0.0000115
51	NM_145172	WDR63	WD repeat domain 63	4.3	0.0000206
52	NM_004585	RARRES3	Retinoic acid receptor responder (tazarotene induced) 3	4.3	0.0002066
53	NM_003739	AKR1C3	Aldo-keto reductase family 1, member C3 (3-alpha hydroxysteroid dehydrogenase, type II)	4.3	0.0000081
54	NM_002993	CXCL6	Chemokine (C-X-C motif) ligand 6 (granulocyte chemotactic protein 2)	4.3	0.0004347
55	NM_016352	CPA4	Carboxypeptidase A4	4.3	0.0000333
56	NM_017554	PARP14	Poly (ADP-ribose) polymerase family, member 14	4.2	0.0019238
57	NM_002982	CCL2	Chemokine (C-C motif) ligand 2	4.2	0.0000148
58	NM_205845	AKR1C2	Aldo-keto reductase family 1, member C2 (dihydrodiol dehydrogenase 2; bile acid binding protein; 3-alpha hydroxysteroid dehydrogenase, type III)	4.2	0.0000279
59	NM_032812	PLXDC2	Plexin domain containing 2	4.1	0.0000003
60	NM_138818	PRUNE2	Prune homolog 2 (Drosophila)	4	0.0000703
61	NM_001935	DPP4	Dipeptidyl-peptidase 4 (CD26, adenosine deaminase complexing protein 2)	4	0.0000083
62	NM_001013442	EPGN	Epithelial mitogen homolog (mouse)	3.9	0.0000298
63	NM_000186	CFH	Complement factor H	3.9	0.0000126
64	NM_014314	DDX58	DEAD (Asp-Glu-Ala-Asp) box polypeptide 58	3.8	0.0033267
65	NM_182767	SLC6A15	Solute carrier family 6, member 15	3.8	0.000131
66	NM_080671	KCNE4	Potassium voltage-gated channel, Isk-related family, member 4	3.7	0.0004738
67	NM_001390	DTNA	Dystrobrevin, alpha	3.7	0.0000589
68	NM_175861	TMTC1	Transmembrane and tetratricopeptide repeat containing 1	3.7	0.0000083
69	NM_006072	CCL26	Chemokine (C-C motif) ligand 26	3.6	0.0000234
70	NM_144646	IGJ	Immunoglobulin J polypeptide, linker protein for immunoglobulin alpha and	3.6	0.0011411
			mu polypeptides		(continues)

# TABLE 4 (continued). Upregulated Homozygous GCD II-Related Genes

1NL.003851CREC1Cellular expressor of E1A-stimulated genes 13.62NL.015703POLOC3.63NM.007115TWAPP6Tumor necrosis factor, alpha-induced protein 63.65NM.016848MIC12Multiple C2 domain, containing transforming protein 33.55NM.01819MIC122Multiple C2 domain, containing it ransforming protein 33.55NM.015123FRMD/DBFERM domain containing 4B3.55NM.015123FRMD/DBFERM domain containing 4B3.55NM.015123LAMA3Laminin, alpha 33.55NM.01528ATTC Minding cascet: sub-family 4 (ABC1), member 93.44NM.01011FZRL2Coaguitation factor II (Irombin) receptor-like 23.44NM.01011FZRL2Coaguitation factor II (Irombin) receptor-like 23.45NM.005028TTKKTRAF2 and NCK Interacting kinase3.55NM.00503NEBLNebulette3.55NM.00503NEBLNebulette3.55NM.00503NEBLNebulette3.55NM.0015EDXNBEndothelin receptor type 13.65NM.00161ERZVSamily conductin receptor-like 23.16NM.010463STEP1Taste receptor, type 2, member 43.57NM.00463STEP1Samily conductin receptor-like 23.17NM.00463STEP1Samily conductin receptor-like 23.1	No.	Gene Accession	Gene Symbol	Gene Description	Change	Р
73       NNL_007115       TVM:4076       Tumor necrosis factor, alpha-induced protein 6       3.6         74       NNL_016848       SHC3       SHC (Src homology 2 domain containing) transforming protein 3       3.5         75       NNL_015125       FRMD49       BERM domain containing 48       3.5         78       NNL_015125       FRMD49       EERM domain containing 48       3.5         78       NNL_015125       FRMD49       EERM domain containing 48       3.5         78       NNL_01512       FRMD49       EERM domain containing 48       3.5         78       NNL_00151       FROM 14       From 15 (alpha)       3.4         78       NNL_015028       TVK       TRAF2 and NCK interacting kinase       3.4         78       NNL_00101       FZRL7       Lexicen rich repeat containing 17       3.3         78       NNL_00035       NFBI       Nebulatine       3.3         78       NNL_00184       IRXEX       Notocharia receptor, type 3, member 43       3.3         78       NNL_00213       FROM0246       FROM0246       3.2         79       NNL_00246       TASEX43       Taste receptor, type 2, member 43       3.5         70       NNL_00246       TASEX43       Taste receptor, type 3		NM_003851		Cellular repressor of E1A-stimulated genes 1		0.000007
74NM_001628ARR1B1Aldoketo reductase family 1, member B1 (aldose reductase)3.575NM_018848MCTP2Multiple C2 domains, transmembrane 23.576NM_01512FREMDAPFREM domain containing itb3.578NM_01512FREMDAPFREM domain containing itb3.578NM_01512FREMDAPFREM domain containing itb3.578NM_080283ABC49ATP-brinding casette, sub-family A (ABC1), member 93.481NM_001315PROMProtein 5 (ajpha)3.483NM_001011FZRL2Coaguitation factors II (thrombin) receptor-like 23.484NM_0010124ATX14Hypotherical protein IOCS41053.385NM_005054LERK17Leucine rich repeat containing 173.386NM_00101924ATX14Hypotherical protein IOCS41063.387NM_006305NEBLTaste receptor, type 2, member 433.380NM_10566SVEPLSub-it cort 1Fcbrate 143.291NM_016246HEDZ1744Hydroxysteroid (17-beta) dehydrogenase 143.292NM_00213FUNDFobromodulin3.293NM_001632FIFLSublicate 23.194NM_00532FIFL30Interferon, gamma-inducible protein 303.195NM_00532FIFL30Interferon, gamma-inducible protein 303.196NM_00532FIFL30Interferon, gamma-inducible protein 303.197NM_00664 <td></td> <td></td> <td></td> <td></td> <td></td> <td>0.0000006</td>						0.0000006
75NM_016848SHC (Sr. bomology 2 domain containing transforming protein 335.76NM_015125FERM 04BFERM domain containing 4B35.77NM_015125FERM 04BFERM domain containing 4B35.78NM_018129LAMA3Laminin, alpha 335.80NM_080284ARC40ATF-binding casette, sub-family A (ABC1), member 934.81NM_000315FEROSTProtein 5 (alpha)34.82NM_01010FZALCoagulation factor II (thrombin) receptor-like 234.83NM_001010FZALCoagulation factor II (Chrombin) receptor-like 234.84NM_010101024MITSTMitochondrial tumor suppressor 135.86NM_00101024MITSTMitochondrial tumor suppressor 135.87NM_002053NEBEndothelin receptor type 1835.88NM_01054ENDAREndothelin receptor type 18.35.90NM_02015EDNAREndothelin receptor type 14.32.91NM_02023FEMDFibromodulin32.92NM_020131GHIR2Suffatase 231.93NM_020242MHIP3Matrix metalloperidase 3 (stromelysin 1, progelatinase)31.94NM_020314GHIR2Batalitase 231.95NM_00242MHIP3Matrix metalloperidase 3 (stromelysin 1, progelatinase)31.96NM_020450FTAP4STEAP family member 432.97NM_002113GETAP4STEAP fa						0.0009063
76       NM_018349       MCTP2       Multiple C2 domains, transmembrane 2       3.5         77       NM_015529       MOXD1       Konnooxygenase, DBHike 1       3.5         78       NM_019529       MOXD1       Monooxygenase, DBHike 1       3.5         78       NM_019529       LMMA3       Laminin, alpha 3       3.5         78       NM_0190284       ABC49       ATP-binding cassette, sub-family A CABC1), member 9       3.4         78       NM_010161       FZR21       Congulation factor II (furombin) receptor-like 2       3.4         78       NM_00101       FZR21       Congulation factor II (furombin) receptor-like 2       3.4         78       NM_00100124       MTX51       Mutchondati tumor suppressor 1       3.5         78       NM_0010304       MEX1       Netheter       1.7       3.5         78       NM_001560       SYEM       Sabaditation factor Rice factor		-				0.000003
7       NN_015123       PRMD04B       FERM domain containing 40       35         75       NN_1198129       LAMA3       Laminin, alpha 3       35         78       NN_0108129       LAMA3       Laminin, alpha 3       35         81       NM_0000313       PROS1       Protein S (alpha)       34         82       NM_01028       T/NK       TRAZ and NCK interacting kinase       34         83       NM_00101       F2RL2       Coagulation factor II (thrombin) receptor-like 2       34         84       NM_01739       Lagr.7/141       Hydrothecial protein to IOCS1103       33         85       NM_0018241       LRRC17       Leucine rich repcat containing 17       33         86       NM_1058844       TASZR43       Taste receptor, type 2, member 43       33         87       NM_01015       EDXMAS       Endedhelin receptor type 1       33         88       NM_002023       FMOD       Fibromodulin       32       34         91       NM_010243       Matrix metallopeptides 3 (stromelysin 1, progelatinase)       31         92       NM_002453       JERZP       Sulfatase 2       31         93       NM_00143       Buttrix metallopeptides 3 (stromelysin 1, progelatinase)       31		—				0.000021 0.000013
78       NM_015529       MOXD1       Monoxygenase, DBH4lke 1       3.5         79       NM_080285       ARCA9       ATTPibniding cassette, sub-family A (ABC1), member 9       3.4         81       NM_001313       PRK01       Protein S (alpha)       3.4         81       NM_001013       PRK02       Protein S (alpha)       3.4         81       NM_001018       PRK12       Congulation factor II (chrombin) receptor-like 2       3.4         81       NM_0017430       Icag7.1314       Hypothetical protein LOCS1103       3.3         81       NM_00101924       MITCS1       Mitochondrial tumor suppressor 1       3.3         81       NM_00115       EDNAB       Endothelin receptor type 1, member 4       3.3         81       NM_00213       FIRIN       Sublectite       3.3         91       NM_00213       FIRIN       Sublectite       3.2         92       NM_00213       FIRIN       Sublectite       3.2         93       NM_00213       FIRIN       Complement factor HyreLated 1       3.2         94       NM_02436       STEL44       STEL4 Pamily member 4       3.2         95       NM_00245       FIRIN       Sublectite       3.1         96       <						0.0000545
79       NM_108129       LAMA3       Laminin_alpha 3       35.5         80       NM_000315       PROS1       Protein S (alpha)       34.4         81       NM_001015       PROS1       Protein S (alpha)       34.4         82       NM_01028       TXIK       TRAT2 and NCK interacting kinase       34.4         83       NM_001011       F2RL2       Coagulation factor II (thrombin) receptor-like 2       34.4         84       NM_0010124       ATK21       Leucine rich repeat containing 17       35.3         85       NM_000533       NERL       Nebulette       35.3         80       NM_000154       ATK21       Stationdria factor type 2, member 4.5       35.3         80       NM_000154       MLV21       Nucloaded factor type 4, EGF and pentraxin domain containing 1       32.2         81       NM_006345       STERP1       Sushi, von Wildbrondria factor the related 1       32.2         81       NM_00634       ATK214       TTKAP family member 4       32.2         81       NM_00634       ATK214       TTKAP family member 4       32.2         81       NM_00634       ATK14       TTKAP family member 4       32.2         81       NM_00634       ATK214       NTKAP family member 4				-		0.0000004
81         NML_000313 <i>PROSI</i> Frotein S (alpha)         5.4           82         NML_004101 <i>P2RL2</i> Coagulation factor II (thrombin) receptor-like 2         3.4           83         NML_005824 <i>LRRC17</i> Leucine rich repeat containing 17         3.5           84         NML_005933 <i>LRRC17</i> Leucine rich repeat containing 17         3.5           85         NML_0005933 <i>NEBL</i> Nebulette         3.5           80         NML_005933 <i>NEBL</i> Nebulette         3.5           80         NML_006154 <i>EDNRB</i> Endothelin receptor type 3.         3.6           81         NML_016346 <i>HSD17B14</i> Hydroxysteroid (17-beta) dehydrogenase 14         3.2           91         NML_016346 <i>HSD17B14</i> TREV family member 4         3.2           92         NML_00245 <i>HML</i> 4         TREV family member 4         3.2           93         NML_017841 <i>BHMT2</i> Batase 2         3.1           94         NML_017841 <i>BHMT2</i> Batase 2         3.1           97         NML_017841 <i>BHMT2</i> Batase 2         3.1           98         NML_017841 <td></td> <td></td> <td></td> <td></td> <td></td> <td>0.0000003</td>						0.0000003
12NN_015028TVKTRAF2 and $\hat{N}$ CK interacting kinase3.48NN_00101 <i>IZL2</i> Cogulation factor (I (knombin) receptor-like 23.48NN_001001924 <i>IRRC17</i> Leucine rich repeat containing 173.38NN_001001924 <i>MTUS1</i> Mitochondrial tumor suppressor 13.38NN_175884 <i>IZRL2</i> Taste receptor, type 2, member 433.38NN_00105 <i>EDNBB</i> Endothelin receptor type 13.39NN_0015 <i>EDNBB</i> Endothelin receptor type 3, EG and pentraxin domain containing 13.220NN_002023 <i>FMOD</i> Fibromodulin3.221NN_004024 <i>MIP3</i> Matrix metallopeptidase 3 (stromelysin 1, progelatinase)3.123NN_004035 <i>ILPL2</i> Sulfatase 23.124NN_004036 <i>ILPL2</i> Sulfatase 23.125NN_004036 <i>ILPL2</i> Sulfatase 23.126NN_004036 <i>ILPL2</i> Complement factor H-related 13.237NN_004036 <i>ILPL2</i> Sulfatase 23.138NN_006332 <i>ILPL2</i> Sulfatase 23.139NN_004036 <i>ILPL2</i> Fitzederetated protein3.130NN_004036 <i>ILPL2</i> Complement factor H3.130NN_004037 <i>LPL2</i> Charderetar 0.23.030NN_004037 <i>LPL2</i> Charderetar 0.23.030NN_004057 <i>LPL2</i> Apolipoprotein 7023.030NN_004057 <i></i>	80	NM_080283	ABCA9	ATP-binding cassette, sub-family A (ABC1), member 9	3.4	0.0002608
88       NN_001101 <i>F2RL2</i> Coagulation factor II (thrombin) receptor-like 2       3.4         84       NN_005824 <i>LRRC17</i> Leucine rich repeat containing 17       3.3         85       NN_00001924 <i>HTVS1</i> Nictochondrial tumor suppressor 1       3.3         87       NN_0001924 <i>HTVS1</i> Nictochondrial tumor suppressor 1       3.3         88       NN_17684 <i>TAS2R43</i> Taste receptor, type 2, member 43       3.3         89       NN_01556 <i>SVLP1</i> Subi, von Wilbennd factor type A, EGF and pentraxin domain containing 1       3.2         91       NN_016246 <i>HSD17B1/4</i> Hydroxysteroid (17-beta) dehydrogenase 14       3.2         92       NN_002423 <i>HMP</i> Matrix metallopeptidaes 3 (stromelysin 1, progelatinase)       3.1         93       NN_016466 <i>STR24</i> MTRP family member 4       3.1         94       NN_001632 <i>HFR2</i> Butiatase 2       3.1         97       NN_001633 <i>HR2</i> Betaine-homocysteine methyltransferase 2       3.1         98       NN_00632 <i>HFR2</i> Britzed-refacted protein       3.1         91       NN_001632 <i>HFR2</i> Frizzed-refacted protein 30       3.1	81	NM_000313	PROS1	Protein S (alpha)	3.4	0.0000002
84NN_017439 <i>Icag</i> 7.1314Hypothetical protein LOCS11033.385NN_001001924 <i>MTUS1</i> Mitochondrial tumor suppressor 13.386NN_005039 <i>NEBL</i> Nebulette3.387NN_005039 <i>NEBL</i> Nebulette3.388NN_175884 <i>TASLR43</i> Taste receptor, type 2, member 433.389NN_00015 <i>EDNRB</i> Endochelin receptor type 13.390NN_016266 <i>HSDP11H</i> Hyperoxysteroid (17-Deta) delydrogenase 143.291NN_016266 <i>HSDP11H</i> Hyperoxysteroid (17-Deta) delydrogenase 143.292NN_002023 <i>FMOD</i> Fibromodulin3.293NN_0020242 <i>MHP3</i> Matrix merallopeptidase 3 (stromelysin 1, progelatinase)3.196NN_018837 <i>SLLP2</i> Sulfarase 23.197NN_01614 <i>HHT2</i> Berlame-bonocysteine methyltransferase 23.198NN_006332 <i>HR30</i> Interferon, gamma-inducible protein 303.199NN_001463 <i>FR2B</i> Frizzder drated protein3.1100NN_201463 <i>FR2B</i> Frizzder drated protein 7023.0101NN_001710 <i>CRB</i> Complement factor B3.0103NN_175567 <i>AHD7</i> Abydrokase domain containing 73.1104NN_001637 <i>ZPD72</i> Zic chemokane (C.X-C motil) ligand 23.0105NN_00579 <i>FL2B</i> Chemokane (C.X-C motil) ligand 23.0106NN_00570 <i>HZD153</i> Hypothe				6		0.0016728
85       NM_0001924 <i>LR</i> C17       Leicher fich 'repeat containing 17       3.3         86       NM_0001924 <i>LR</i> C17       NC       3.3         87       NM_000393 <i>NEBL</i> Nebulette       3.3         88       NM_170841 <i>LASZR43</i> Taste receptor, type 2, member 43       3.3         89       NM_015566 <i>SVPI</i> Tsubi, von Wilbernon factor type A, EGF and pentraxin domain containing 1       3.2         91       NM_016246 <i>IEDJ7B14</i> Hydroxysteroid (17-beta) dehydrogenase 14       3.2         93       NM_002423 <i>IMU</i> O <i>IFDromodulin</i> 3.2         94       NM_004666 <i>STLP4</i> STR24 Partily member 4       3.2         95       NM_00521 <i>IFI2</i> Sulfase 2       3.1         96       NM_01633 <i>IFI2</i> Butfase 2       3.1         97       NM_001643 <i>FRZB</i> Frizzled-related protein       3.1         98       NM_00532 <i>IFI3</i> Interferon, gamma-inducible protein 30       3.1         91       NM_01645 <i>FRZB</i> Frizzled-related protein       3.1         91       NM_00570 <i>CRD</i> Aphydrolase domain containing 7       3.1		_				0.0000043
86       NN_0000939       MTUS1       Mitochondrial tumor suppressor 1       3.3         87       NN_006939       NEH       Nebulette       3.3         88       NN_1758844       TAS2R43       Taste receptor, type 2, member 43       3.3         90       NN_00015       EDNRB       Endothelin receptor type 4       EGF and pentraxin domain containing 1       3.2         91       NN_016246       HSD/7B/4       Hydroxysteroid (7/2beta) dehydrogenase 14       3.2         92       NN_002023       FMOD       Fibromodulin       3.2         93       NN_002023       FMOD       Fibromodulin       3.2         94       NN_016246       HSTEAP family member 4       3.2         95       NN_0043837       SULP2       Sulfnase 2       3.1         96       NN_00438       FR2B       Fitzcle-related protein       3.1         97       NN_01463       FR2B       Fitzcle-related protein       3.1         98       NN_00438       FR3D       Complement factor B       3.1         90       NN_01463       FR2B       Fitzcle-related protein       3.1         100       NN_201463       FR2D       Apolipoprotein D       3.0         101       NN_005474			0			0.0007954
87NM_006393NEBLNebulette3.388NM_108841TASZR43Taste receptor, type 2, member 433.389NM_000115EDNRBEndothelin receptor type 83.390NM_15366JSVEP1Subi, von Wildbrand factor type A, EGF and pentraxin domain containing 13.291NM_016346HSD17B14Hydroxysteroid (17-beta) dehydrogenase 143.292NM_002033FMODFibromodulin3.293NM_02113CHIR1Complement factor H-calatel 13.294NM_024636STEAP4STEAP faulty member 43.295NM_001422MMP3Matrix metallopeptidase 3 (stromelysin 1, progelatinase)3.196NM_001435FEZBFrazkedreitated protein3.197NM_00143FEZBFrazkedreitated protein3.198NM_00143FEZBComplement component 1, s subcomponent3.190NM_00143FEZBComplement factor B3.1910NM_001710CRBComplement factor B3.0910NM_001647APODApolipoprotein D3.0910NM_001647APODApolipoprotein D3.0910NM_001030FEZIFasciculation and elongation protein zeta 1 (zygin 1)2.9910NM_000306SAMP25Sterike aphysicular protein F1J30333.0910NM_000306SAMP25Sterike aphysicular protein f1230333.0911NM_000306SAMP25Sterike aphysicular pro		-				0.0000081
88       NNL 1768841       Taste receptor, type 2, member 43       33         90       NNL 153366       SVEP1       Sushi, von Willebrand factor type A, EGF and pentraxin domain containing 1       3.2         91       NNL 106246       HSDTB/14       Hydroxysteroid (7)Peta) dehydrogenase 14       3.2         92       NNL 002035       FMOD       Fibromodulin       3.2         93       NNL 002042       MMP       STEAP 4       STEAP 4         94       NNL 024636       STEAP 4       STEAP 5       STEAP 4         95       NNL 002422       MMP3       Matrix menallopeptidise 3 (stromelysin 1, progelatinase)       3.1         96       NNL 017614       BILMT2       BetaineFonomyosteine methyltransferase 2       3.1         97       NNL 001463       FRZB       Frizzle4related protein       3.1         98       NNL 00532       IFBX 052       Ebox protein 32       3.1         101       NNL 058229       FRX 052       Ebox protein 32       3.0         102       NNL 00167       APDD       Abplipoprotein D       3.0         103       NNL 00167       APDD       Abplipoprotein D       3.0         104       NNL 00167       FVDD       Abplipoprotein D       3.0		- ,				0.0002024
89     NNL_000115     ED/R/B     Endothelin receptor type B     33       91     NNL_016246     HSD17B14     Hydroxysteroid (17-beta) dehydrogenase 14     32       92     NNL_002035     FM/OD     Fibromodulin     32       93     NNL_016246     HSD17B14     Hydroxysteroid (17-beta) dehydrogenase 14     32       94     NNL_002135     CHRI     Complement factor Hr-clatted 1     32       95     NNL_002422     MMP3     Matrix metallopeptidase 3 (stromelysin 1, progelatinase)     31       96     NNL_003422     HMP3     Matrix metallopeptidase 3 (stromelysin 1, progelatinase)     31       97     NNL_003422     HZP2     Sulfatase 2     31       98     NNL_003423     HZ90     Interferon, gamma-inducible protein 30     31       100     NNL_01463     HZB     Crigothydrogenase domain containing 7     31       101     NNL_003542     HZ032     Fbox protein 32     30       102     NNL_001617     APD/D     Apolipoprotein 70     30       103     NNL_17567     ABI/D7     Abiydrolase domain containing 7     31       104     NNL_0005474     PDPN     Podoplanin     30       105     NN_000578     Z/F702     Xine finger protein 702     30       106     NN_						0.0000077 0.0015163
90NM_153366SVEP1Sushi, von Wilkebranf factor type A, EGF and pentraxin domain containing 13.291NM_002023FMODFibromodulin3.293NM_002113CFHR1Complement factor Hr-clatted 13.294NM_024636STEAP4STEAP family member 43.295NM_002422MHP3Matrix metallopeptidase 3 (stromelysin 1, progelatinase)3.196NM_018837SUL72Sulfarase 23.197NM_00532IFJ30Interferon, gamma-inducible protein 303.198NM_006532IFJ30Interferon, gamma-inducible protein 303.199NM_001652FRZBFrizzled-related protein 103.1101NM_058229FBX032Fbox protein 323.1103NM_01677ABHD7Abhydrolase domain containing 73.1104NM_00647APDDApolipoprotein D3.0105NR_003578ZNF702Zinc finger protein 7023.0106NM_001047APDNYelodynain3.0107NM_0010360CXC12Chemokine (CX-C moti) ligand 23.0108NM_108550CXD957Firzielatin and forgation protein affarme 633.0109NM_001032677FIJ31033Hypothetical protein FIJ310333.0110NM_00103060SERPING1Serpin peptidase inhibitor, clade G (C1 inhibitor), member 1, (angioedema, hypothetical protein FIJ325801 (FIJ25801, mRNA2.9117NM_00062SERPING1Serpin peptidase inhibitor			-			0.0010103
91NM_016246HSD17B14Hydroxysteroid (17-beta) dehydrogenase 143227NM_002113CHRLComplement factor H-related 13228NM_002113CHRLComplement factor H-related 13229NM_00422MMP3Matrix metallopeptidase 3 (stromelysin 1, progelatinase)3131Matrix metallopeptidase 3 (stromelysin 1, progelatinase)3137NM_016357SUL72Sulfatase 23138NM_006352IF30Interferon, gamma-inducible protein 303139NM_00163FRZBFrizzled-related protein3130NM_01645FRZBFrizzled-related protein 323131NM_01710CFBComplement factor B3131NM_001647APODApolipoprotein D3030NM_002674PDDApolipoprotein D3030NM_002677EXF702Zinc finger protein 7023030NM_002689CL20rf63Chromosome 12 open reading frame 6330311NM_0026057EZ/415Fasciculation and clogation protein zeta 1 (zygin 1)29311NM_0006274FLJ51033Hypothetical protein 17J510330311NM_000667FLJ510763Fasciculation and clogation protein zeta 1 (zygin 1)20312NM_001012667FLJ510733Hypothetical protein 15D330313NM_00062754FLJ510763FLJ52501 (FLJ52501), mRNA29314NM_0005567IZM4157Gomplement factor 15 <td></td> <td></td> <td></td> <td></td> <td></td> <td>0.0000004</td>						0.0000004
92NM_002023FMODFibromodulin3-193NM_002113CFHR1Complement factor H-related 13-294NM_024636STEAP4STEAP family member 43-295NM_002422MMP3Matrix metallopeptidaes 3 (stromelysin 1, progelatinase)3-196NM_018837SUL72Sulfatase 23-197NM_00632IFR30Interferon, gamma-inducible protein 303-198NM_00632IFR30Interferon, gamma-inducible protein 303-199NM_001663FRZBFrizzled-related protein 103-1101NM_58229FBX032Fbox protein 323-1103NM_173567ABHD7Abhydrolase domain containing 73-1104NM_001647APODApolipoprotein D3-0105NR_003578ZNF702Zinc finger protein 7023-0106NM_006474PDPNPodoplanin3-0107NM_0089CL22Chemokine (C-XC motif) ligand 23-0108NM_0089578ZNF415Zinc finger protein 1203-0109NM_00103060SAMD5Sterlie alpha motif domain containing 52-9118NM_0003060SAMD5Sterlie alpha motif domain containing 52-9118NM_0003326754FJJ25801Hypothetical protein FJJ25801, mRNA2-9118NM_001372CSerJ15Sterlie alpha motif domain containing 52-9119NM_0013628BJG4LNTTEeta1, 3-Ascertygalactosaminyftransferase 1						0.0000521
99NN_002113 94CHERI NN_024636CHERI STEAP family member 43295NM_002462MHP3 Matrix metallopeptidase 3 (stromelysin 1, progelatinase)3.196NM_018857SULP2 SULP2Sulfatase 23.197NN_016514BHM72 BHM72Betaine-homocysteine methyltransferase 23.198NN_006532IFI30Interferon, gamma-inducible protein 303.1100NN_001656FRZB Frizled-related protein3.1101NN_02142CISComplement component 1, s subcomponent3.1102NN_001657FRZB Frizled-related protein 323.1103NM_17567ABHD7Abbiydrolase domain containing 73.1104NN_001647APOD Apolipoprotein D3.0105NR_002878ZMF702Zine finger protein 7023.0106NM_006474PDPN POdoplanin9.0107NM_002089CCL22Chemosine (CX-C motil) ligand 23.0108NM_018555ZJ#115Zine finger protein 7023.0110NM_00102967FJJ1033Hypothetical protein FJJ510333.0111NM_000503FEZ1Fasciculation and clogation protein zeta 1 (zygin 1)2.9112NM_000062SERPINGSerpin peptidase inhibitor, clade G (C1 inhibitor), member 1, (angioedema, Lerctin, galactoside-binding, soluble, 3 binding protein2.9112NM_0000526754ILJ25801Hypothetical protein FJ25801 (FJ25801), mRNA2.9115NM_0000		-				0.0000113
94       NM.024636       STEAP 4       Standard 1000000000000000000000000000000000000	-	—				0.0004559
96NNL018887SULT2Sulfarase 2Sulfarase 2Sulfar			STEAP4	•	3.2	0.0013693
97NM_017614BHMT2Betaine-homocysteine methyltransferase 23.198NM_006332IFJ30Interferon, gamma-inducible protein 303.198NM_001403FRZBFrizzled-related protein3.1100NM_201442C1SComplement component 1, s subcomponent3.1101NM_058229FRX032Fbox protein 323.1102NM_01170CFBComplement factor B3.1103NM_175567ABHD7Abhydrolase domain containing 73.1104NM_001647APODApolipoprotein D3.0105NR_003578ZVF702Zinc finger protein 7023.0106NM_0012089CXCL2Chemokine (CxXC motif) ligand 23.0107NM_98520CL20rf03Hypothetical protein Fl310333.0108NM_198520CL20rf03Hypothetical protein Fl310333.0109NM_0013067FLJ31033Hypothetical protein Fl310333.0110NM_00503FEZ1Fasciculation and elongation protein zeta 1 (zygin 1)2.9123NM_00062SERPING1Serpin peptidase inhibitor, clade G (C1 inhibitor), member 1, (angioedema, hereditary)2.9114ENST00000326754FL/25801Hypothetical protein fly25801 (FL/25801), mRNA2.9115NM_000580ALDH1A1Aldehyde dehydrogenase 1 family, member A12.9116NM_000580ALDH1A1Aldehyde dehydrogenase 1 family, member A12.9117NM_0005867FL/25801Growth	95	NM_002422	MMP3	Matrix metallopeptidase 3 (stromelysin 1, progelatinase)	3.1	0.0000206
98NM_006332 <i>IFI30</i> Interferon, gamma-inducible protein 303.199NM_001463 <i>FRZB</i> Frizzled-related protein3.1100NM_201442 <i>C1S</i> Complement component 1, s subcomponent3.1101NM_058229 <i>FBX032</i> Fbxo protein 323.1102NM_001710 <i>CFB</i> Complement factor B3.1103NM_173567 <i>ABHD7</i> Abhydrolase domain containing 73.0104NM_001647 <i>APDD</i> Apolioportein D3.0105NR_003578 <i>ZNF702</i> Zinc finger protein 7023.0106NM_006474 <i>PDPN</i> Podoplanin3.0107NM_002089 <i>CXL2</i> Chemokine (CX-C motil) ligand 23.0108NM_0112857 <i>LJST63</i> 3.0119NM_00103060 <i>FZJ1</i> Fasciculation and elongation protein zeta 1 (zygin 1)2.9121NM_000062 <i>SAMD5</i> Sterile alpha motif domain containing 52.9121NM_0000326754 <i>FLJ25801</i> Hypothetical protein FLJ25801 (FLJ25801), mRNA2.9125NM_00036754 <i>FLJ25801</i> Hypothetical protein FLJ25801) (FLJ25801), mRNA2.9126NM_00757 <i>GKH13</i> Aldehyde dehydrogenase 1 family, member A12.9127NM_000689 <i>ALDH1A1</i> Aldehyde dehydrogenase 1 family, member A12.9128NM_00757 <i>CFH15</i> Growth differentiation factor 152.9129NM_001710 <i>CFB</i> Complement factor B2.9121NM_000757 <td>96</td> <td>NM_018837</td> <td>SULF2</td> <td>Sulfatase 2</td> <td>3.1</td> <td>0.0000052</td>	96	NM_018837	SULF2	Sulfatase 2	3.1	0.0000052
99NM_001463FRZBFrizzled-related protein3.1100NM_201442C1SComplement component 1, s subcomponent3.1101NM_058229FBX032Fbxo protein 323.1102NM_01710CFBComplement factor B3.1103NM_173567ABHD7Abhydrolase domain containing 73.1104NM_001647APODApolipoprotein D3.0105NM_003578ZNF702Zinc finger protein 7023.0106NM_006474PDPNPodoplanin3.0107NM_008520C120rf03Chromosome 12 open reading frame 633.0108NM_198520C120rf03Chromosome 12 open reading frame 633.0109NM_001012967FIJ31033Hypothetical protein FIJ310333.0111NM_000503FEZIFasciculation and elongation protein zeta 1 (zygin 1)2.9113NM_000060SAMD5Sterlie lapha motif domain containing 53.9114ENST00000326754FIJ25801FIJ25801 (FIJ25801), mRNA2.9115NM_0005567IGAL33BPLectin, galactoside-binding, soluble, 3 binding protein2.9116NM_000757CSF1Colony stimulating factor 1 (macrophage)2.9117NM_000757CSF1Colony stimulating factor 1 (TMEM144), mRNA2.8128NM_01710CFBComplement factor B2.9129NM_001757CSF1Colony stimulating factor 1 (macrophage)2.9120NM_001757 </td <td>97</td> <td>NM_017614</td> <td>BHMT2</td> <td>Betaine-homocysteine methyltransferase 2</td> <td></td> <td>0.0000017</td>	97	NM_017614	BHMT2	Betaine-homocysteine methyltransferase 2		0.0000017
						0.0000761
101         NM_001710 <i>CFB</i> Complement factor B         3.1           102         NM_001710 <i>CFB</i> Complement factor B         3.1           103         NM_173567 <i>ABHD7</i> Abhydrolase domain containing 7         3.1           104         NM_001647 <i>APOD</i> Apolipoprotein D         3.0           105         NR_003578 <i>ZNF702</i> Zinc finger protein 702         3.0           106         NM_005474 <i>PDPN</i> Podoplanin         3.0           107         NM_002089 <i>CXCL2</i> Chemokine (CX-C motif) ligand 2         3.0           108         NM_198520 <i>C120763</i> Chromosome 12 open reading frame 63         3.0           108         NM_001012967 <i>FLJ31033</i> Hypothetical protein FLJ31033         3.0           110         NM_001030060 <i>SAMD5</i> Serrile alpha motif domain containing 5         2.9           113         NM_000062 <i>SERPINCI</i> Beaci-Li3-Nacetylgalactosaminyltransferase 1 (globoside blood group)         2.9           114         ENST0000526754 <i>FLJ25801</i> Hyzothetical protein fLJ25801 (FLJ25801), mRNA         2.9           117         NM_000688 <i>BGALNTTI</i>				1		0.0012231
102         NM_01710 <i>GFB</i> Complement factor B         3.1           103         NM_173567 <i>ABHD7</i> Abhydrolase domain containing 7         3.1           104         NM_001647 <i>APOD</i> Apolipoprotein D         3.0           105         NR_003578 <i>ZNF702</i> Zinc finger protein 702         3.0           106         NM_000289 <i>CXCL2</i> Chemokine (CX-C motif) ligand 2         3.0           107         NM_00112967 <i>FUJ3103</i> Hypothetical protein FJ31033         3.0           108         NM_01012957 <i>FUJ3103</i> Hypothetical protein FJ31033         3.0           111         NM_0013006 <i>FEZ1</i> Fasciculation and elongation protein zeta 1 (zygin 1)         2.9           112         NM_00130062 <i>SERPIN51</i> Sterpin peptidase inhibitor, clade G (CL inhibitor), member 1, (angioedema, hereditary)         2.9           114         ENT00000326754 <i>FUJ25801</i> Hypothetical protein FIJ25801 (FUJ25801), mRNA         2.9           115         NM_000580 <i>ABGALNTI</i> Beta1, 5-Nacetylgalctosaninyltransferase 1 (globoside blood group)         2.9           116         NM_000587 <i>CALJSBP</i> Lecttin, galctoside-binding, soluble, 3 binding protein <td></td> <td>—</td> <td></td> <td></td> <td></td> <td>0.0000036</td>		—				0.0000036
103NM_173567ABHD7Abhydrolase domain containing 73.1104NM_001647APODApolipoprotein D3.0105NR_003578ZNF702Zinc finger protein 7023.0106NM_002089CXCL2Chemokine (CX-C motif) ligand 23.0107NM_002089CZ20763Chromosome 12 open reading frame 633.0108NM_018355ZNF45Zinc finger protein 4153.0109NM_001012967FIJ31033Hypothetical protein FIJ310333.0111NM_0018355ZNF415Zinc finger protein 4153.0112NM_00103006SAMD5Sterlie alpha motif domain containing 52.9113NM_000062SERPING1Serpin peptidase inhibitor, clade G (C1 inhibitor), member 1, (angioedema, hereditary)2.9114ENST00000326754FIJ25801Hypothetical protein FIJ25801 (FIJ25801), mRNA2.9115NM_0005567LGAUS32PLectin, galactoside-binding, soluble, 3 binding protein2.9117NM_000689ALDH1A1Aldehyde dehydrogenase 1 family, member A12.9118NM_000757CSF1Colony stimulating factor 1 (macrophage)2.9120NM_0018322LGMU332CGorf132Cas121NM_001710CFBGomplement factor B2.9122NM_012302LPHX2Latrophilin 22.8233NM_018242JEAKHD24Paraneoplastic atrigen MA22.8244NM_007257DIKA433DIRA5 family, GTP-binding fasHile			-			0.0000464
104NM_001647 $APOD$ Apolipoprotein D3.0105NR_003578 $ZNF702$ Zinc finger protein 7023.0106NM_000578 $ZNF702$ Zinc finger protein 7023.0107NM_002089 $CXCL2$ Chemokine (C-X-C motif) ligand 23.0108NM_198520 $CL2orf63$ Chromosome 12 open reading frame 633.0109NM_001012967 $FIJ31033$ Hypothetical protein FIJ310333.0110NM_005103 $FEZI$ Fasciculation and elongation protein zeta 1 (zygin 1)2.9112NM_001030060 $SAMD5$ Sterile alpha motif domain containing 52.9113NM_000062 $SERPING1$ Serpin peptidase inhibitor, clade G (C1 inhibitor), member 1, (angioedema, 2.9 $hereditary)$ 114ENT00000326754 $FIJ25801$ Hypothetical protein FIJ25801 (FIJ25801), mRNA2.9115NM_001038628 $B3GALNT$ Beta-1.5-Nacetyglactosamiyftransferase 1 (globoside blood group)2.9116NM_000567 $IGAL33BP$ Lectin, galactoside-binding, soluble, 3 binding protein2.9118NM_000757 $CSFI$ Colony stimulating factor 1 (macrophage)2.9120NM_00113732 <i>CBoT138</i> Chromosome 6 open reading frame 1382.9121NM_001013732 <i>LPHV2</i> Latrophilin 22.8122NM_012302 <i>LPHV2</i> Latrophilin 22.8123NM_183376ARRDC4Arrestin domain containing fame 1382.8124NM_00757DIRA43DIRA5 family, GTP-				*		0.0011518
				, –		0.0016296 0.0048695
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$				* * *		0.0003033
						0.0000074
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111NM_00103FEZ1Fasciculation and elongation protein zeta 1 (zygin 1)2.9112NM_001030060SAMD5Sterile alpha motif domain containing 52.9113NM_000062SERPING1Serpin peptidase inhibitor, clade G (C1 inhibitor), member 1, (angioedema, hereditary)2.9114ENST00000326754FLJ25801Hypothetical protein FLJ25801 (FLJ25801), mRNA2.9115NM_001038628B3GALNT1Beta-1,3-N-acetylgalactosaminyltransferase 1 (globside blood group)2.9116NM_005567LGALS3BPLectin, galactoside-binding, soluble, 3 binding protein2.9117NM_000689ALDH1A1Aldehyde dehydrogenase 1 family, member A12.9118NM_001757CSF1Colony stimulating factor 1 (macrophage)2.9120NM_001710CFBComplement factor B2.9121NM_001013732C6orf138Chromosome 6 open reading frame 1382.9122NM_012302LPHN2Latrophilin 22.8123NM_183376ARRDC4Arrestin domain containing 42.8124NM_007257PNMA2Paraneoplastic antigen MA22.8125ENST0000296529TMEM144Transmembrane protein 144 (TMEM144), mRNA2.8126NM_052831C6orf192Chromosome 6 open reading frame 1922.8127NM_004675DIRAS family, GTP-binding RAS-like 32.8128NM_172069PLEKHH2Pleckstrin homology domain containing, family H (with MyTH4 domain)2.8129NM_018	.09	NM_001012967	0	· ·	3.0	0.0010071
112NM_001030060SAMD5Sterile alpha motif domain containing 52.9113NM_000062SERPING1Serpin peptidase inhibitor, clade G (C1 inhibitor), member 1, (angioedema, hereditary)2.9114ENST00000326754FLJ25801Hypothetical protein FLJ25801 (FLJ25801), mRNA2.9115NM_001038628B3GALNT1Beta-1,3-N-acetylgalactosaminyltransferase 1 (globoside blood group)2.9116NM_005667LGALS3BPLectin, galactoside-binding, soluble, 3 binding protein2.9117NM_000689ALDH1A1Aldehyde dehydrogenase 1 family, member A12.9118NM_000757CSF1Colony stimulating factor 1 (macrophage)2.9120NM_00113752Cforf138Growth differentiation factor 152.9121NM_00113752Cforf138Chromosome 6 open reading frame 1382.9122NM_012302LPHN2Latrophilin 22.8123NM_183376ARRDC4Arrestin domain containing 42.8124NM_007257PNMA2Paraneoplastic antigen MA22.8125ENST00000296529TMEM144Transmembrane protein 144 (TMEM144), mRNA2.8126NM_052831Cfoorf192Chromosome 6 open reading frame 1922.8127NM_004675DIRAS3DIRAS family, GTP-binding RAS-like 32.8128NM_172069PLEKHH2Pleckstrin homology domain containing, family H (with MyTH4 domain) member 22.8129NM_182969XRRA1X-ray radiation resistance associated 12	10	NM_018355	ZNF415	Zinc finger protein 415	3.0	0.0001087
113NM_000062SERPING1Serpin peptidase inhibitor, clade G C1 inhibitor), member 1, (angioedema, hereditary)2.9 hereditary)114ENST00000326754FLJ25801Hypothetical protein FLJ25801 (FLJ25801), mRNA2.9115NM_001038628B3GALNT1Beta 1, 3-Naccetylgalactosaminyltransferase 1 (globoside blood group)2.9116NM_005567LGALS3BPLectin, galactoside-binding, soluble, 3 binding protein2.9117NM_000689ALDH1A1Aldehyde dehydrogenase 1 family, member A12.9118NM_000757CSF1Colony stimulating factor 1 (macrophage)2.9120NM_00113732C6orf138Chromosome 6 open reading frame 1382.9121NM_00113732Loforf138Chromosome 6 open reading frame 1382.8123NM_183376ARRDC4Arrestin domain containing 42.8124NM_007257PNMA2Paraneoplastic antigen MA22.8125ENST00000296529TMEM144Transmebrane protein 144 (TMEM144), mRNA2.8126NM_04675DIRAS3DIRAS family, GTP-binding RAS-like 32.8129NM_182969XRRA1X-ray radiation resistance associated 12.8130NM_017549EPDR1Ependymin related protein 1 (zebrafish)2.8131NM_017549EPDR1Ependymin related protein 1 (zebrafish)2.8133NM_004827ABCG2ATP-binding cassette, sub-family G (WHITE), member 22.7134NM_003543HISTIH4HHistone cluster 1, H4h	11	NM_005103	FEZ1			0.0013669
Intereditary)Intereditary)114ENST00000326754FIJ25801Hypothetical protein FIJ25801 (FIJ25801), mRNA2.9115NM_00138628B3GALNT1Beta-1,3-N-acetylgalactosaminyltransferase 1 (globoside blood group)2.9116NM_005567IGALS3BPLectin, galactoside-binding, soluble, 3 binding protein2.9117NM_000689ALDH1A1Aldehyde dehydrogenase 1 family, member A12.9118NM_000757CSF1Colony stimulating factor 1 (macrophage)2.9119NM_004864GDF15Growth differentiation factor 152.9120NM_001710CFBComplement factor B2.9121NM_001013732C6orf138Chromosome 6 open reading frame 1382.9122NM_012302LPHN2Latrophilin 22.8123NM_183376ARRDC4Arrestin domain containing 42.8124NM_007257PNMA2Paraneoplastic antigen MA22.8125ENST00000296529TMEM144Transmembrane protein 144 (TMEM144), mRNA2.8126NM_05567DIRAS3DIRAS family, GTP-binding RAS-like 32.8127NM_004675DIRAS3DIRAS family, GTP-binding RAS-like 32.8128NM_172069PLEKHH2Pleckstrin homology domain containing, family H (with MyTH4 domain) member 22.8129NM_182969XRRA1X-ray radiation resistance associated 12.8131NM_003844AK3L1Adenylate kinase 3-like 12.8133NM_003844 <td>12</td> <td></td> <td></td> <td></td> <td></td> <td>0.0003825</td>	12					0.0003825
115NM_001038628 $B_3^3GALNT1$ Beta-1,3-N-acetylgalactosaminyltransferase 1 (globoside blood group)2.9116NM_005567 $LGAL33BP$ Lectin, galactoside-binding, soluble, 3 binding protein2.9117NM_000689 $ALDH1A1$ Aldehyde dehydrogenase 1 family, member A12.9118NM_000757 $CSF1$ Colony stimulating factor 1 (macrophage)2.9120NM_001710 $CFB$ Growth differentiation factor 152.9121NM_0013732 $C6orf138$ Chromosome 6 open reading frame 1382.9122NM_012302 $LPHN2$ Latrophilin 22.823NM_183376 $ARRDC4$ Arrestin domain containing 42.8124NM_007257 $PNMA2$ Paraneoplastic antigen MA22.8125ENST00000296529 $TMEM144$ Transmembrane protein 144 (TMEM144), mRNA2.8126NM_052831 $C6orf192$ Chromosome 6 open reading frame 1922.8127NM_004675 $DIRAS3$ $DIRAS family, GTP-binding RAS-like 32.8128NM_172069PLEKHH2Pleckstrin homology domain containing, family H (with MyTH4 domain)member 22.8130NM_018242SLC47A1Solute carrier family 47, member 12.8131NM_017549EPDR1Ependymin related protein 1 (zebrafish)2.8132NM_03844TNFRSF10ATumor necrosis factor receptor superfamily, member 22.7134NM_003844TNFRSF10ATumor necrosis factor receptor, type 12.7136<$		_		hereditary)		0.0017786
116NM_005567IGALS3BPLectin, galactoside-binding, soluble, 3 binding protein2.9117NM_000689ALDH1A1Aldehyde dehydrogenase 1 family, member A12.9118NM_000757CSF1Colony stimulating factor 1 (macrophage)2.9119NM_004864GDF15Growth differentiation factor 152.9120NM_001710CFBComplement factor B2.9121NM_001013732C6orf138Chromosome 6 open reading frame 1382.9122NM_012302LPHN2Latrophilin 22.8123NM_183376ARRDC4Arrestin domain containing 42.8124NM_007257PNMA2Paraneoplastic antigen MA22.8125ENST00000296529TMEM144Transmebrane protein 144 (TMEM144), mRNA2.8126NM_052831C6orf192Chromosome 6 open reading frame 1922.8127NM_004675DIRAS3DIRAS family, GTP-binding RAS-like 32.8128NM_172069PLEKHH2Pleckstrin homology domain containing, family H (with MyTH4 domain) member 22.8129NM_182969XRRA1X-ray radiation resistance associated 12.8131NM_017549EPDR1Ependymin related protein 1 (zebrafish)2.8132NM_203844TNFRSF10ATumor necrosis factor receptor superfamily, member 10a2.7134NM_003844TNFRSF10ATumor necrosis factor receptor superfamily, member 10a2.7136NM_003543HISTIH4HHistone cluster 1, H4h <td></td> <td></td> <td></td> <td></td> <td></td> <td>0.00033</td>						0.00033
117NM_000689 $ALDH1A1$ Aldehyde dehydrogenase I family, member A12.9118NM_000757 $CSF1$ Colony stimulating factor 1 (macrophage)2.9119NM_004864 $GDF15$ Growth differentiation factor 152.9120NM_001710 $CFB$ Complement factor B2.9121NM_01013732 $C6orf138$ Chromosome 6 open reading frame 1382.9122NM_012302 $LPHN2$ Latrophilin 22.8123NM_183376 $ARRDC4$ Arrestin domain containing 42.8124NM_007257 $PNMA2$ Paraneoplastic antigen MA22.8125ENST00000296529 $TMEM144$ Transmembrane protein 144 (TMEM144), mRNA2.8126NM_052831 $C6orf192$ Chromosome 6 open reading frame 1922.8127NM_004675 $DIRAS3$ DIRAS family, GTP-binding RAS-like 32.8128NM_172069 $PLEKHH2$ Pleckstrin homology domain containing, family H (with MyTH4 domain) member 22.8130NM_018242 $SLC47A1$ Solute carrier family 47, member 12.8131NM_007549 $EPDR1$ Ependymin related protein 1 (zebrafish)2.8132NM_203844 $ABCG2$ $ATP-binding cassette, sub-family G (WHITE), member 22.7134NM_003844TNFRSF10ATumor necrosis factor receptor superfamily, member 10a2.7135NM_003543HISTIH4HHistone cluster 1, H4h2.7$						0.000004
118NM_000757 $CSFI$ Colony stimulating factor 1 (macrophage)2.9119NM_004864 $GDF15$ Growth differentiation factor 152.9120NM_001710 $CFB$ Complement factor B2.9121NM_010113732 $C6orf138$ Chromosome 6 open reading frame 1382.9122NM_012302 $IPHN2$ Latrophilin 22.8123NM_183376 $ARRDC4$ Arrestin domain containing 42.8124NM_007257 $PNMA2$ Paraneoplastic antigen MA22.8125ENST00000296529 $TMEM144$ Transmembrane protein 144 (TMEM144), mRNA2.8126NM_052831 $C6orf192$ Chromosome 6 open reading frame 1922.8127NM_004675 $DIRAS3$ DIRAS family, GTP-binding RAS-like 32.8128NM_172069 $PLEKHH2$ Pleckstrin homology domain containing, family H (with MyTH4 domain) member 22.8130NM_018242 $SLC47A1$ Solute carrier family 47, member 12.8131NM_017549 $EPDR1$ Ependymin related protein 1 (zebrafish)2.8132NM_004827 $ABCG2$ ATP-binding cassette, sub-family G (WHITE), member 22.7134NM_003844 $TNFRSF10A$ Tumor necrosis factor receptor superfamily, member 10a2.7135NM_003543 $HISTIH4H$ Histone cluster 1, H4h2.7						0.0004468
119NM_004864GDF15Growth differentiation factor 152.9120NM_001710CFBComplement factor B2.9121NM_01013732C6orf138Chromosome 6 open reading frame 1382.9122NM_012302LPHN2Latrophilin 22.8123NM_183376ARRDC4Arrestin domain containing 42.8124NM_007257PNMA2Paraneoplastic antigen MA22.8125ENST00000296529TMEM144Transmembrane protein 144 (TMEM144), mRNA2.8126NM_052831C6orf192Chromosome 6 open reading frame 1922.8127NM_004675DIRAS3DIRAS family, GTP-binding RAS-like 32.8128NM_172069PLEKHH2Pleckstrin homology domain containing, family H (with MyTH4 domain) member 22.8130NM_018242SLC47A1Solute carrier family 47, member 12.8131NM_017549EPDR1Ependymin related protein 1 (zebrafish)2.8132NM_203464AK3L1Adenylate kinase 3-like 12.8133NM_004827ABCG2ATP-binding cassette, sub-family G (WHITE), member 22.7134NM_002222ITPR1Inositol 1,4,5-triphosphate receptor, type 12.7136NM_003543HISTIH4HHistone cluster 1, H4h2.7						0.0019248
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$						0.0000119 0.0001212
121NM_001013732C6orf138Chromosome 6 open reading frame 1382.9122NM_012302LPHN2Latrophilin 22.8123NM_183376ARRDC4Arrestin domain containing 42.8124NM_007257PNMA2Paraneoplastic antigen MA22.8125ENST00000296529TMEM144Transmembrane protein 144 (TMEM144), mRNA2.8126NM_052831C6orf192Chromosome 6 open reading frame 1922.8127NM_004675DIRASDIRAS family, GTP-binding RAS-like 32.8128NM_172069PLEKHH2Pleckstrin homology domain containing, family H (with MyTH4 domain)2.8129NM_182969XRRA1X-ray radiation resistance associated 12.8130NM_018242SLC47A1Solute carrier family 47, member 12.8131NM_017549EPDR1Ependymin related protein 1 (zebrafish)2.8133NM_004827ABCG2ATP-binding cassette, sub-family G (WHITE), member 22.7134NM_003844TNFRSF10ATumor necrosis factor receptor superfamily, member 10a2.7136NM_003543HISTIH4HHistone cluster 1, H4h2.7		-				0.0013733
122 $NM_012302$ $LPHN2$ Latrophilin 22.8123 $NM_183376$ $ARRDC4$ Arrestin domain containing 42.8124 $NM_007257$ $PNMA2$ Paraneoplastic antigen MA22.8125 $ENST00000296529$ $TMEM144$ Transmembrane protein 144 (TMEM144), mRNA2.8126 $NM_052831$ $C6orf192$ Chromosome 6 open reading frame 1922.8127 $NM_004675$ $DIRAS$ DIRAS family, GTP-binding RAS-like 32.8128 $NM_172069$ $PLEKHH2$ Pleckstrin homology domain containing, family H (with MyTH4 domain) member 22.8129 $NM_182969$ $XRRA1$ X-ray radiation resistance associated 12.8130 $NM_018242$ $SLC47A1$ Solute carrier family 47, member 12.8131 $NM_017549$ $EPDR1$ Ependymin related protein 1 (zebrafish)2.8132 $NM_203464$ $AK3L1$ Adenylate kinase 3-like 12.8133 $NM_004827$ $ABCG2$ $ATP-binding cassette, sub-family G (WHITE), member 22.7134NM_003844TNFRSF10ATumor necrosis factor receptor superfamily, member 10a2.7136NM_003543HISTIH4HHistone cluster 1, H4h2.7$		_		1		0.0005379
$\begin{array}{cccccccccccccccccccccccccccccccccccc$				1 0		0.0001229
$\begin{array}{cccccccccccccccccccccccccccccccccccc$						0.0000015
125ENST00000296529TMEM144Transmembrane protein 144 (TMEM144), mRNA2.8126NM_052831 $C6orf192$ Chromosome 6 open reading frame 1922.8127NM_004675 $DIRA53$ DIRAS family, GTP-binding RAS-like 32.8128NM_172069 $PLEKHH2$ Pleckstrin homology domain containing, family H (with MyTH4 domain) member 22.8129NM_182969 $XRRA1$ X-ray radiation resistance associated 12.8130NM_018242 $SLC47A1$ Solute carrier family 47, member 12.8131NM_017549 $EPDR1$ Ependymin related protein 1 (zebrafish)2.8133NM_004827 $ABCG2$ ATP-binding cassette, sub-family G (WHITE), member 22.7134NM_003844 $TNFRSF10A$ Tumor necrosis factor receptor superfamily, member 10a2.7136NM_003543 $HISTIH4H$ Histone cluster 1, H4h2.7						0.0052895
127NM_004675DIRAS3DIRAS family, GTP-binding RAS-like 32.8128NM_172069PLEKHH2Pleckstrin homology domain containing, family H (with MyTH4 domain) member 22.8129NM_182969XRRA1X-ray radiation resistance associated 12.8130NM_018242SLC47A1Solute carrier family 47, member 12.8131NM_017549EPDR1Ependymin related protein 1 (zebrafish)2.8132NM_203464AK3L1Adenylate kinase 3-like 12.8133NM_004827ABCG2ATP-binding cassette, sub-family G (WHITE), member 22.7134NM_003844TNFRSF10ATumor necrosis factor receptor superfamily, member 10a2.7135NM_002222ITPR1Inositol 1,4,5-triphosphate receptor, type 12.7136NM_003543HISTIH4HHistone cluster 1, H4h2.7	25	ENST00000296529	TMEM144		2.8	0.0056544
128NM_172069PLEKHH2Pleckstrin homology domain containing, family H (with MyTH4 domain) member 22.8129NM_182969XRRA1X-ray radiation resistance associated 12.8130NM_018242SLC47A1Solute carrier family 47, member 12.8131NM_017549EPDR1Ependymin related protein 1 (zebrafish)2.8132NM_203464AK3L1Adenylate kinase 3-like 12.8133NM_004827ABCG2ATP-binding cassette, sub-family G (WHITE), member 22.7134NM_003844TNFRSF10ATumor necrosis factor receptor superfamily, member 10a2.7135NM_002222ITPR1Inositol 1,4,5-triphosphate receptor, type 12.7136NM_003543HISTIH4HHistone cluster 1, H4h2.7	26	NM_052831	C6orf192	Chromosome 6 open reading frame 192	2.8	0.0000583
member 2129NM_182969XRRA1X-ray radiation resistance associated 12.8130NM_018242SLC47A1Solute carrier family 47, member 12.8131NM_017549EPDR1Ependymin related protein 1 (zebrafish)2.8132NM_203464AK3L1Adenylate kinase 3-like 12.8133NM_004827ABCG2ATP-binding cassette, sub-family G (WHITE), member 22.7134NM_003844TNFRSF10ATumor necrosis factor receptor superfamily, member 10a2.7135NM_002222ITPR1Inositol 1,4,5-triphosphate receptor, type 12.7136NM_003543HISTIH4HHistone cluster 1, H4h2.7	.27	NM_004675	DIRAS3			0.0000624
130 $NM_018242$ $SLC47A1$ Solute carrier family 47, member 12.8131 $NM_017549$ $EPDR1$ Ependymin related protein 1 (zebrafish)2.8132 $NM_203464$ $AK3L1$ Adenylate kinase 3-like 12.8133 $NM_004827$ $ABCG2$ $ATP$ -binding cassette, sub-family G (WHITE), member 22.7134 $NM_003844$ $TNFRSF10A$ Tumor necrosis factor receptor superfamily, member 10a2.7135 $NM_002222$ $ITPR1$ Inositol 1,4,5-triphosphate receptor, type 12.7136 $NM_003543$ $HISTIH4H$ Histone cluster 1, H4h2.7				member 2		0.0001397
131NM_017549EPDR1Ependymin related protein 1 (zebrafish)2.8132NM_203464AK3L1Adenylate kinase 3-like 12.8133NM_004827ABCG2ATP-binding cassette, sub-family G (WHITE), member 22.7134NM_003844TNFRSF10ATumor necrosis factor receptor superfamily, member 10a2.7135NM_002222ITPR1Inositol 1,4,5-triphosphate receptor, type 12.7136NM_003543HISTIH4HHistone cluster 1, H4h2.7		-		•		0.0000341
132NM_203464AK3L1Adenylate kinase 3-like 12.8133NM_004827ABCG2ATP-binding cassette, sub-family G (WHITE), member 22.7134NM_003844TNFRSF10ATumor necrosis factor receptor superfamily, member 10a2.7135NM_002222ITPR1Inositol 1,4,5-triphosphate receptor, type 12.7136NM_003543HISTIH4HHistone cluster 1, H4h2.7		-				0.0001539
133NM_004827ABCG2ATP-binding cassette, sub-family G (WHITE), member 22.7134NM_003844TNFRSF10ATumor necrosis factor receptor superfamily, member 10a2.7135NM_002222ITPR1Inositol 1,4,5-triphosphate receptor, type 12.7136NM_003543HISTIH4HHistone cluster 1, H4h2.7		-				0.0000008
134NM_003844TNFRSF10ATumor necrosis factor receptor superfamily, member 10a2.7135NM_002222ITPR1Inositol 1,4,5-triphosphate receptor, type 12.7136NM_003543HISTIH4HHistone cluster 1, H4h2.7		-				0.0001709
135         NM_002222 <i>ITPR1</i> Inositol 1,4,5-triphosphate receptor, type 1         2.7           136         NM_003543 <i>HISTIH4H</i> Histone cluster 1, H4h         2.7						0.0000899
136         NM_003543         HISTIH4H         Histone cluster 1, H4h         2.7						0.0004671 0.0000039
		-				0.0001016
137 NM_148954 <i>PSMB9</i> Proteasome (prosome, macropain) subunit, beta type, 9 (large 2.7						0.003365
multifunctional peptidase 2)		·····			,	(continues)

# TABLE 4 (continued). Upregulated Homozygous GCD II-Related Genes

No.	Gene Accession	Gene Symbol	Gene Description	Change	Р
138	NM_148954	PSMB9	Proteasome (prosome, macropain) subunit, beta type, 9 (large multifunctional peptidase 2)	2.7	0.003365
139	NM_002800	PSMB9	Proteasome (prosome, macropain) subunit, beta type, 9 (large multifunctional peptidase 2)	2.7	0.003365
140	NM_021244	RRAGD	Ras-related GTP binding D	2.7	0.0004553
141	NM_178826	TMEM16D	Transmembrane protein 16D	2.6	0.0000977
142	NM_000877	IL1R1	Interleukin 1 receptor, type 1	2.6	0.0000427
143	NM_133631	ROBO1	Roundabout, axon guidance receptor, homolog 1 (Drosophila)	2.6	0.000011
144	NM_014141	CNTNAP2	Contactin associated protein-like 2	2.6	0.0000317
145	NM_001334	CTSO	Cathepsin O	2.6	0.0000504
146	NM_001085423	C17orf60	Chromosome 17 open reading frame 60	2.6	0.0002676
147	NM_002045	GAP43	Growth associated protein 43	2.6	0.0000103
148	NM_024686	TTLL7	Tubulin tyrosine ligase-like family, member 7	2.6	0.0000499
149	NM_005502	ABCA1	ATP-binding cassette, sub-family A (ABC1), member 1	2.6	0.0000177
150	NM_000593	TAP1	Transporter 1, ATP-binding cassette, sub-family B (MDR/TAP)	2.6	0.0031895
151	NM_000593	TAP1	Transporter 1, ATP-binding cassette, sub-family B (MDR/TAP)	2.6	0.0031895
152	NM_000593	TAP1	Transporter 1, ATP-binding cassette, sub-family B (MDR/TAP)	2.6	0.0031895
153	NM_005779	LHFPL2	Lipoma HMG1C fusion partner-like 2	2.6	0.0001421
154	NM_007047	BTN3A2	Butyrophilin, subfamily 3, member A2	2.6	0.0000841
155	NM_012472	LRRC6	Leucine rich repeat containing 6	2.5	0.0006272
156	NM_001159	AOX1	Aldehyde oxidase 1	2.5	0.000033
157	NM_017734	PALMD	Palmdelphin	2.5	0.0003744
158	NM_004170	SLC1A1	Solute carrier family 1 (neuronal/epithelial high affinity glutamate transporter, system Xag), member 1	2.5	0.000006
159	NM_000311	PRNP	Prion protein (p27-30) (Creutzfeldt-Jakob disease, Gerstmann-Strausler- Scheinker syndrome, fatal familial insomnia)	2.5	0
160	NM_005025	SERPINI1	Serpin peptidase inhibitor, clade 1.(neuroserpin), member 1	2.5	0.0001759
161	NM_001946	DUSP6	Dual specificity phosphatase 6	2.5	0.0000949
162	NM_000212	ITGB3	Integrin, beta 3 (platelet glycoprotein IIIa, antigen CD61)	2.5	0.0001519
164	NR_003530	MEG3	Maternally expressed 3	2.5	0.0001135
165	NM_015274	MAN2B2	Mannosidase, alpha, class 2B, member 2	2.5	0.0000109
166	NM_006207	PDGFRL	Platelet-derived growth factor receptor-like	2.5	0.0001507
167	NM_000722	CACNA2D1	Calcium channel, voltage-dependent, alpha 2/delta subunit 1	2.5	0.0000006
168	NM_001975	ENO2	Enolase 2 (gamma, neuronal)	2.5	0.000141
169	NM_002637	PHKA1	Phosphorylase kinase, alpha 1 (muscle)	2.5	0.0000154
170	NM_022469	GREM2	Gremlin 2, cysteine knot superfamily, homolog (Xenopus laevis)	2.5	0.0000111
171	NM_001040458	ARTS-1	Type 1 tumor necrosis factor receptor shedding aminopeptidase regulator	2.5	0.0000227
172	NM_001962	EFNA5	Ephrin-A5	2.5	0.0000425
173	NM_001850	COL8A1	Collagen, type VIII, alpha 1	2.5	0.0000884
174	NM_014367	C3orf28	Chromosome 3 open reading frame 28	2.5	0.0038544
175	NM_024621	VEPH1	Ventricular zone expressed PH domain homolog 1 (zebrafish)	2.5	0.000141
176	NM_017901	TPCN1	Two pore segment channel 1	2.5	0.0000426
177	NM_003551	NME5	Non-metastatic cells 5, protein expressed in (nucleoside-diphosphate kinase)	2.5	0.0014518
178	NM_203380	ACSL5	Acyl-CoA synthetase long-chain family member 5	2.5	0.004572
179	NM_007036	ESM1	Endothelial cell-specific molecule 1	2.5	0.0005156
180	NM_006587	CORIN	Corin, serine peptidase	2.5	0.000425
181	NM_138554	TLR4	Toll-like receptor 4	2.5	0.0000129
182	NM_000187	HGD	Homogentisate 1,2-dioxygenase (homogentisate oxidase)	2.4	0.000498
183	NM_000187	HGD	Homogentisate 1,2-dioxygenase (homogentisate oxidase)	2.4	0.000498
184	NM_005391	PDK3	Pyruvate dehydrogenase kinase, isozyme 3	2.4	0.0017101
185	NM_173508	SLC35F3	Solute carrier family 35, member F3	2.4	0.0002497
186	NM_000147	FUCA1	Fucosidase, alpha-L-1, tissue	2.4	0.0001624
187	NM_181785	SLC46A3	Solute carrier family 46, member 3	2.4	0.0000173
188	NM_002031	FRK	Fyn-related kinase	2.4	0.0002699
189	NM_206996	SPAG17	Sperm associated antigen 17	2.4	0.0002856
190	NM_006307	SRPX	Sushi-repeat-containing protein, X-linked	2.4	0.0003416
191	NM_007366	PLA2R1	Phospholipase A2 receptor 1, 180kDa	2.4	0.000002
192	NM_020041	SLC2A9	Solute carrier family 2 (facilitated glucose transporter), member 9	2.4	0.0001373
193	NM_031419	NFKBIZ	Nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor, zeta	2.4	0.0001795
194	NM_000214	JAG1	Jagged I (Alagille syndrome)	2.4	0.0004701
195	NM_001979	EPHX2	Epoxide hydrolase 2, cytoplasmic	2.4	0.0002466
196	NM_006095	ATP8A1	ATPase, aminophospholipid transporter (APLT), Class 1, type 8A, member 1	2.4	0.0000686
197	NM_053276	VIT	Vitrin	2.4	0.0000835
198	NM_001146	ANGPT1	Angiopoietin 1	2.4	0.0003832
199	NM_001040457	RHBDD2	Rhomboid domain containing 2	2.4	0.0000221
200	NM_138287	DTX3L	Deltex 3-like (Drosophila)	2.4	0.0052558
201	NM_003812	ADAM23	ADAM metallopeptidase domain 23	2.4	0.0000041
202	NM_006994	BTN3A3	Butyrophilin, subfamily 3, member A3	2.4	0.0003593
204	NM_018936	PCDHB2	Protocadherin beta 2	2.4	0.0002569
					(continues)

# TABLE 4 (continued). Upregulated Homozygous GCD II-Related Genes

No.	Gene Accession	Gene Symbol	Gene Description	Change	Р
205	NM_015194	MYOID	Myosin ID	2.4	0.0000391
206	NM_001086	AADAC	Arylacetamide deacetylase (esterase)	2.3	0.0000226
207	NM_014467	SRPX2	Sushi-repeat-containing protein, X-linked 2	2.3	0.0000049
208	NM_024726	IQCA	IQ motif containing with AAA domain	2.3	0.0001621
209	NM_002016	FLG	Filaggrin	2.3	0.002256
210	NM_003243	TGFBR3	Transforming growth factor, beta receptor III	2.3	0.0000001
211	NM_052867	NALCN	Sodium leak channel, non-selective	2.3	0.0001055
212	NM_004337	OSGIN2	Oxidative stress induced growth inhibitor family member 2	2.3	0.0000301
213	NM_000958	PTGER4	Prostaglandin E receptor 4 (subtype EP4)	2.3	0.0006466
214	NM_001033045	GPR155	G protein-coupled receptor 155	2.3	0.0000117
215	NM_032587	CARD6	Caspase recruitment domain family, member 6	2.3	0.0007864
216	NM_021197	WFDC1	WAP four-disulfide core domain 1	2.3	0.0001014
217	NM_018938	PCDHB4	Protocadherin beta 4	2.3	0.0002702
218	NM_013391	DMGDH KCNMB4	Dimethylglycine dehydrogenase	2.3	0.0007769
219	NM_014505	KCNMB4	Potassium large conductance calcium-activated channel, subfamily M, beta member 4	2.3	0.0000254
220	NM_172366	FBXO16	F-box protein 16	2.3	0.0000801
221	NM_203403	C90rf150	Chromosome 9 open reading frame 150	2.3	0.0009304
222	NM_007048	BTN3A1	Butyrophilin, subfamily 3, member A1	2.3	0.0002037
223	NM_014737	RASSF2	Ras association (RalGDS/AF-6) domain family 2	2.3	0.0002623
224	NM_001148	ANK2	Ankyrin 2, neuronal	2.3	0.0003172
225	NM_018421	TBC1D2	TBC1 domain family, member 2	2.3	0.002261
226	NM_000824	GLRB	Glycine receptor, beta	2.3	0.000148
227	NM_002121	HLA-DPB1	Major histocompatibility complex, class II, DP beta 1	2.3	0.0011187
228	NM_001289	CLIC2	Chloride intracellular channel 2	2.3	0.0000485
229	NM_020848	KIAA1462	KIAA1462	2.3	0.0000095
230	NM_004065	CDR1	Cerebellar degeneration-related protein 1, 34kDa	2.2	0.000323
231	NM_031935	HMCN1	Hemicentin 1	2.2	0.0001081
232	NM_001621	AHR	Aryl hydrocarbon receptor	2.2	0.0000101
233	NM_002231	CD82	CD82 molecule	2.2	0.0000261
234	NM_018295	TMEM140	Transmembrane protein 140	2.2	0.0008474
235	NM_002970	SAT1	Spermidine/spermine N1 acetyltransferase 1	2.2	0.0000077
236	NM_001531	MR1	Major histocompatibility complex, class I-related	2.2	0.0000163
237	NM_003043	SLC6A6	Solute carrier family 6 (neurotransmitter transporter, taurine), member 6	2.2	0.0001361
238	NM_012157	FBXL2	F-box and leucine-rich repeat protein 2	2.2	0.0000359
239	NM_002309	LIF	Leukemia inhibitory factor (cholinergic differentiation factor)	2.2	0.0007509
240	NM_024763	WDR78	WD repeat domain 78	2.2	0.0017849
241	NM_021945	C6orf85	Chromosome 6 open reading frame 85	2.2	0.0017489
242	NM_001218	CA12	Carbonic anhydrase XII	2.2	0.000822
243	NM_002160	TNC	Tenascin C (hexabrachion)	2.2	0.0000479
244	NM_005516	HLA-E	Major histocompatibility complex, class 1, E	2.2 2.2	0.0000489
245 246	NM_005516 NM_003263	HLA-E TLR1	Major histocompatibility complex, class 1, E Toll-like receptor 1	2.2	0.0000489 0.0014844
240	NM_002117	HLA-C	Major histocompatibility complex, class 1, C	2.2	0.00014844
248	NM_000247	MICA	MHC class I polypeptide-related sequence A	2.2	0.0000444
249	NM_000202	IDS	Iduronate 2-sulfatase (Hunter syndrome)	2.2	0.0000043
250	NM_032857	LACTB	Lactamase, beta	2.2	0.0001232
251	NM_002198	IRF1	Interferon regulatory factor 1	2.2	0.001252
252	NM_145235	FANK1	Fibronectin type III and ankyrin repeat domains 1	2.2	0.0002057
254	NM_182943	PLOD2	Procollagen-lysine, 2-oxoglutarate 5-dioxygenase 2	2.2	0.0000188
255	NM 005562	LAMC2	Laminin, gamma 2	2.2	0.0012097
256	NM 144629	RFTN2	Raftlin family member 2	2.2	0.0012097
257	NM_002581	PAPPA	Pregnancy-associated plasma protein A, pappalysin 1	2.2	0.000067
258	NM 004090	DUSP3	Dual specificity phosphatase 3 (vaccinia virus phosphatase VHI-related)	2.2	0.0000206
259	NM_006291	TNFAIP2	Tumor necrosis factor, alpha-induced protein 2	2.2	0.0008835
260	NM_145176	SLC2AI2	Solute carrier family 2 (facilitated glucose transporter), member 12	2.2	0.0003708
261	NM_005516	HLA-E	Major histocompatibility complex, class 1, E	2.2	0.0000376
262	NM_020909	EPB41L5	Erythrocyte membrane protein band 4.1 like 5	2.2	0.0000017
263	NM_002117	HLA-C	Major histocompatibility complex; class 1, C	2.2	0.0000294
264	NM_003688	CASK	Calcium/calmodulin-dependent serine protein kinase (MAGUK family)	2.2	0.0000365
265	NM_001005340	GPNMB	Glycoprotein (transmembrane) nmb	2.2	0.0000069
266	NM_012420	IFIT5	Interferon-induced protein with tetratricopeptide repeats 5	2.2	0.0013319
267	NM_138980	MAPK10	Mitogen-activated protein kinase 10	2.2	0.0001154
268	NM_002350	LYN	V-yes-1 Yamaguchi sarcoma viral related oncogene homolog	2.2	0.0001236
269	NM_007173	PRSS23	Protease, serine, 23	2.1	0.0000224
270	ENST00000222553	PBEF1	Pre-B-cell colony enhancing factor 1 (PBEF1), mRNA	2.1	0.0006919
271	NM_014936	ENPP4	Ectonucleotide pyrophosphatase/phosphodiesterase 4 (putative function)	2.1	0.0000373
272	NM_021626	SCPEP1	Serine carboxypeptidase 1	2.1	0.0000678
273	NM_173505	ANKRD29	Ankyrin repeat domain 29	2.1	0.0000555
274	NM_000120	EPHX1	Epoxide hydrolase 1, microsomal (xenobiotic)	2.1	0.0000223
	—				(continues)

### TABLE 4 (continued). Upregulated Homozygous GCD II-Related Genes

No.	Gene Accession	Gene Symbol	Gene Description	Change	Р
275	NM_001039580	MAP9	Microtubule-associated protein 9	2.1	0.0003664
276	NM_005746	PBEF1	Pre-B-cell colony enhancing factor 1	2.1	0.0007562
277	NM_000204	CF1	Complement factor 1	2.1	0.0015781
278	NM_021034	IFITM3	Interferon induced transmembrane protein 3 (I-8U)	2.1	0.0000542
279	NM_004734	DCLK1	Doublecortin-like kinase 1	2.1	0.0005205
280	NM_004696	SLC16A4	Solute carrier family 16, member 4 (monocarboxylic acid transporter 5)	2.1	0.0002086
281	NM_213589	RAPH1	Ras association (RalGDS/AF-6) and pleckstrin homology domains 1	2.1	0.0000129
282	NM_002395	ME1	Malic enzyme 1, NADP(+)-dependent, cytosolic	2.1	0.0000103
283	NM_014157	CCDC113	Coiled-coil domain containing 113	2.1	0.0002231
284	NR_002157	OR2A9P	Olfactory receptor, family 2, subfamily A, member 9 pseudogene	2.1	0.0008517
285	NM_007112	THBS3	Thrombospondin 3	2.1	0.0000632
286	NM_005514	HLA-B	Major histocompatibility complex, class 1, B	2.1	0.000079
287	NM_018933	PCDHB13	Protocadherin beta 13	2.1	0.0006096
288	NM_138452	DHRS1	Dehydrogenase/reductase (SDR family) member 1	2.1	0.0014038
289	NM_144599	NIPA1	Non imprinted in Prader-Willi/Angelman syndrome 1	2.1	0.0000307
290	XR_019525	LOC390345	Hypothetical LOC390345	2.1	0.0045174
291	NM_024642	GALNT12	UDP-N-acetyl-alpha-D-galactosamine:polypeptide N-	2.1	0.0001604
			acetylgalactosaminyltransferase 12 (GalNAc-T12)		
292	NM_020422	TMEM159	Transmembrane protein 159	2.1	0.0006667
293	NM_080593	HIST1H2BK	Histone cluster 1, H2bk	2.1	0.0001187
294	NM_198503	KCNT2	Potassium channel, subfamily T, member 2	2.1	0.0035322
295	NM_007199	IRAK3	Interleukin-1 receptor-associated kinase 3	2.1	0.0030475
297	NM_005514	HLA-B	Major histocompatibility complex, class 1, B	2	0.0002145
298	NM_003328	TXK	TXK tyrosine kinase	2	0.0010901
290	NM_005419	STAT2	Signal transducer and activator of transcription 2, 113kDa	2	0.0012848
300	NM_001039706	FLJ21062	Hypothetical protein FLJ21062	2	0.001607
301	NM_015090	NFASC	Neurofascin homolog (chicken)	2	0.0000349
302	NM_004159	PSMB8	Proteasome (prosome, macropain) subunit, beta type, 8 (large multifunctional peptidase 7)	2	0.0001761
303	NM_004159	PSMB8	Proteasome (prosome, macropain) subunit, beta type, 8 (large multifunctional peptidase 7)	2	0.0001761
304	NM_004159	PSMB8	Proteasome (prosome, macropain) subunit, beta type, 8 (large multifunctional peptidase 7)	2	0.0001761
305	NM_000247	MICA	MHC class I polypeptide-related sequence A	2	0.0000572
306	NM_002754	MAPK13	Mitogen-activated protein kinase 13	2	0.0009883
307	NM_005929	MF12	Antigen p97 (melanoma associated) identified by monoclonal antibodies 133.2 and 96.5	2	0.0001076
308	NM_005514	HLA-B	Major histocompatibility complex, class 1, B	2	0.000205
309	NM_018050	MANSC1	MANSC domain containing 1	2	0.0000755
310	NM_002121	HLA-DPB1	Major histocompatibility complex, class II, DP beta 1	2	0.000209
311	NM_018317	TBC1D19	TBC1 domain family, member 19	2	0.0000012
312	NR_003322	SNORD116-7	Small nucleolar RNA, C/D box 116-7	2	0.0051387
313	NR_003320	SNORD116-5	Small nucleolar RNA, C/D box 116-5	2	0.0051387
314	NM_020139	BDH2	3-hydroxybutyrate dehydrogenase, type 2	2	0.0000086
315	NM_004052	BNIP3	BCL2/adenovirus E1B 19kDa interacting protein 3	2	0.0001215
316	NM_021199	SQRDL	Sulfide quinone reductase-like (yeast)	2	0.0008101
317	NM_153704	TMEM67	Transmembrane protein 67	2	0.0019696
318	NM_001831	CLU	Clusterin	2	0.0001778
319	NM_014585	SLC40A1	Solute carrier family 40 (iron-regulated transporter), member 1	2	0.0002529

among stromal TGFBIp deposits.<sup>25</sup> These studies suggest that altered ECM proteolytic enzyme activities affect TGFBIp deposits by degrading ECM molecules, by either scission of covalent bonds or cleavage of mutant TGFBIp. Several investigations suggest that abnormal proteolysis is involved in deposits of TGFBIp in the cornea of the TGFBI gene associated with corneal dystrophy.<sup>26</sup> This finding is consistent with the fact that amyloid precursor proteins associated with other amyloid diseases generally undergo proteolysis during amyloid generation. Such proteins include gelsolin in both lattice corneal dystrophy type I and Finnish-type familial amyloidosis,<sup>27,28</sup> amyloid  $\beta$  precursor protein in familial Alzheimer's disease,<sup>29,30</sup> and BRI2 in familial British dementia.<sup>31,32</sup> Our microarray data show differential expression of endopeptidaserelated genes such as serine-type endopeptidase activityrelated genes, serine-type endopeptidase inhibitor-related genes, aspartic-type endopeptidase activity, and metalloendopeptidase activity-related genes. Although ECM proteolytic enzymes such as MMPs for TGFBIp remain unidentified, our data suggest that proteolytic enzymes associated with ECM turnover may be involved in the generation of TGFBIp deposits in GCD II. Further studies are needed to identify specific proteolytic enzymes responsible for TGFBIp deposits in the cornea.

### **Cell Adhesion and Integrin Signaling**

TGFBIp contains a domain rich in cysteine residues (EMI domain), four highly conserved fasciclin-like (FAS) domains, and a COOH-terminal Arg-Gly-Asp (RGD) motif. The presence of the FAS domains and the RGD motif suggests that TGFBIp may play a functional role in cell adhesion. More recently, it was found that TGFBIp plays an inhibitory role in the attachment of human scleral fibroblasts to collagen type I through interaction

# TABLE 5. Downregulated Homozygous GCD II-Related Genes

No.	Gene Accession	Gene Symbol	Gene Description	Change	Р
1	NM_181503	EXOSC8	Exosome component 8	-2.0	0.0011677
2	NM_152524	SGOL2	Shugoshin-like 2 (S. pombe)	-2.0	0.0050817
3	NR_002564	SNORD26	Small nucleolar RNA, C/D box 26	-2.0	0.0002281
4	NM_003534	HIST1H3G	Histone cluster 1, H3g	-2.0	0.0002008
5	NM_012074	DPF3	D4, zinc and double PHD fingers, family 3	-2.0	0.0000953
6	NM_018193	FANC1	Fanconi anemia, complementation group 1	-2.0	0.0026856
7	NM_052917	GALNT13	UDP-N-acetyl-alpha-D-galactosamine:polypeptide N- acetylgalactosaminyltransferase 13 (GalNAc-T13)	-2.0	0.0008409
8	NM_152754	SEMA3D	Sema domain, immunoglobulin domain (Ig), short basic domain, secreted, (semapborin) 3D	-2.0	0.0021798
9	NM_032117	MND1	Meiotic nuclear divisions 1 homolog (S. cerevisiae)	-2.0	0.0035557
10	NM_000059	BRCA2	Breast cancer 2, early onset	-2.0	0.0049817
11	NM_006079	CITED2	Cbp/p300-interacting transactivator, with Glu/Asp-rich carboxy-terminal domain, 2	-2.0	0.0016884
12	NM_002192	INHBA	Inhibin, beta A	-2.0	0.0001218
13	NM_033518	SLC38A5	Solute carrier family 38, member 5	-2.0	0.0003078
14	NM_005239	ETS2	V-ets erythroblastosis virus E26 oncogene homolog 2 (avian)	-2.0	0.0000035
15	NM_001039841	ARHGAP11B	Rho GTPase activating protein 11B	-2.1 -2.1	0.0002937
16 17	NM_016426 NM_022111	GTSE1 CLSPN	G-2 and S-phase expressed 1 Claspin homolog (Xenopus laevis)	-2.1 -2.1	0.0008579 0.0013778
18	NM_021968	HIST1H4J	Histone cluster 1, H4j	-2.1 -2.1	0.0004086
19	BC067351	GUSBL1	Glucuronidase, beta-like 1	-2.1	0.0000052
20	NM_018353	C14orf106	Chromosome 14 open reading frame 106	-2.1	0.0021285
21	NM_001099293	KIF4B	Kinesin family member 4B	-2.1	0.0007975
22	NM_181802	UBE2C	Ubiquitin-conjugating enzyme E2C	-2.1	0.0016383
23	NM_014573	TMEM97	Transmembrane protein 97	-2.1	0.0004448
34	NM_182909	FILIP1L	Filamin A interacting protein 1-like	-2.1	0.0014915
35	NM_002823	PTMA	Prothymosin, alpha (gene sequence 28)	-2.1	0.0028224
36	NM_000956	PTGER2	Prostaglandin E receptor 2 (subtype EP2), 53kDa	-2.1	0.0025474
37	NM_004817	TJP2	Tight junction protein 2 (zona occludens 2)	-2.1	0.0000007
38	NM_007317	KIF22	Kinesin family member 22	-2.1	0.000031
39	NR_002562	SNORD28	Small nucleolar RNA, C/D box 28	-2.1	0.001433
40	NM_016095	GINS2	GINS complex subunit 2 (Psf2 homolog)	-2.1	0.0018093
41	NM_007317	KIF22	Kinesin family member 22	-2.1	0.0000356
42	NM_004731	SLC16A7	Solute carrier family 16, member 7 (monocarboxylic acid transporter 2)	-2.1	0.0000023
43	NM_005496	SMC4	Structural maintenance of chromosomes 4	-2.1	0.0004444
44	NM_144586	LYPD1	LY6/PLAUR domain containing 1	-2.1	0.0005818
45 46	NM_001129	AEBP1	AE binding protein 1	-2.1 -2.1	0.0000008
40 47	NM_014783 NM_019035	ARHGAP11A PCDH18	Rho GTPase activating protein 11A Protocadherin 18	-2.1 -2.1	0.0009603 0.000004
48	NM_013277	RACGAP1	Rac GTPase activating protein 1	-2.1	0.0006113
49	NM_006739	MCM5	Minichromosome maintenance complex component 5	-2.1	0.0002303
50	NM_152270	SLFN11	Schlafen family member 11	-2.1	0.0011236
51	NM_007243	NRM	Nurim (nuclear envelope membrane protein)	-2.2	0.000234
52	NM_007243	NRM	Nurim (nuclear envelope membrane protein)	-2.2	0.000234
53	NR_003125	LOC85391	RNA, small nucleolar	-2.2	0.0004524
54	NM_182751	MCM10	Minichromosome maintenance complex component 10	-2.2	0.0041059
55	NM_001048201	UHRF1	Ubiquitin-like, containing PHD and RING finger domains, 1	-2.2	0.0001459
56	NM_014465	SULT1B1	Sulfotransferase family, cytosolic, 1B, member 1	-2.2	0.0065522
57	NM_002760	PRKY	Protein kinase, Y-linked	-2.2	0.0047595
58	NM_001827	CKS2	CDC28 protein kinase regulatory subunit 2	-2.2	0.0009191
59	NM_004772	C50rf13	Chromosome 5 open reading frame 13	-2.2	0.0006237
60	NM_005497	GJA7	Gap junction protein, alpha 7, 45kDa	-2.2	0.0001851
61	NM_001744	CAMK4	Calcium/calmodulin-dependent protein kinase IV	-2.2	0.0016928
62 63	NM_152495	CNIH3	Cornichon homolog 3 (Drosophila)	-2.2 -2.2	0.0032016
64	NM_006963 NM 014363	ZNF22 SACS	Zinc finger protein 22 (KOX 15) Spastic ataxia of Charlevoix-Saguenay (sacsin)	-2.2 -2.2	0.0005145 0.0000886
65	NM_014303 NM_018476	BEX1	Brain expressed, X-linked 1	-2.2	0.0043276
66	NM_006727	CDH10	Cadherin 10, type 2 (T2-cadherin)	-2.2 -2.2	0.0003019
67	NM_003545	HIST1H4E	Histone cluster 1, H4e	-2.2	0.0001393
68	NM_004415	DSP	Desmoplakin	-2.2	0.0000256
69	NM_001761	CCNF	Cyclin F	-2.2	0.0000636
70	NM_018101	CDCA8	Cell division cycle associated 8	-2.3	0.0015208
71	NM_021018	HIST1H3F	Histone cluster 1, H3f	-2.3	0.0038466
72	NM_004572	PKP2	Plakophilin 2	-2.3	0.0008219
73	NM_003517	HIST2H2AC	Histone cluster 2, H2ac	-2.3	0.0003061
74	NM_022908	NT5DC2	5'-nucleotidase domain containing 2	-2.3	0.0003366
75	NM_018410	DKFZp762E1312	Hypothetical protein DKFZp762E1312	-2.3	0.0010354
76	NM_024908	WDR76	WD repeat domain 76	-2.3	0.0029464
77	NM_004456	EZH2	Enhancer of zeste homolog 2 (Drosophila)	-2.3	0.000033
					(continues)

# TABLE 5 (continued). Downregulated Homozygous GCD II-Related Genes

No.	Gene Accession	Gene Symbol	Gene Description	Change	Р
78	NM_198433	AURKA	Aurora kinase A	-2.3	0.0009593
79	NM_001878	CRABP2	Cellular retinoic acid binding protein 2	-2.3	0.0003869
80	NM_014865	NCAPD2	Non-SMC condensin 1 complex, subunit D2	-2.3	0.0000146
81	NM_006479	RAD51AP1	RAD51 associated protein 1	-2.3	0.0004349
82	NM_003541	HIST1H4K	Histone cluster 1, H4k	-2.3	0.0001022
83	NM_005480	TROAP	Trophinin associated protein (tastin)	-2.3	0.0007361
84	NM_130398	EXO1	Exonuclease 1	-2.3	0.0007009
85	NM_003530	HIST1H3D	Histone cluster 1, H3d	-2.3	0.0000989
86	NM_012484	HMMR	Hyaluronan-mediated motility receptor (RHAMM)	-2.3	0.0010368
87	BX641032	WEE1	WEE1 homolog (S. pombe)	-2.3	0.0020117
88	NM_005491	CXorf6	Chromosome X open reading frame 6	-2.3	0.000069
89	NM_004900	APOBEC3B	Apolipoprotein B mRNA editing enzyme, catalytic polypeptide-like 3B	-2.3	0.002503
90	NM_020890	KIAA1524	KIAA1524	-2.3	
-	_			-2.4	0.0035147
91	NM_012177	FBXO5	F-box protein 5		0.0029497
92	ENST00000377738	KRTAP2-4	Keratin associated protein 2-4 (KRTAP2-4), mRNA	-2.4	0.0003921
93	NM_013230	CD24	CD24 molecule	-2.4	0.0032149
94	NM_001813	CENPE	Centromere protein E, 312kDa	-2.4	0.0019189
95	NM_007174	CIT	Citron (rho-interacting, serine/threonine kinase 21)	-2.4	0.0000603
96	NM_002106	H2AFZ	H2A histone family, member Z	-2.4	0.0010744
97	NM_003524	HIST1H2BH	Histone cluster 1, H2bh	-2.4	0.0001753
98	NM_003784	SERPINB7	Serpin peptidase inhibitor, clade B (ovalbumin), member 7	-2.4	0.0011738
99	NM_017669	ERCC6L	Excision repair cross-complementing rodent repair deficiency, complementation group 6-like	-2.4	0.0037181
100	ENST00000377738	KRTAP2-4	Keratin associated protein 2-4 (KRTAP2-4), mRNA	-2.4	0.0006498
101	ENST00000377738	KRTAP2-4	Keratin associated protein 2-4 (KRTAP2-4), mRNA	-2.4	0.0006498
102	NM_021052	HIST1H2AE	Histone cluster 1, H2ae	-2.4	0.0004919
102	NM 002263	KIFC1	Kinesin family member C1	-2.4	0.0004717
				-2.4	
104	NM_003258	TK1	Thymidine kinase 1, soluble		0.0006185
105	NM_001048198	SNHG3-RCC1	Regulator of chromosome, condensation 1	-2.4	0.0000584
106	NM_013296	GPSM2	G-protein signaling modulator 2 (AGS3-like, C. elegans)	-2.4	0.0006993
107	NM_031217	KIF18A	Kinesin family member 18A	-2.5	0.0001562
108	NM_001017420	ESCO2	Establishment of cohesion 1 homolog 2 (S. cerevisiae)	-2.5	0.0013571
109	NM_014264	PLK4	Polo-like kinase 4 (Drosophila)	-2.5	0.0031529
110	ENST00000302536	KIAA1576	KIAA1576 protein (KIAA1576), mRNA	-2.5	0.0000329
111	NM_031966	CCNB1	Cyclin B1	-2.5	0.0000813
112	NM_003877	SOCS2	Suppressor of cytokine signaling 2	-2.5	0.0000898
113	NM_005325	HIST1HIA	Histone cluster 1, H1a	-2.5	0.0000106
114	NM_138555	KIF23	Kinesin family member 23	-2.5	0.0005602
115	NM_001012507	C6orf173	Chromosome 6 open reading frame 173	-2.5	0.0003908
116	NM_002466	MYBL2	V-myb mycloblastosis viral oncogene homolog (avian)-like 2	-2.5	0.0000271
117	NM_013372	GREM1	Gremlin 1, cysteine knot superfamily, homolog (Xenopus laevis)	-2.5	0.000007
118	NM_003529	HIST1H3A	Histone cluster 1, H3a	-2.5	0.0012216
119	NM_001034	RRM2	Ribonucleotide reductase M2 polypeptide	-2.5	0.0034171
120		IGFBP5	Insulin-like growth factor binding protein 5	-2.6	0.0039748
	NM_000599	-		-2.0 -2.6	
121	NM_001033049	ADARB1	Adenosine deaminase, RNA-specific, B1 (RED1 homolog rat)		0.0000097
122	NM_000561	GSTM1	Glutathione S-transferase M1	-2.6	0.0003801
	NM_005517	HMGN2	High-mobility group nucleosomal binding domain 2	-2.6	0.0001929
124	NM_175065	HIST2H2AB	Histone cluster 2, H2ab	-2.6	0.0001294
125	NM_006682	FGL2	Fibrinogen-like 2	-2.6	0.0004615
126	NM_001012410	SGOL1	Shugoshin-like 1 (S. pombe)	-2.6	0.0072724
127	NM_003544	HIST1H4B	Histone cluster 1, H4b	-2.6	0.0001657
128	NM_153262	SYT14	Synaptotagmin XIV	-2.6	0.0000915
129	NM_002263	KIFC1	Kinesin family member C1	-2.7	0.0013435
130	NM_182705	FAM101B	Family with sequence similarity 101, member B	-2.7	0.0000477
131	NM_006558	KHDRBS3	KH domain containing, RNA binding, signal transduction associated 3	-2.7	0.0000787
132	NM 001943	DSG2	Desmoglein 2	-2.7	0.0000628
133	NM_015975	TAF9B	TAF9B RNA polymerase II, TATA box binding protein (TBP)-associated	-2.7	0.0001503
134	NM_016591	GCNT4	factor, 31kDa Glucosaminyl (N-acetyl) transferase 4, core 2 (beta-1,6-N- acetylglucosaminyltransferase)	-2.7	0.0002032
135	NM_014875	KIF14	Kinesin family member 14	-2.7	0.0026412
136	BX641032	WEE1	WEE1 homolog (S. pombe)	-2.7	0.0018471
137	NM_016588	NRN1	Neuritin 1	-2.7	0.0000023
138	NM_003546	HIST1H4L	Histone cluster 1, H4l	-2.7	0.0000023
	-			-2.7 -2.7	
139	NM_006845	KIF2C	Kinesin family member 2C		0.0020828
140	NR_002612	DLEU2	Deleted in lymphocytic leukemia, 2	-2.7	0.0017015
141	NM_031299	CDCA3	Cell division cycle associated 3	-2.7	0.0002869
142	NM_018849	ABCB4	ATP-binding cassette, sub-family B (MDR/TAP), member 4	-2.8	0.000121
143	NM_001067	TOP2A	Topoisomerase (DNA) II alpha 170kDa	-2.8	0.0004533
144	NM_020242	KIF15	Kinesin family member 15	-2.8	0.0002493
					(continues)

# TABLE 5 (continued). Downregulated Homozygous GCD II-Related Genes

170         NM_020675           171         NM_170589           172         NM_002497           173         NM_004701           174         NM_00318           175         NM_00313           176         NM_018131           177         NM_00313           178         NM_001322           179         NM_001322           179         NM_001322           179         NM_001322           179         NM_001322           179         NM_001322           179         NM_001711           181         NM_001711           182         NM_004934           183         NM_018136           184         NM_020859           185         NM_006147           186         NM_005321           188         NM_017779           189         NM_002783           190         NM_005322           192         NM_005322           193         NM_202002           194         NM_005030           195         NM_006069           193         NM_005634           197         NM_006609           198	Gene Accession	Gene Symbol	Gene Description	Change	Р
147         NM_002398           148         NM_173084           149         NM_003533           150         NM_145061           151         NM_001786           152         NM_00101           153         NM_012112           154         NM_015359           155         NM_015341           157         NM_012310           158         NM_001211           159         NM_003522           160         NM_152515           161         NM_152562           162         NM_001884           164         NR_001544           165         NM_002367           167         NM_001884           164         NR_0016350           166         NM_0020675           171         NM_0020675           172         NM_002131           175         NM_0020675           176	M_004439	EPHA5	EPH receptor A5	-2.8	0.0000033
148         NM_173084           149         NM_003533           150         NM_145061           151         NM_001786           152         NM_0012112           154         NM_016359           155         NM_003540           156         NM_012112           154         NM_012310           158         NM_001211           159         NM_012310           158         NM_001221           160         NM_152515           161         NM_152562           162         NM_178229           163         NM_001884           164         NR_001884           165         NM_001884           166         NM_002306           167         NM_001884           168         NM_0020675           171         NM_0020675           171         NM_0020675           171         NM_0020675           172         NM_0020675           173         NM_0020675           174         NM_0020675           175         NM_002497           175         NM_002131           177         NM_00318           177 <td></td> <td>PRC1</td> <td>Protein regulator of cytokinesis 1</td> <td>-2.8</td> <td>0.0054775</td>		PRC1	Protein regulator of cytokinesis 1	-2.8	0.0054775
149         NM_003533           150         NM_145061           151         NM_001786           152         NM_001786           152         NM_0012112           154         NM_013540           155         NM_003540           156         NM_012310           158         NM_003540           157         NM_012310           158         NM_001211           159         NM_003522           160         NM_152515           161         NM_15252           162         NM_001884           164         NR_001544           165         NM_001884           164         NR_001884           164         NM_002346           166         NM_002346           168         NM_0020675           171         NM_002497           173         NM_002497           173         NM_002129           176         NM_002129           177         NM_00318           175         NM_001322           179         NM_001322           179         NM_0010322           179         NM_0010322           179		MEIS1	Meis homeobox 1	-2.8	0.0003329
150         NM_145061           151         NM_001786           152         NM_001786           152         NM_012112           154         NM_016359           155         NM_003540           156         NM_012310           158         NM_0015341           157         NM_012310           158         NM_001544           165         NM_021346           166         NM_001884           166         NM_002367           167         NM_001804           168         NM_0020675           171         NM_170589           172         NM_002497           173         NM_001322           174         NM_001322           175         NM_001322           176         NM_001322           177         NM_0010522           178		TRIM59	Triparite motif-containing 59	-2.8	0.001123
151         NM_001786           152         NM_00111           153         NM_012112           154         NM_016359           155         NM_003540           156         NM_015341           157         NM_012110           158         NM_001211           159         NM_003522           160         NM_152515           161         NM_152522           160         NM_152515           161         NM_152522           160         NM_178229           163         NM_001884           164         NR_001544           165         NM_0022346           166         NM_002367           167         NM_0010847           168         NM_0020675           171         NM_170589           172         NM_002497           173         NM_002497           173         NM_002129           176         NM_001322           179         NM_001322           179         NM_001322           179         NM_0010322           179         NM_001647           180         NM_0101555           180		HIST1H31 C13orf3	Histone cluster 1, H3i Chromosome 13 open reading frame 3	-2.8 -2.8	0.0000119 0.0003047
152         NM_006101           153         NM_012112           154         NM_016359           155         NM_003540           156         NM_015341           157         NM_0015211           159         NM_003522           160         NM_152515           161         NM_152522           160         NM_152515           161         NM_152522           160         NM_1022346           166         NM_002867           167         NM_001684           166         NM_002867           167         NM_001684           168         NM_002087           167         NM_002047           168         NM_002047           173         NM_002497           174         NM_002497           175         NM_002497           176         NM_002129           176         NM_00131           177         NM_001322           179         NM_001331           178         NM_0010711           181         NM_0101431           177         NM_006147           183         NM_018685           187		C130/J3 CDC2	Cell division cycle 2, G1 to S and G2 to M	-2.8 -2.8	0.0035238
153         NM_012112           154         NM_016359           155         NM_003540           156         NM_012310           158         NM_001211           157         NM_012310           158         NM_001211           159         NM_003522           160         NM_152515           161         NM_152562           162         NM_178229           163         NM_001884           164         NR_001544           165         NM_022346           166         NM_002867           167         NM_001884           168         NM_002867           167         NM_001804           168         NM_002675           171         NM_020497           172         NM_002497           173         NM_002497           174         NM_00318           175         NM_002129           176         NM_010313           177         NM_001221           179         NM_001221           179         NM_001221           179         NM_001671           181         NM_018136           184		NDC80	NDC80 homolog, kinetochore complex component (S. cerevisiae)	-2.9	0.0012085
154         NM_016359           155         NM_003540           156         NM_015341           157         NM_012310           158         NM_001211           159         NM_003522           160         NM_152515           161         NM_152562           162         NM_001884           164         NR_001544           165         NM_002376           167         NM_001884           166         NM_002346           166         NM_002367           167         NM_0010804           168         NM_002675           171         NM_170589           172         NM_002497           173         NM_004701           174         NM_00318           175         NM_004701           174         NM_00313           178         NM_001322           179         NM_001321           178         NM_0010711           181         NM_0016147           183         NM_0101644           183         NM_0107779           189         NM_002783           190         NM_002783           190		TPX2	TPX2, microtubule-associated, homolog (Xenopus laevis)	-2.9	0.0000403
156         NM_015341           157         NM_012310           158         NM_001211           159         NM_003522           160         NM_152515           161         NM_152562           162         NM_178229           163         NM_001884           164         NR_001544           165         NM_022346           166         NM_001804           168         NM_002667           170         NM_002497           173         NM_002497           173         NM_002497           173         NM_002497           174         NM_002497           175         NM_002497           174         NM_00318           175         NM_002497           173         NM_001321           178         NM_001322           179         NM_001322           179         NM_001322           179         NM_001322           179         NM_010322           179         NM_001322           179         NM_001322           179         NM_0016147           180         NM_017779           185		NUSAP1	Nucleolar and spindle associated protein 1	-2.9	0.0011078
157         NM_012310           158         NM_001211           159         NM_003522           160         NM_152515           161         NM_152562           162         NM_01884           164         NR_001844           165         NM_001884           166         NM_002346           166         NM_002867           167         NM_001804           168         NM_0020675           170         NM_002497           173         NM_002497           173         NM_002129           176         NM_001313           177         NM_003138           175         NM_001322           179         NM_001322           179         NM_001322           179         NM_0010322           179         NM_0010322           179         NM_0010322           179         NM_0010322           179         NM_0016325           180         NM_010711           181         NM_001647           183         NM_01835           187         NM_005321           188         NM_017779           189	M_003540	HIST1H4F	Histone cluster 1, H4f	-2.9	0.0010387
158         NM_001211           159         NM_003522           160         NM_152515           161         NM_152562           162         NM_001884           163         NM_001884           164         NR_001544           165         NM_002867           167         NM_001884           166         NM_002867           167         NM_0010804           168         NM_0020675           171         NM_170589           172         NM_002497           173         NM_002129           176         NM_001322           179         NM_001322           179         NM_0010322           179         NM_0010322           179         NM_0010322           179         NM_0010322           179         NM_0010322           179         NM_0010321           180         NM_0120859           180         NM_012783           190         NM_005321           188         NM_017779           189         NM_005321           188         NM_017779           189         NM_005321           188<	M_015341	NCAPH	Non-SMC condensin 1 complex, subunit H	-2.9	0.0003153
159         NM_003522           160         NM_152515           161         NM_152515           161         NM_152515           162         NM_001884           164         NR_001544           166         NM_0022346           166         NM_002867           167         NM_0010804           168         NM_002675           170         NM_002675           171         NM_002497           173         NM_004701           174         NM_002497           175         NM_002129           176         NM_001322           179         NM_0010322           179         NM_0010322           179         NM_0010322           179         NM_0010322           179         NM_0010322           179         NM_0010322           179         NM_0016147           181         NM_018685           187         NM_005321           188         NM_017779           189         NM_005330           190         NM_005330           191         NM_005330           195         NM_006461           196<		KIF4A	Kinesin family member 4A	-2.9	0.0001634
160         NM_152515           161         NM_152562           162         NM_178229           163         NM_001884           164         NR_001544           165         NM_022346           166         NM_002867           167         NM_001804           168         NM_002667           167         NM_0026075           171         NM_02497           173         NM_002497           174         NM_002497           175         NM_002129           176         NM_001318           177         NM_0012129           176         NM_0010322           179         NM_0010313           178         NM_0010711           181         NM_0010711           182         NM_001631           177         NM_0016351           183         NM_018136           184         NM_001631           183         NM_018685           184         NM_002859           185         NM_005321           188         NM_017779           189         NM_002783           190         NM_005301           195 <td></td> <td>BUB1B</td> <td>BUB1 budding uninhibited by benzimidazoles 1 homolog beta (yeast)</td> <td>-2.9</td> <td>0.0000898</td>		BUB1B	BUB1 budding uninhibited by benzimidazoles 1 homolog beta (yeast)	-2.9	0.0000898
161         NM_152562           162         NM_178229           163         NM_001884           164         NR_001544           165         NM_022346           166         NM_002867           167         NM_0010804           168         NM_002675           170         NM_020675           171         NM_170589           172         NM_002129           176         NM_0012129           176         NM_0012129           176         NM_001313           177         NM_0012129           176         NM_001322           179         NM_001321           178         NM_001322           179         NM_001321           180         NM_0101711           181         NM_001634           183         NM_018136           184         NM_020859           185         NM_006147           186         NM_017779           189         NM_002783           190         NM_002783           190         NM_002783           191         NM_005322           192         NM_016343           197		HIST1H2BF	Histone cluster 1, H2bf	-2.9	0.0011487
162         NM_178229           163         NM_001884           164         NR_001544           165         NM_022346           166         NM_002867           167         NM_0010804           168         NM_002675           171         NM_170589           172         NM_002497           173         NM_004701           174         NM_00318           175         NM_0012129           176         NM_018131           177         NM_001322           179         NM_001321           176         NM_010322           179         NM_001321           177         NM_001322           179         NM_001322           179         NM_001322           179         NM_001321           180         NM_010147           183         NM_01647           184         NM_020859           185         NM_001647           186         NM_017779           189         NM_002783           190         NM_002783           190         NM_002783           193         NM_002002           194		CKAP2L CDCA2	Cytoskeleton associated protein 2-like	-3.0 -3.0	0.0008625 0.0001478
163         NM_001884           164         NR_001544           165         NM_022346           166         NM_0010804           168         NM_0010804           168         NM_000350           169         ENST0000038           170         NM_020675           171         NM_170589           172         NM_002497           173         NM_002497           173         NM_002497           173         NM_002497           174         NM_002497           175         NM_002497           174         NM_002497           175         NM_002497           174         NM_002497           175         NM_002131           177         NM_001322           179         NM_001321           180         NM_010141           181         NM_001647           186         NM_0120859           185         NM_006147           186         NM_017779           189         NM_002783           190         NM_0025321           188         NM_017779           189         NM_002783           190 <td></td> <td>IQGAP3</td> <td>Cell division cycle associated 2 IQ motif containing GTPase activating protein 3</td> <td>-3.0 -3.0</td> <td>0.0001478</td>		IQGAP3	Cell division cycle associated 2 IQ motif containing GTPase activating protein 3	-3.0 -3.0	0.0001478
164         NR_001544           165         NM_022346           166         NM_002867           167         NM_0010804           168         NM_002675           170         NM_020675           171         NM_002497           173         NM_002497           173         NM_002497           173         NM_002109           176         NM_001313           177         NM_001322           179         NM_001322           179         NM_0010322           179         NM_0016343           184         NM_012865           187         NM_005321           188         NM_017779           189         NM_002763           190         NM_005322           192         NM_00532           193         NM_00532           194         NM_005030           195         NM_006461           196 <td></td> <td>HAPLN1</td> <td>Hyaluronan and proteoglycan link protein 1</td> <td>-3.0</td> <td>0.0003171</td>		HAPLN1	Hyaluronan and proteoglycan link protein 1	-3.0	0.0003171
165         NM_022346           166         NM_002867           167         NM_0010804           168         NM_000350           169         ENST0000038           170         NM_020675           171         NM_170589           172         NM_002497           173         NM_004701           174         NM_001318           175         NM_001322           179         NM_0010322           179         NM_0010322           179         NM_0010322           179         NM_0010322           179         NM_0010322           179         NM_0010322           179         NM_0016323           180         NM_001711           181         NM_001631           178         NM_001836           184         NM_018136           184         NM_0108685           187         NM_005321           188         NM_017779           189         NM_005322           190         NM_005320           191         NM_005300           195         NM_00530           195         NM_00609           198<	_	CYorf14	Chromosome Y open reading frame 14	-3.0	0.0001937
166         NM_002867           167         NM_0010804           168         NM_000350           169         ENST0000038           170         NM_020675           171         NM_002497           173         NM_002129           176         NM_001318           175         NM_001322           176         NM_010322           177         NM_0010322           178         NM_0010322           179         NM_0010322           179         NM_0010322           179         NM_0010711           181         NM_0010711           182         NM_001711           183         NM_018136           184         NM_006147           186         NM_018685           187         NM_005321           188         NM_017779           189         NM_005322           190         NM_005321           188         NM_017779           189         NM_002783           190         NM_005300           195         NM_005301           195         NM_005301           196         NM_016343           197<		NCAPG	Non-SMC condensin 1 complex, subunit G	-3.0	0.0016196
167         NM_0010804           168         NM_006350           169         ENST000038           170         NM_020675           171         NM_170589           172         NM_002497           173         NM_002129           176         NM_001313           177         NM_001313           178         NM_0010322           179         NM_001255           180         NM_0010711           181         NM_001071           182         NM_001071           183         NM_018136           184         NM_0016147           185         NM_006147           186         NM_018685           187         NM_005321           188         NM_017779           189         NM_005321           188         NM_017779           189         NM_005321           188         NM_017779           189         NM_005321           188         NM_0107779           189         NM_005301           191         NM_005303           192         NM_005303           193         NM_005303           194 <td></td> <td>RAB3B</td> <td>RAB3B, member RAS oncogene family</td> <td>-3.0</td> <td>0.0000771</td>		RAB3B	RAB3B, member RAS oncogene family	-3.0	0.0000771
169         ENST000038           170         NM_020675           171         NM_170589           172         NM_002497           173         NM_004701           174         NM_00318           175         NM_002129           176         NM_018131           177         NM_001322           179         NM_001711           181         NM_018136           184         NM_020859           185         NM_006147           186         NM_016343           190         NM_002783           190         NM_002783           190         NM_005322           192         NM_005322           193         NM_00532           194         NM_00532           195         NM_006461           196         NM_016343           197		MBOAT1	Membrane bound O-acyltransferase domain containing 1	-3.1	0.0000156
170         NM_020675           171         NM_170589           172         NM_002497           173         NM_004701           174         NM_00318           175         NM_001131           176         NM_018131           177         NM_001322           179         NM_001322           179         NM_001322           179         NM_001322           179         NM_001322           179         NM_001322           179         NM_001711           181         NM_001711           182         NM_004934           183         NM_018136           184         NM_020859           185         NM_006147           186         NM_005321           188         NM_017779           189         NM_005321           188         NM_017779           189         NM_005321           188         NM_002783           190         NM_002783           193         NM_005322           193         NM_005320           194         NM_005030           195         NM_0066461           196	4_006350	FST	Follistatin	-3.1	0.0008267
171         NM_170589           172         NM_002497           173         NM_002497           173         NM_002497           173         NM_002129           176         NM_00313           177         NM_003513           178         NM_001322           179         NM_001321           181         NM_018136           184         NM_020859           185         NM_006147           186         NM_018685           187         NM_005321           188         NM_017779           189         NM_002783           190         NM_002732           192         NM_005321           193         NM_202002           194         NM_00532           190         NM_00532           192         NM_016343           197         NM_00609           198         NM_016343           197	IST00000389239	FAM64A	Family with sequence similarity 64, member A (FAM64A), mRNA	-3.1	0.0003557
172         NM_002497           173         NM_004701           174         NM_003318           175         NM_002129           176         NM_018131           177         NM_001322           179         NM_0010322           179         NM_0010322           179         NM_0010322           179         NM_001711           181         NM_001711           182         NM_004934           183         NM_018136           184         NM_002859           185         NM_006147           186         NM_017779           189         NM_005321           188         NM_017779           189         NM_005322           190         NM_005322           192         NM_005321           188         NM_017779           189         NM_002783           190         NM_005322           192         NM_005300           195         NM_006030           195         NM_006069           198         NM_016343           197         NM_006069           198         NM_0145697           200		SPC25	SPC25, NDC80 kinetochore complex component, homolog (S. cerevisiae)	-3.1	0.0024131
173         NM_004701           174         NM_00318           175         NM_002129           176         NM_018131           177         NM_0010322           178         NM_0010322           179         NM_0010322           179         NM_0010322           179         NM_001711           181         NM_001711           182         NM_004934           183         NM_018136           184         NM_0020859           185         NM_005321           188         NM_017779           189         NM_005321           188         NM_017779           189         NM_005321           188         NM_017779           189         NM_005321           190         NM_005321           191         NM_005321           192         NM_005321           193         NM_202002           194         NM_005301           195         NM_005030           195         NM_006091           198         NM_016343           197         NM_0060691           198         NM_0145697           200 <td>-</td> <td>CASC5</td> <td>Cancer susceptibility candidate 5</td> <td>-3.1</td> <td>0.0006033</td>	-	CASC5	Cancer susceptibility candidate 5	-3.1	0.0006033
174         NM_003318           175         NM_002129           176         NM_0018131           177         NM_0010322           179         NM_0010322           179         NM_001255           180         NM_001711           181         NM_001632           183         NM_001711           184         NM_004934           183         NM_018136           184         NM_0020859           185         NM_005321           188         NM_017779           189         NM_005321           188         NM_017779           189         NM_005321           190         NM_005321           191         NM_005321           192         NM_005321           193         NM_202002           194         NM_005301           195         NM_005303           196         NM_014736           197         NM_006069           198         NM_016343           197         NM_006069           198         NM_0145697           200         NM_005573           201         NM_002573           202		NEK2	NIMA (never in mitosis gene a)-related kinase 2	-3.1	0.0035344
175         NM_002129           176         NM_018131           177         NM_001322           179         NM_001325           180         NM_001711           181         NM_001711           182         NM_004934           183         NM_018136           184         NM_004934           183         NM_018136           184         NM_002859           185         NM_005211           186         NM_017779           187         NM_005321           188         NM_017779           189         NM_005556           191         NM_005322           192         NM_005322           192         NM_005300           195         NM_005301           196         NM_005302           192         NM_005303           193         NM_202002           194         NM_005303           195         NM_006461           196         NM_016343           197         NM_006603           198         NM_0168689           199         NM_145697           200         NM_003638           203		CCNB2	Cyclin B2	-3.1	0.0006401
176         NM_018131           177         NM_003513           178         NM_0010322           179         NM_001255           180         NM_001255           180         NM_001711           181         NM_004934           183         NM_018136           184         NM_020859           185         NM_005321           188         NM_01779           189         NM_005321           188         NM_0107556           191         NM_005322           192         NM_014736           193         NM_202002           194         NM_005322           192         NM_014736           193         NM_202002           194         NM_005030           195         NM_006461           196         NM_016343           197         NM_00609           198         NM_016889           199         NM_145697           200         NM_003538           201         NM_003538           202         NM_003537           203         NM_014750           204         NM_003538           205		TTK	TTK protein kinase	-3.1 -3.1	0.0011001
177         NM_003513           178         NM_0010322           179         NM_001255           180         NM_001711           181         NM_001711           182         NM_0018136           183         NM_0018136           184         NM_0020859           185         NM_006147           186         NM_005321           188         NM_007779           189         NM_002783           190         NM_005322           192         NM_014736           193         NM_202002           194         NM_005030           195         NM_006461           196         NM_016343           197         NM_00609           198         NM_016343           197         NM_000601           196         NM_016343           197         NM_000603           198         NM_016343           197         NM_000603           198         NM_016343           197         NM_000603           198         NM_0145697           2001         NM_003638           203         NM_014750           204		HMGB2 CEP55	High-mobility group box 2 Centrosomal protein 55kDa	-3.1 -3.1	0.0003609 0.0053938
178         NM_0010322           179         NM_001255           180         NM_001255           180         NM_001255           180         NM_001711           181         NM_004934           183         NM_018136           184         NM_020859           185         NM_006147           186         NM_017779           189         NM_002783           190         NM_005322           192         NM_014736           193         NM_202002           194         NM_005322           193         NM_202002           194         NM_005322           193         NM_202002           194         NM_005030           195         NM_006461           196         NM_016343           197         NM_00609           198         NM_016343           197         NM_00609           198         NM_016343           197         NM_00609           198         NM_0145697           2001         NM_005573           2011         NM_003638           205         NM_003638           205		HIST1H2AB	Histone cluster 1, H2ab	-3.1	0.000027
179         NM_001255           180         NM_001711           181         NM_001711           182         NM_001711           182         NM_001711           182         NM_001711           182         NM_001711           182         NM_018136           184         NM_020859           185         NM_006147           186         NM_018685           187         NM_005321           188         NM_017779           189         NM_002783           190         NM_005322           192         NM_014736           193         NM_202002           194         NM_005030           195         NM_006461           196         NM_016343           197         NM_00609           198         NM_016343           197         NM_000609           198         NM_0146697           200         NM_005573           201         NM_005030           1202         NM_00613           203         NM_014750           204         NM_003638           205         NM_003537           206		TMPO	Thymopoietin	-3.2	0.0003481
180         NM_001711           181         NM_001071           182         NM_004934           183         NM_018136           184         NM_0020859           185         NM_006147           186         NM_0180685           187         NM_005321           188         NM_017779           189         NM_002783           190         NM_005556           191         NM_005322           192         NM_014736           193         NM_202002           194         NM_005030           195         NM_006461           196         NM_016343           197         NM_00609           198         NM_016343           197         NM_0005573           201         NM_005573           201         NM_005573           201         NM_006033           202         NM_00613           203         NM_014750           204         NM_003638           205         NM_003537           206         NM_00276           207         NR_003106           208         NM_002763           209		CDC20	Cell division cycle 20 homolog (S. cerevisiae)	-3.2	0.0000258
182         NM_004934           183         NM_018136           184         NM_020859           185         NM_006147           186         NM_018685           187         NM_005321           188         NM_00773           190         NM_005756           191         NM_005322           192         NM_014736           193         NM_202002           194         NM_00530           195         NM_006461           196         NM_016343           197         NM_006461           196         NM_016343           197         NM_006461           196         NM_016343           197         NM_006461           196         NM_016343           197         NM_006461           196         NM_0145697           200         NM_005733           201         NM_203401           202         NM_00638           203         NM_014750           204         NM_003638           205         NM_003166           208         NM_002276           209         NM_002276           209		BGN	Biglycan	-3.2	0.0000375
183         NM_018136           184         NM_020859           185         NM_006147           186         NM_005321           187         NM_005321           188         NM_01779           189         NM_005321           190         NM_005556           191         NM_005556           192         NM_014736           193         NM_202002           194         NM_005330           195         NM_006461           196         NM_016343           197         NM_006609           198         NM_0168689           199         NM_145697           200         NM_005733           201         NM_203401           202         NM_006388           203         NM_014750           204         NM_003638           205         NM_014932           207         NR_003106           208         NM_002276           209         NM_0027633           210         NM_001290	M_001071	TYMS	Thymidylate synthetase	-3.2	0.0032506
184         NM_020859           185         NM_006147           186         NM_018685           187         NM_005321           188         NM_01779           189         NM_005321           180         NM_005321           190         NM_005321           190         NM_005321           190         NM_005322           192         NM_014736           193         NM_202002           194         NM_005030           195         NM_006461           196         NM_016343           197         NM_000609           198         NM_016368           199         NM_145697           200         NM_005733           201         NM_003638           203         NM_014750           204         NM_003638           205         NM_003638           206         NM_014932           207         NR_003106           208         NM_002276           209         NM_005733           210         NM_001290	4_004934	CDH18	Cadherin 18, type 2	-3.2	0.0000862
185         NM_006147           186         NM_018685           187         NM_005321           188         NM_017779           189         NM_002783           190         NM_002783           190         NM_005322           191         NM_005322           192         NM_014736           193         NM_202002           194         NM_005030           195         NM_006461           196         NM_016343           197         NM_000609           198         NM_018689           199         NM_145697           200         NM_005733           201         NM_203401           202         NM_006013           203         NM_014750           204         NM_003638           205         NM_003638           206         NM_014932           207         NR_003106           208         NM_002763           209         NM_005733           210         NM_005733           210         NM_005733		ASPM	Asp (abnormal spindle) homolog, microcephaly associated (Drosophila)	-3.2	0.0001314
186         NM_018685           187         NM_005321           188         NM_017779           189         NM_002783           190         NM_002556           191         NM_005322           192         NM_014736           193         NM_202002           194         NM_005030           195         NM_006461           196         NM_016343           197         NM_000609           198         NM_018689           199         NM_145697           200         NM_00573           201         NM_006013           203         NM_014750           204         NM_003638           205         NM_003537           206         NM_014932           207         NR_003106           208         NM_00276           209         NM_005733           210         NM_0027633           210         NM_00276		SHROOM3	Shroom family member 3	-3.2	0.0002947
187         NM_005321           188         NM_017779           189         NM_002783           190         NM_005556           191         NM_005322           192         NM_014736           193         NM_202002           194         NM_005030           195         NM_006461           196         NM_016343           197         NM_000609           198         NM_018689           199         NM_145697           200         NM_005733           201         NM_005030           202         NM_006013           203         NM_014750           204         NM_003638           205         NM_003537           206         NM_014932           207         NR_003106           208         NM_00276           209         NM_005733           210         NM_005733           210         NM_00276	_	IRF6	Interferon regulatory factor 6	-3.2	0.0002558
188         NM_017779           189         NM_002783           190         NM_005556           191         NM_005322           192         NM_014736           193         NM_202002           194         NM_00530           195         NM_006461           196         NM_016343           197         NM_000609           198         NM_018689           199         NM_145697           200         NM_005733           201         NM_00538           203         NM_014750           204         NM_003638           205         NM_003537           206         NM_014932           207         NR_003106           208         NM_00276           209         NM_005733           210         NM_005733           210         NM_005733	_	ANLN	Anillin, actin binding protein	-3.2	0.0004383
189         NM_002783           190         NM_005556           191         NM_005322           192         NM_014736           193         NM_202002           194         NM_00530           195         NM_006461           196         NM_006643           197         NM_000609           198         NM_018689           199         NM_145697           200         NM_005573           201         NM_203401           202         NM_006013           203         NM_014750           204         NM_003638           205         NM_003537           206         NM_014932           207         NR_003106           208         NM_002276           209         NM_005733           210         NM_001290		HIST1H1E DEPDC1	Histone cluster 1, H1e	-3.3 -3.3	0.0000589 0.0005434
190         NM_005556           191         NM_005322           192         NM_014736           193         NM_202002           194         NM_005030           195         NM_006461           196         NM_016343           197         NM_000609           198         NM_018689           199         NM_005573           201         NM_006013           203         NM_014750           204         NM_003638           205         NM_003537           206         NM_014932           207         NR_003106           208         NM_002276           209         NM_005733           210         NM_001290		PSG7	DEP domain containing 1 Pregnancy specific beta-1-glycoprotein 7	-3.3	0.0003434
191         NM_005322           192         NM_014736           193         NM_202002           194         NM_005030           195         NM_006461           196         NM_016343           197         NM_006601           198         NM_018689           199         NM_045697           200         NM_005573           201         NM_006013           202         NM_006038           203         NM_014750           204         NM_003638           205         NM_003537           206         NM_014932           207         NR_003106           208         NM_002276           209         NM_005733           210         NM_005733           210         NM_001290		KRT7	Keratin 7	-3.4	0.00002987
192         NM_014736           193         NM_202002           194         NM_005030           195         NM_006461           196         NM_016343           197         NM_000609           198         NM_018689           199         NM_145697           200         NM_005573           201         NM_003638           203         NM_014750           204         NM_003638           205         NM_003537           206         NM_014932           207         NR_003106           208         NM_002276           209         NM_005733           210         NM_005733           210         NM_0021290		HIST1H1B	Histone cluster 1, H1b	-3.4	0.000073
193         NM_202002           194         NM_005030           195         NM_006461           196         NM_016343           197         NM_000609           198         NM_018689           199         NM_145697           200         NM_005573           201         NM_005573           202         NM_006013           203         NM_014750           204         NM_003638           205         NM_003537           206         NM_014932           207         NR_003106           208         NM_002276           209         NM_005733           210         NM_001290		KIAA0101	KIAA0101	-3.4	0.0073048
194         NM_005030           195         NM_006461           196         NM_016343           197         NM_000609           198         NM_018689           199         NM_145697           200         NM_005573           201         NM_006013           202         NM_006013           203         NM_014750           204         NM_003638           205         NM_0014932           206         NM_014932           207         NR_003106           208         NM_002276           209         NM_001290		FOXM1	Forkhead box M1	-3.4	0.0009265
196         NM_016343           197         NM_000609           198         NM_018689           199         NM_145697           200         NM_005573           201         NM_005073           202         NM_0006013           203         NM_014750           204         NM_003638           205         NM_003537           206         NM_014932           207         NR_003106           208         NM_002276           209         NM_005733           210         NM_001290	M_005030	PLK1	Polo-like kinase 1 (Drosophila)	-3.4	0.0000316
197         NM_000609           198         NM_018689           199         NM_145697           200         NM_005573           201         NM_203401           202         NM_006013           203         NM_014750           204         NM_003638           205         NM_003537           206         NM_014932           207         NR_003106           208         NM_002276           209         NM_005733           210         NM_001290		SPAG5	Sperm associated antigen 5	-3.4	0.0002157
198         NM_018689           199         NM_145697           200         NM_005573           201         NM_003573           202         NM_006013           203         NM_014750           204         NM_003638           205         NM_003537           206         NM_014932           207         NR_003106           208         NM_002276           209         NM_005733           210         NM_001290		CENPF	Centromere protein F, 350/400ka (mitosin)	-3.5	0.0053205
199         NM_145697           200         NM_005573           201         NM_203401           202         NM_006013           203         NM_014750           204         NM_003638           205         NM_014932           206         NM_014932           207         NR_003106           208         NM_002276           209         NM_005733           210         NM_001290		CXCL12	Chemokine (C-X-C motif) ligand 12 (stromal cell-derived factor 1)	-3.5	0.0000196
200         NM_005573           201         NM_203401           202         NM_006013           203         NM_014750           204         NM_003638           205         NM_003537           206         NM_014932           207         NR_003106           208         NM_002276           209         NM_005733           210         NM_001290		KIAA1199	KIAA1199	-3.6	0.0000461
201         NM_203401           202         NM_006013           203         NM_014750           204         NM_003638           205         NM_003537           206         NM_014932           207         NR_003106           208         NM_002276           209         NM_005733           210         NM_001290	_	NUF2 1 mnr 1	NUF2, NDC80 kinetochore complex component, homolog (S. cerevisiae)	-3.6	0.0008586
202         NM_006013           203         NM_014750           204         NM_003638           205         NM_014932           206         NM_014932           207         NR_003106           208         NM_002276           209         NM_005733           210         NM_001290	_	LMNB1 STMN1	Lamin B1 Stathmin 1/oncoprotein 18	-3.7 -3.8	0.0000014 0.0000397
203         NM_014750           204         NM_003638           205         NM_003537           206         NM_014932           207         NR_003106           208         NM_002276           209         NM_005733           210         NM_001290	-	RPL10	Ribosomal protein L10	-3.8	0.0000397
204NM_003638205NM_003537206NM_014932207NR_003106208NM_002276209NM_005733210NM_001290		DLG7	Discs, large homolog 7 (Drosophila)	-3.9	0.0004194
205         NM_003537           206         NM_014932           207         NR_003106           208         NM_002276           209         NM_005733           210         NM_001290		ITGA8	Integrin, alpha 8	-4.0	0.0005969
206NM_014932207NR_003106208NM_002276209NM_005733210NM_001290		HIST1H3B	Histone cluster 1, H3b	-4.0	0.0033207
207NR_003106208NM_002276209NM_005733210NM_001290		NLGN1	Neuroligin 1	-4.2	0.0048918
209 NM_005733 210 NM_001290		PWCR1	Prader-Willi syndrome chromosome region 1	-4.2	0.0041387
210 NM_001290		KRT19	Keratin 19	-4.2	0.0002805
_		KIF20A	Kinesin family member 20A	-4.3	0.005152
	_	LDB2	LIM domain binding 2	-4.4	0.0000202
	M_001080428	ODZ2	Odz, odd Oz/ten-m homolog 2 (Drosophila)	-4.5	0.0001199
212 NM_003521		HIST1H2BM	Histone cluster 1, H2bm	-4.5	0.0000106
213 NM_018284		GBP3 TRHDE	Guanylate binding protein 3 Thyroteopin releasing hormone degrading enzyme	-4.6 -4.7	0.0002522 0.0001288
214 NM_013381	1_013301	INIDE	Thyrotropin-releasing hormone degrading enzyme	4./	( <i>continues</i> )

TABLE 5 (continued).	Downregulated	Homozygous	GCD	II-Related Genes

No.	Gene Accession	Gene Symbol	Gene Description	Change	Р
215	NM_001040152	PEG10	Paternally expressed 10		0.0000323
216	NM_005159	ACTC1	Actin, alpha, cardiac muscle 1	-4.7	0.0000545
217	NM_003542	HIST1H4C	Histone cluster 1, H4c	-5.2	0.0002514
218	NM_022350	LRAP	Leukocyte-derived arginine aminopeptidase	-5.2	0.0000817
219	NM_002421	MMP1	Matrix metallopeptidase 1 (interstitial collagenase)	-5.5	0.0047864
220	NM_002781	PSG5	Pregnancy specific beta-1-glycoprotein 5	-5.6	0.0000083
221	NM_005711	EDIL3	EGF-like repeats and discoidin 1-like domains 3	-6.5	0.0000014
222	NM_003411	ZFY	Zinc finger protein, Y-linked	-6.5	0.0000338
223	NM_005434	MALL	Mal, T-cell differentiation protein-like	-7.5	0.0000132
224	NM_004653	JARID1D	Jumonji, AT rich interactive domain 1D	-9.0	0.0000055
225	NM_001005852	CYorf15A	Chromosome Y open reading frame 15A	-9.7	0.0000309
226	NM_004932	CDH6	Cadherin 6, type 2, K-cadherin (fetal kidney)	-10.2	0.0000005
227	NM_032576	CYorf15B	Chromosome Y open reading frame 15B	-11.1	0.0000012
228	NM_007125	UTY	Ubiquitously transcribed tetratricopeptide repeat gene, Y-linked	-11.2	0.0000027
229	NM_014893	NLGN4Y	Neuroligin 4, Y-linked	-11.8	0.0001143
230	NM_021013	KRT34	Keratin 34	-12.1	0.0000017
231	NM_004654	USP9Y	Ubiquitin specific peptidase 9, Y-linked (fat facets-like, Drosophila)	-16.3	0.0000009
232	NM_005045	RELN	Reelin	-17.4	0.0001692
233	NM_004681	EIF1AY	Eukaryotic translation initiation factor 1A, Y-linked	-19.5	0.0014353
234	NM_001008	RPS4Y1	Ribosomal protein S4, Y-linked 1	-27.2	0.0000016
235	NM_001999	FBN2	Fibrillin 2 (congenital contractural arachnodactyly)	-47.8	0.0000903
236	NM_004660	DDX3Y	DEAD (Asp-Glu-Ala-Asp) box polypeptide 3, Y-linked	-59.9	0.0002855

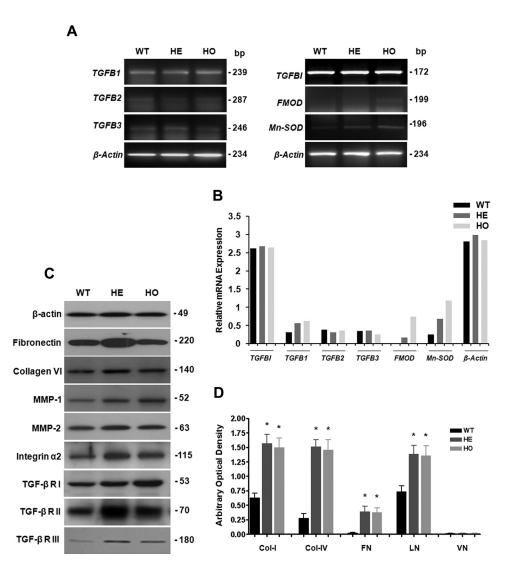
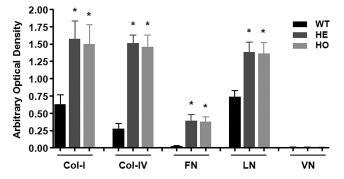


FIGURE 2. Relative quantification of 10 representative genes identified in the microarray. (A) RT-PCR was performed, and amplification products were subjected to agarose gel electrophoresis and were stained with ethidium bromide. (B) Each group was represented by two different cases whose RNA was pooled (sample pairs 1 and 2). Relative mRNA expression levels were normalized against  $\beta$ -actin. (C) Western blot analysis was performed using heterozygous GCD II, homozygous GCD II, and wild-type PCFs. (D) Each group was represented by two different cases whose protein was pooled (sample pairs 2 and 3). Relative protein expression levels were normalized to  $\beta$ -actin. Antibodies used are indicated to the *left* of each blot. WT, wild-type; HE, heterozygous GCD II; HO, homozygous GCD II. \*P < 0.05.



**FIGURE 3.** Cell adhesion profiles of heterozygous GCD II, homozygous GCD II, and wild-type PCFs. Each column represents the mean value of four microspots; error bar, SD. PCF attachment experiments were performed with different ECM proteins. The experiment was repeated three times. The results are expressed as the mean  $\pm$  SD (n = 3). BSA, bovine serum albumin; Col-I, type I collagen; Col-IV, type IV collagen; FN, fibronectin; LN, laminin; TN, tenascin; VN, vitronectin; WT, wild-type; HE, heterozygous GCD II; HO, homozygous GCD II. \*P < 0.05.

with both  $\alpha v\beta 3$  and  $\alpha v\beta 5$  integrin receptors.<sup>33</sup> In the present investigation, we showed that heterozygous and homozygous GCD II PCFs tightly attached to collagen-I, collagen-IV, fibronectin, and lamine, compared with wild-type cells. These results support those in previous studies that show that TGF-BIp plays a functional role in cell-ECM adhesion in the corneal stroma. However, our data suggest that tight attachment of heterozygous and homozygous GCD II PCFs to some ECM molecules is not due to a direct interaction between TGFBIp and the ECM. There are at least two possible explanations for this observation. First, TGFBIp expression was not significantly different in the heterozygous GCD II, homozygous GCD II, and wild-type PCFs.<sup>15</sup> Second, although TGFBIp can bind to collagens I, II, and III<sup>34</sup> and to fibronectin,<sup>35</sup> mutations in the *TGFBI* that commonly occur in certain corneal dystrophies do not apparently affect its binding to type I collagen, fibronectin, and laminin.<sup>36</sup> It is possible that signaling through integrins is involved in the attachment of GCD II PCFs to the ECM, especially since TGFBIp directly interacts with integrins.<sup>37</sup> This possibility is supported by the fact that increased integrin  $\alpha_2$ expression was detected in heterozygous and homozygous GCD II PCFs. Therefore, we suggest that increased cell adhesion does not result from structural changes, as a result of mutation, in the RGD motif and FAS domain of TGFBIp, but rather because of downstream signaling events that occur as a result of interactions between integrins and mutant TGFBIp.

In conclusion, our data suggest that the altered receptormediated signaling pathway of TGF- $\beta$  and integrins play a key role in GCD II pathophysiology. This study also identified other novel factors involved in this process that could aid in the design of future experiments to further investigate the development of this disease.

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