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Differential gene expression profiling of the sciatic nerve in type 1 and type 2 diabetic mice

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Abstract. Diabetic peripheral neuropathy (DPN) is a common complication of diabetes mellitus (DM). The pathogenic mechanisms of DPN and the therapeutic interventions required may be distinct between type 1 (T1) and type 2 (T2) DM. However, the molecular mechanisms underlying the pathogenesis of DPN in both types of diabetes remain unclear. The aim of the current study was to identify the changes in genes and pathways associated with DPN in sciatic nerves of T1- and T2DM mice using bioinformatics analysis. The microarray profiles of sciatic nerves of T1DM (GSE11343) and T2DM (GSE27382) mouse models were downloaded from the Gene Expression Omnibus database to identify differentially expressed genes (DEGs) in each. DEGs in the two types of DM (with fold change ≥2 and $P<0.05$) were identified with BRB-ArrayTools. Gene Ontology (GO) term and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment analyses were performed using the Database for Annotation, Visualization and Integrated Discovery. A protein-protein interaction (PPI) network was constructed using the Search Tool for the Retrieval of Interacting Genes/Proteins and visualized using Cytoscape. Compared with control samples, 623 and 1,890 DEGs were identified in sciatic nerves of T1- and T2DM mice, respectively. Of these, 75 genes were coordinately dysregulated in the sciatic nerves of both models. Many DEGs unique to T1DM mice were localized to the nucleoplasm and were associated with regulation of transcription processes, while many unique to T2DM mice were localized at cell junctions and were associated with ion transport. In addition, certain DEGs may be associated with the different treatment strategies used for the two types of DM. This analysis provides insight into the functional gene sets and pathways operating in sciatic nerves in T1- and T2DM. The results should improve understanding of the molecular mechanisms underlying the pathophysiology of DPN, and provide information for the development of therapeutic strategies for DPN specific to each type of DM.

Introduction

Diabetic peripheral neuropathy (DPN) is a common complication of diabetes mellitus (DM). More than half of patients with DM worldwide suffer from DPN during the course of the disease (1,2). DPN is characterized by distal-to-proximal nerve damage leading to neuropathic pain and loss of sensation (3). It is also associated with notably high morbidity and mortality: Previous studies reported that the mortality rate approximated to 25-50% within 5-10 years following onset of diabetic neuropathy (4,5). Strict maintenance of normal glycemic level is the only effective treatment available for DPN at present (6).

Though the occurrence of DPN is common to both type 1 (T1) and type 2 (T2)DM, a number of studies have suggested that its pathogenic mechanism may differ between the two (7,8). For example, more abnormalities at the molecular, functional and morphometric levels including increased frequencies of denervated Schwann cells and significant fiber loss have been observed in the peripheral nerve of T1DM mice compared with in T2DM mice (8,9). In addition, different structural changes may lead to variation in nerve conduction velocity for DPN in the two diabetic models (10). These fundamentally different mechanisms for DPN may lead to varying effects of the common treatments, such as in control of glucose, which has been suggested to be more beneficial for DPN in T1DM than in T2DM (7). Therefore, determining the distinct molecular mechanisms underlying DPN in T1- and T2DM is of paramount importance for the development of successful therapeutic interventions.

In the last decade, the development of high-throughput platforms including microarray technology has allowed researchers to concurrently determine the expression levels of several thousands of differentially expressed genes (DEGs) in diseases (11,12). In addition, the comparison of gene expression profiles of DEGs through microarray technology using bioinformatics analysis has determined distinct pathophysiological mechanisms in different diseases or syndromes including neuropathic pain and chronic radicular

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pain (13). For instance, Zhang *et al* (14) screened a number of DEGs in a control (healthy) group of mice and a group with streptozotocin (STZ)-induced diabetes, and identified genes co-regulated by both STZ and rosiglitazone, which may be potential targets in the treatment of DPN. However, there are few studies that have compared the gene expression profiles of DEGs between DPN in T1- and T2DM through microarray profiling. In the present study, the aim was to compare the DEGs between the sciatic nerves of T1- and T2DM mouse models by microarray profiling. Furthermore, the distinct biological processes and pathways associated with DPN in T1- or T2DM were analyzed and compared based on gene ontology (GO) and pathway enrichment analyses. This was hoped to provide novel insights into the distinct pathophysiological mechanisms and implicate drug therapies for DPN specific to the different types of DM.

Materials and methods

Source of microarray data. The gene expression profiles of GSE11343 and GSE27382 were obtained from the Gene Expression Omnibus (GEO) database (http://www.ncbi.nlm.nih.gov/geo/). The annotation platforms for GSE11343 and GSE27382 were GPL1261 and GPL9746, respectively.

For GSE11343 submitted by Wiggin *et al* (15), included datasets were of five sciatic nerve samples from mice with T1DM induced by STZ (GSM286169, GSM286173, GSM286176, GSM286178 and GSM286430) and four sciatic nerve samples from normal mice (GSM286159, GSM286160, GSM286163 and GSM286165).

For GSE27382 submitted by Pande *et al* (16), included datasets were of six sciatic nerve samples from db/db mice with T2DM (GSM677112-GSM677117) and seven sciatic nerve samples from db/+ (normal) mice (GSM677105-GSM677111).

Pre-processing of microarray data and identification of DEGs. Pre-processing for the cell intensity (CEL) files including conversion into expression measures, background correction and quartile data normalization was performed with BRB-ArrayTools (version 4.5.1) (17). The univariate t-test with a fold change ≥2 and nominal significance level of 0.05 was applied in BRB-ArrayTools to identify the DEGs between the diabetic and normal groups.

Gene ontology and pathway enrichment analyses. To identify the DEGs determined with BRB-ArrayTools, GO and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment analyses were performed via the Database for Annotation, Visualization and Integrated Discovery (DAVID 6.8; http://david.abcc.ncifcrf.gov/) (18,19). GO terms [categorized into molecular function (MF), biological process (BP) and cellular component (CC)] and KEGG pathways with P<0.05 were considered significantly enriched by the DEGs.

Construction of protein-protein interaction (PPI) network and module analysis. With the purpose of evaluating the relationships among DEGs from the perspective of protein interaction, a protein-protein interaction (PPI) network was constructed with the Search Tool for the Retrieval of Interacting Genes/Proteins (STRING 10.5; http://www.string-db.org) and visualized using Cytoscape software (version 3.4.0; http://cytoscape.org/) (18). A combined score >0.4 was selected to determine significant interactions among DEGs. In accordance with a previous analysis (20), the connectivity degree of a protein, namely the number of proteins it connected with, was considered to indicate importance of the protein in the PPI network.

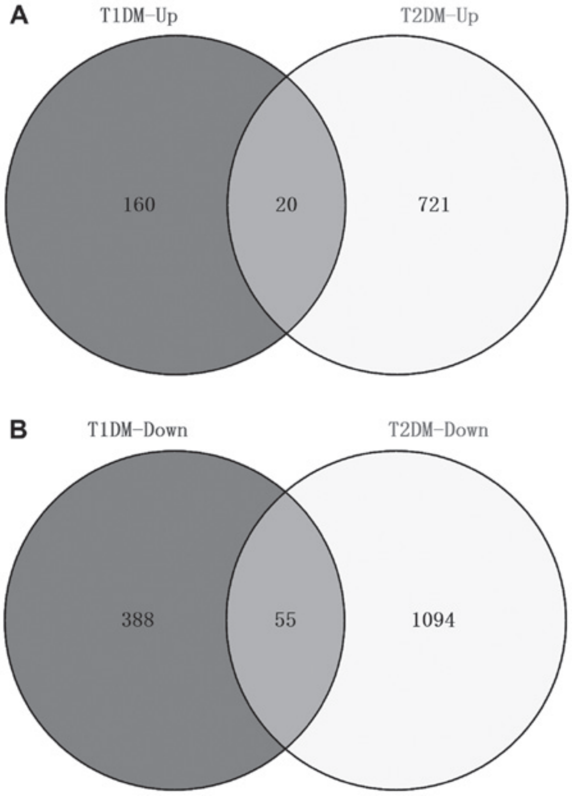

Figure 1. Numbers of (A) upregulated and (B) downregulated differentially expressed genes in the sciatic nerve of T1- and T2DM mouse models. T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus.

Module analysis was performed in the plugin ClusterONE (version 1.0) in Cytoscape with a threshold of P<0.001. In addition, function and pathway enrichment analyses were performed for DEGs in the modules with a threshold of P<0.05.

Results

Identification of DEGs. Based on the criteria of a nominal significance level of 0.05 and fold change ≥2, 623 and 1,890 DEGs were identified in sciatic nerves of T1DM (GSE11343) and T2DM (GSE27382) mice, respectively, as compared with the control samples. Among them, 75 genes were identified to be coordinately dysregulated in sciatic nerves of both models, with 20 genes upregulated and 55 genes downregulated (Fig. 1 and Table SI). Meanwhile, 160 upregulated and 388 downregulated DEGs were unique to T1DM (Fig. 1 and Table SII), and 721 upregulated and 1,094 downregulated DEGs were unique to T2DM (Fig. 1 and Table SIII).

GO and pathway enrichment analyses. There were 60 coincident enriched GO terms for DEGs in T1- and T2DM, the top 20 of which are listed in Table I. In addition, the top 20 enriched GO terms for DEGs that were unique to sciatic nerves from the T1- or T2DM model are presented in Table II. Besides these,

Table SI. List of genes coordinately regulated in type 1 and type 2 diabetes mellitus.

Gene count	Gene symbol	Gene count	Gene symbol	Gene count	Gene symbol
Upregulated					
1	C1qtnf9	8	Myo5b	15	Hipk3
2	Hspb7	9	Tcf15	16	Hif3a
3	Fmo2	10	Ltbp2	17	Pde2a
4	Cyp1a1	11	Tlr7	18	Fkbp5
5	Gpihbp1	12	Map3k6	19	8430436 N08Rik
6	Mbd1	13	Angptl4	20	Dnah11
7	Gm4876	14	D8Ertd82e		
Downregulated					
1	Kcna2	20	Pcyox1l	39	Tmem229a
2	Kif5b	21	Rapgef4	40	Rian
3	Cct4	22	Sptssb	41	C1ql3
4	Fchsd2	23	5930427L02Rik	42	Chic1
5	Fgf14	24	Efcab14	43	Cntn3
6	Fndc5	25	Frzb	44	Map1b
7	Kcna1	26	Cemip	45	Slc35f1
8	Slc25a27	27	Zic2	46	Sox9
9	Galnt3	28	Zic1	47	Gpm6b
10	Ncald	29	Slc1a3	48	Slc47a1
11	Senp8	30	Snhg14	49	Elavl2
12	Asph	31	Bmp5	50	Ptn
13	Pdia3	32	Lamc3	51	Dcc
14	Bicd1	33	Nipal1	52	Atp13a5
15	Elovl4	34	C78859	53	Hpca
16	Npas3	35	Glipr2	54	Sox8
17	Opcml	36	Enah	55	Zic5
18	Nr2f2	37	Gm19935		
19	Ntrk3	38	Paqr8		

21 and 27 KEGG pathways were enriched for DEGs in T1- and T2DM, respectively. Among them, 4 pathways were coincident in both models (Table III), while 17 and 23 pathways were unique to T1- and T2DM respectively (Table IV).

PPI network. A total of 419 nodes and 1,343 edges were involved in the PPI for T1DM, whereas 1,416 nodes and 11,077 edges were involved in that for T2DM (data not shown). The top 10 proteins in each of T1- and T2DM with a relatively high degree of connectivity in the PPI network are presented in Table V.

Extent of enriched function and topological structure analysis for the modules of the PPI networks. Based on the module analysis by ClusterONE, a single module was determined in the PPI for T1DM (Fig. 2A) and 7 modules for T2DM (Fig. 2B-H). The information on the modules, including node number, P-value, protein with highest degree of connectivity, and numbers of GO terms and KEGG pathways are shown in Table VI.

Discussion

DPN is among the most frequent complications for T1- and T2DM. It is generally considered that DPN results from damage by hyperglycemia, regardless of the type of DM (3). In

Table SII. List of genes specific to type 1 diabetes mellitus.

Gene count	Gene symbol	Gene count	Gene symbol	Gene count	Gene symbol
Upregulated					
1	Myh2	55	Wdr63	108	Bbd9
2	Doc2b	56	Gm17455	109	Klk1b24
3	Atxn7l1	57	Per2	110	Acer2
4	Tbata	58	Gimap8	111	Angpt2
5	Rph3al	59	Cpa3	112	BC003965
6	Apoc3	60	C77370	113	Rtp3
7	Nr5a2	61	Rgs3	114	Iffo1
8	Alpk3	62	Oosp1	115	Lhx6
9	Tal1	63	Dbp	116	Tmem88
10	Aldh3b2	64	Dll4	117	4930539E08Rik
11	Rasd2	65	Mapk12	118	Adcyap1r1
12	Iigp1	66	D7Bwg0826e	119	Anapc11
13	Etnppl	67	Myct1	120	Clca3a2
14	Colec11	68	Ranbp17	121	Cyyr1
15	Ifi44	69	Adcy4	122	Lrpap1
16	Krt18	70	Shisa6	123	Cdh13
17	Gimap4	71	Asxl1	124	Abcg1
18	Adgrf5	72	Ppp1r3d	125	Syt7
19	Spns2	73	Camk2n1	126	Jag2
20	Cabp4	74	Mboat1	127	Odf3b
21	D7Wsu130e	75	Arrdc4	128	Rilp
22	Ms4a2	76	Ctsg	129	Sox7
23	Exoc3l2	77	Pvr	130	9430030N17Rik
24	Ms4a8a	78	Tox	131	Adgrl4
25	Csf2rb2	79	4833438C02Rik	132	Usp3
26	Ace2	80	Rasgrf2	133	Vps51
27	Itih4	81	Tnfsf13os	134	Kcnq1
28	Robo4	82	Gm11772	135	Krt20
29	Gm11716	83	4833411I10Rik	136	Rabgap1l
30	4921507P07Rik	84	Mfng	137	Sphk2
31	Gp1bb	85	Sox17	138	1810021B22Rik
32	Vwf	86	D930003E18Rik	139	4930447M23Rik
33	Erg	87	Rtn4rl2	140	Arhgef15
34	Eng	88	Kank3	141	Cpsf1
35	Mettl22	89	Ptprb	142	Foxp4
36	Lama3	90	Rpusd2	143	Sema5b
37	5730458M16Rik	91	Sigirr	144	Actr1b
38	4833403J16Rik	92	Trim47	145	Hsd17b11
39	Tceanc2	93	Adamdec1	146	Myrip
40	Fam107a	94	Cgrrf1	147	Gimap5
41	Slc27a2	95	Tigd3	148	Prkcg
42	Zfpm1	96	Spn	149	Abi3
43	Clec14a	97	Car7	150	Bmp4
44	Oasl1	98	Mettl13	151	Mgst2
45	Anxa8	99	Rap1gap	152	Ppp1r13l
46	D130037M23Rik	100	2210019G11Rik	153	Selo
47	Fam189a1	101	6330403A02Rik	154	Sema3f
48	Clca3a1	102	Tmprss2	155	Mocs1
49	Mmrn2	103	Ak8	156	Nos3
50	Cbfa2t3	104	Cyp11a1	157	Pold1
51	Notch4	105	Ushbp1	158	AU022252
52	She	106	Slc6a7	159	D630045J12Rik
53	Soat2	107	6330416G13Rik	160	Ngef
54	Unc45bos				
Downregulated					
1	Ccnt2	131	9530029O12Rik	260	Dag1
2	Col4a5	132	A330075M08Rik	261	Itm2a
3	Crkl	133	Abce1	262	Luc7l2
4	Dnajc18	134	Anp32a	263	Marcks
5	Ebf2	135	Arhgef6	264	Nktr
6	Lamb1	136	Chl1	265	Saa1
7	Pbrm1	137	Cp	266	Senp6
8	R3hdm4	138	Ctse	267	Serinc1
9	Rab10	139	Dcbld2	268	Sfrp1

Table SII. Continued.

Gene count	Gene symbol	Gene count	Gene symbol	Gene count	Gene symbol
10	Rbfox2	140	Eif4a1	269	Slc25a24
11	Rsl24d1	141	Epb41l2	270	Snx18
12	Sat1	142	Far1	271	Snx5
13	Slc25a3	143	Gatm	272	Tbl1xr1
14	Smarcc1	144	Gpbp1l1	273	Zic4
15	Spry2	145	Hba-a2	274	9930031P18Rik
16	Suz12	146	Hmgcr	275	Akap13
17	Timp2	147	Igf1r	276	Dtx3l
18	Zfp626	148	Klhl28	277	Hsph1
19	Actb	149	Mboat7	278	Lin7c
20	Amd1	150	Pddc1	279	Peg3
21	Arf1	151	Ppp1r10	280	Ppp4c
22	Arhgap29	152	Prpf39	281	Pum2
23	Atp6v1b2	153	Pura	282	Rad51c
24	C030046G05	154	Rbm25	283	Scd2
25	Cbx5	155	Rnd3	284	Slc12a2
26	Cd47	156	Slc7a11	285	Sp7
27	Cryzl1	157	Trps1	286	Stk25
28	D2Ertd640e	158	Ttc14	287	Txnip
29	Elavl1	159	Vma21	288	Usp48
30	Hist1h1c	160	Vps13a	289	Zfp825
31	Il6st	161	Yipf4	290	AA409587
32	Katnbl1	162	Add3	291	B4galt6
33	Lats2	163	Atxn7l3b	292	D9Ertd292e
34	P4ha1	164	BC052688	293	Dusp3
35	Pi4kb	165	C230076A16Rik	294	Klhl24
36	Plekhg1	166	Col8a1	295	Msn
37	Polb	167	Cpeb2	296	Ppp3cb
38	Pten	168	Cpne3	297	Smad5
39	Rbbp4	169	Dab2	298	Canx
40	Rnf13	170	Hpgds	299	Ccl2
41	Slc25a30	171	Lrrc41	300	Ccl7
42	Srsf11	172	Lrrk1	301	Dnm1l
43	Stard3nl	173	Nrk	302	Fbn2
44	Strn3	174	Pbx1	303	Jmjd1c
45	Tmem39a	175	Prkx	304	Nlgn3
46	Upk1b	176	Rab23	305	Prkacb
47	AI314180	177	Rbms2	306	Selk
48	Ccdc66	178	Sec61a2	307	Smurf2
49	Chst13	179	Srgap2	308	Srsf1
50	Crls1	180	Steap4	309	Ssr1
51	Ddit3	181	Taf15	310	Cd209a
52	Gpc6	182	Tmtc4	311	Dhdh
53	Hrsp12	183	Usp9x	312	Fn1
54	Ikzf2	184	Wac	313	Hacd3
55	Mbnl1	185	Actr2	314	Nbeal1
56	Nit2	186	Cdk6	315	Ncaph2
57	Npr3	187	Cflar	316	Ss18
58	Pja2	188	Ddi2	317	Zfp266
59	S100pbp	189	Dnajc13	318	Zfp36l1
60	Siglech	190	Dyrk2	319	4930447C04Rik
61	Snx27	191	Etnk1	320	Adam10
62	Stk3	192	Gadd45a	321	Arpc4
63	Taok1	193	Khsrp	322	Atp8a1
64	Tgfbr3	194	Mpdz	323	Ddx6
65	Tpbg	195	N4bp2l2	324	Malat1
66	Trak2	196	Otub1	325	Nid1
67	Ttc5	197	Rab31	326	Snhg11
68	Whsc1l1	198	Sorbs1	327	Cx3cr1
69	Zeb2	199	Tacc1	328	Dlk1
70	Atrx	200	Tmem80	329	Etv5
71	Copa	201	Tnrc6a	330	Mier1
72	Cux1	202	Wnt16	331	Rsrc2
73	Dmtf1	203	Zcchc7	332	Sdf2l1
74	Dnajb6	204	Zdhhc2	333	Slc9a2
75	E130308A19Rik	205	Zfand5	334	Atic

Table SII. Continued.

Gene count	Gene symbol	Gene count	Gene symbol	Gene count	Gene symbol
76	Epha7	206	Zfp871	335	Camk1d
77	Fam49a	207	Araf	336	Gm2a
78	Gcc2	208	Brd4	337	Mirg
79	Glg1	209	Cwf19l2	338	Mob1a
80	Kdelr2	210	Decr2	339	Peli2
81	Lnpep	211	Hoxb5os	340	Pknox1
82	Mcf2	212	Hsd17b12	341	Thbs1
83	Pcdhb15	213	Krit1	342	Trove2
84	Pum1	214	Larp4	343	Dyrk1a
85	Rhou	215	Mapre1	344	Efnb2
86	Ssbp2	216	Phip	345	Fgfr2
87	Stoml2	217	Rbms3	346	Gmfb
88	Syne2	218	Rhobtb3	347	Lcor
89	Sypl	219	Tspyl1	348	Slc16a6
90	Tet1	220	Usf1	349	Sox6
91	Tfpi	221	Apool	350	Srrm2
92	Tmed7	222	Ascc3	351	Ugt8a
93	Trp53	223	Cask	352	Arhgef11
94	Usp4	224	Cd247	353	Braf
95	Ywhaz	225	Cdh11	354	Dhcr24
96	Zbtb20	226	Cdkn2c	355	Golt1b
97	Zcchc3	227	Cpxm1	356	Otud4
98	1810014B01Rik	228	Cyp20a1	357	Pfdn2
99	Adamts15	229	Ercc4	358	Saa2
100	Aplnr	230	Fbxl3	359	Smg1
101	Arl8a	231	Ggact	360	Igf2
102	Btbd7	232	Hnrnpl	361	Lsm12
103	Crim1	233	Hook3	362	Malt1
104	Fubp1	234	Kantr	363	Sc5d
105	Kansl1	235	Msi2	364	Tial1
106	LOC552902	236	Rab14	365	Zfp451
107	Lpp	237	Rbm12b1	366	Cxadr
108	Mau2	238	Smek1	367	9430020K01Rik
109	Mmgt1	239	Vti1a	368	Gpc3
110	Mtpn	240	1300017J02Rik	369	Serinc3
111	Ntrk2	241	E030016H06Rik	370	E230029C05Rik
112	Nudcd1	242	Eif4ebp2	371	Rbm5
113	Peak1	243	Gid4	372	Tgfbr1
114	Phf14	244	Hsd17b7	373	Yes1
115	Polh	245	Kat2b	374	Vcan
116	Ppm1k	246	Kif1b	375	Irf2bp2
117	Psmb2	247	Map3k2	376	Dapl1
118	Rrm2b	248	Nek4	377	Pdia4
119	Sfpq	249	Ppig	378	Uba6
120	Sgcd	250	Rbm41	379	Wif1
121	Sp3	251	Tmem45a	380	Slc22a8
122	Srpx	252	Vamp3	381	Ubfd1
123	Stxbp4	253	March7	382	Eya1
124	Tcf7l2	254	9430053O09Rik	383	Slc38a5
125	Vps13b	255	Abi2	384	Nnat
126	Wnt5a	256	Arf6	385	Asgr1
127	Zcchc24	257	Arglu1	386	Ranbp3l
128	Zfp207	258	Cspg5	387	Sall1
129	Zkscan8	259	Cybb	388	Fabp7
130	5830407P18Rik				

recent decades, distinct molecular functions and morphometric abnormalities between DPN in T1- and T2DM have been reported (7,8). In addition, it has been proposed that the therapeutic interventions for DPN should differ based on the type of diabetes (7). For DPN in T1DM, it has been suggested that improved glycemic control may preserve nerve function and/or

Table SIII. List of genes specific to type 2 diabetes mellitus.

Gene count	Gene symbol	Gene count	Gene symbol	Gene count	Gene symbol
Upregulated					
1	Sept2	242	Alcam	48	Bex1
2	Tph2	243	Duoxa1	484	Cables1
3	Lipf	244	Lrrc3	485	Ccl4
4	Ighm	245	Tcerg1l	486	Cnr2
5	Trdn	246	Irx3	487	Epgn
6	Prr32	247	Lep	488	Lpcat3
7	Oxtr	248	Slc16a10	489	Nabp1
8	Cpa2	249	Clspn	490	Slc24a3
9	Gpr50	250	Ctcflos	491	Tnfrsf23
10	Mbnl3	251	Uhrf1	492	Bcl2l13
11	Chil3	252	Ccl2	493	Cd320
12	Ucp1	253	Stc2	494	Paqr9
13	Ubd	254	Gm6484	495	Pih1d2
14	Atp1a4	255	Trav9d-3	496	Tmem252
15	Ighg	256	Gm7694	497	Zwilch
16	Dusp9	257	Iqgap3	498	1700013H16Rik
17	Cdkl4	258	Otop1	499	Dsg1b
18	Hmga2	259	Ocstamp	500	Fabp5
19	Atp6v0d2	260	Mylk	501	Rhod
20	Tfr2	261	Ube2t	502	Trim25
21	Gabrr2	262	C3ar1	503	Wfdc21
22	2010309G21Rik	263	Dhx32	504	Hist1h1e
23	Mmp12	264	Cd200r1	505	Lman1
24	Il1rn	265	Ccl22	506	Rtn2
25	9030619P08Rik	266	Ghrh	507	Hoxc13
26	Arg1	267	A530020G20Rik	508	Krt222
27	Olr1	268	A530053G22Rik	509	Pfkl
28	Slc5a7	269	Aifm2	510	Pik3ap1
29	Ptchd4	270	4933427G17Rik	511	Sh3tc1
30	F7	271	Lat2	512	Srpx2
31	Il7r	272	Prkag3	513	Tmem120b
32	Apoc4	273	Ddias	514	Tmem144
33	Spc25	274	Dgat2	515	Card11
34	Mogat2	275	Trim67	516	Etf1
35	Lppr4	276	Cenpe	517	Plet1os
36	Crisp2	277	Cd164l2	518	Cd68
37	Npr3	278	Mest	519	Cdca2
38	Rnase2a	279	Mgll	520	Ccnd2
39	Rgs1	280	Slc8a1	521	Dcp2
40	4930502E18Rik	281	Gdf3	522	Fgd4
41	Klf14	282	Vsig4	523	Foxm1
42	Crtac1	283	Adora1	524	Gm6377
43	Synpo2	284	Il13ra2	525	Gna13
44	Itgax	285	Tmem37	526	Il2ra
45	Sez6l	286	Cd1d1	527	Llgl2
46	Cdca7l	287	Kif2c	528	Nckap1l
47	Serpine1	288	Rrm2	529	Serpina3m
48	Hmmr	289	Cks2	530	Snta1
49	Iglv1	290	Pdcd1lg2	531	Hpdl
50	Fam110c	291	Ffar2	532	Knstrn
51	Kcnj14	292	Stap1	533	Nedd1
52	Prr16	293	Pm20d1	534	Nf2
53	Cldn23	294	Clec4a2	535	Pitpnm2
54	Cyp2r1	295	Fmr1nb	536	Pole
55	Mc2r	296	Blnk	537	Thbs2
56	Grtp1	297	Tnfrsf12a	538	Cd300lb
57	4930480G23Rik	298	Vegfc	539	Cdc42ep1
58	Dcst1	299	Acaa1b	540	Gm30173
59	Lpgat1	300	Als2cr12	541	Igfals
60	Aadac	301	Car9	542	Kat7
61	2310002L09Rik	302	Gpt	543	Kcnn4
62	Cyp2c70	303	Havcr2	544	Pmch
63	Nek2	304	Marco	545	Fstl3
64	Dnajb13	305	4931406C07Rik	546	Car4
65	Gsdma2	306	Dnmt3a	547	Cd180

Table SIII. Continued.

Gene count	Gene symbol	Gene count	Gene symbol	Gene count	Gene symbol
66	Zranb3	307	Pik3r5	548	Comt
67	Orm2	308	Abcc3	549	Fsd2
68	Krt79	309	Fbp2	550	Itgb1
69	Cxcl2	310	Gm15498	551	Plk4
70	Cdca5	311	Kif1b	552	Spc24
71	Adam8	312	Lpxn	553	Tns1
72	Tcfl5	313	Pmepa1	554	Atp2a3
73	Bub1	314	Slc16a12	555	Myo1f
74	Agtr2	315	Stil	556	Pla2g12a
75	Dcstamp	316	Nup210	557	1700017B05Rik
76	Myl4	317	Gdf5	558	Pou2af1
77	C430042M11Rik	318	Serpina1b	559	Rpl39l
78	Stra6l	319	Bche	560	A930018P22Rik
79	Tshr	320	Ncaph	561	Gm15972
80	S100a8	321	Stom	562	Usp29
81	Ncan	322	Hist1h3d	563	Arl4a
82	S100g	323	Tmem178	564	Ercc6l
83	Kcnj15	324	2610020C07Rik	565	Ccl7
84	Pkp2	325	Rps6ka3	566	Shmt1
85	1600025M17Rik	326	Fam20c	567	Atp10a
86	Gas2l2	327	Trabd2b	568	Glb1l2
87	D830036C21Rik	328	Asf1b	569	Slc2a10
88	Slc37a2	329	Edem1	570	Smoc1
89	Ccnb2	330	Cdt1	571	Zfp106
90	Angptl3	331	Cenpa	572	Arfgef2
91	Htra3	332	AF251705	573	Gcnt1
92	Gpnmb	333	Hipk1	574	Hesx1
93	Cldn15	334	Hn1l	575	Mrc2
94	Cep55	335	Nepn	576	Neurl2
95	Abcb4	336	Sel1l	577	Plk1
96	Gprin3	337	Cyp4b1	578	Zfp426
97	Car6	338	Muc13	579	AI844685
98	Brca1	339	Rhof	580	Ckap2l
99	Igkv15-103	340	Mcm10	581	Clip1
100	Tinag	341	Tnfrsf11a	582	Dyrk2
101	Trim29	342	Ppih	583	E2f7
102	Cela1	343	Rasgrp2	584	Pex16
103	Mki67	344	Srp54b	585	Qpctl
104	Cdk1	345	Gzme	586	Slc22a4
105	Lrrc39	346	Fam126b	587	Tmem132a
106	Dtl	347	Heph	588	Adam23
107	Ugt3a2	348	Cd200r4	589	D17H6S56E-5
108	Dusp3	349	Cnnm2	590	Ece2
109	Tmem182	350	Ghr	591	Lipa
110	Acoxl	351	Cenpw	592	Plek
111	Chrna2	352	Mcm5	593	Tgfb1
112	Apoc2	353	Ska3	594	Adamts9
113	Fzd4	354	Mrgprg	595	Fgfrl1
114	Fads3	355	Pcdh7	596	Mutyh
115	Arhgap25	356	2810408I11Rik	597	Nim1k
116	Dock8	357	E2f8	598	Ptprk
117	Ccnb1	358	5430437J10Rik	599	5830403F22Rik
118	Gm6277	359	Kif18b	600	Aurka
119	4930486L24Rik	360	Akr1c13	601	Fignl1
120	Hephl1	361	Cd300a	602	Isoc1
121	Tpx2	362	Cd84	603	Lss
122	Slpi	363	Lrrc27	604	Tgm2
123	Sirpb1a	364	Mcemp1	605	Trappc13
124	Tlr13	365	Adam12	606	Wipi1
125	Saa3	366	Ckap2	607	Copg2os2
126	9130204L05Rik	367	Fam101b	608	Hvcn1
127	Cfi	368	Igsf6	609	Mpeg1
128	Rbm28	369	Pramef12	610	Sphk1
129	Dnmt3l	370	Tnfrsf22	611	Tpsab1
130	Sucnr1	371	Ttk	612	Rab20
131	Atp6v0a1	372	Car12	613	Skil

Table SIII. Continued.

Gene count	Gene symbol	Gene count	Gene symbol	Gene count	Gene symbol
132	Irak2	373	Depdc1a	614	Gatb
133	Prss27	374	Fam64a	615	Gm11827
134	Birc5	375	Hpgd	616	Ptpn22
135	Mis18bp1	376	Dbf4	617	Stx17
136	Spaca1	377	Igsf21	618	Trib3
137	Adh6b	378	Kcna5	619	E2f2
138	Afp	379	AI481207	620	Itsn1
139	Tk1	380	Cenph	621	C2cd2
140	Cxcl3	381	Gla	622	Cd44
141	Sdsl	382	Hrct1	623	Hfe
142	Tsc22d2	383	Naip1	624	Mmp19
143	Klk1	384	Slc18a1	625	2500002B13Rik
144	Fosl1	385	2210406H18Rik	626	2700099C18Rik
145	Rnf128	386	3930402G23Rik	627	Ano9
146	Cdca8	387	Adap2	628	Ccne1
147	Timp4	388	Palmd	629	Lox
148	Zc3h12d	389	Vldlr	630	Dynlrb2
149	Plin5	390	Mfge8	631	Eny2
150	Ttc39b	391	Mpp7	632	Gm3912
151	AA467197	392	Sgol1	633	Lipg
152	Tenm4	393	Mmp13	634	Maff
153	Nuf2	394	Ms4a6d	635	Milr1
154	8430408G22Rik	395	Tatdn2	636	Tmem82
155	Cdca3	396	Pigt	637	2600006K01Rik
156	Hilpda	397	Sbk1	638	Acvr1c
157	Esco2	398	Lrg1	639	Bcl2l10
158	Slc9a6	399	Oit3	640	Itih5
159	Trem2	400	Qsox1	641	Plekhm1
160	Pkp1	401	Vwa8	642	Slc7a8
161	Tex33	402	Atp8b4	643	Tes
162	Aqp7	403	B430306N03Rik	644	Cd6
163	Fmr1	404	Msr1	645	Gsg2
164	Fggy	405	Nfe2l2	646	Gm2011
165	BE949265	406	Nkd1	647	Incenp
166	Ube2c	407	Ptx3	648	Pold3
167	Pbk	408	Cd22	649	Bst1
168	Wif1	409	Galns	650	Optc
169	Nedd9	410	Afmid	651	Smad6
170	Igfbp3	411	Cd300lg	652	Tmem206
171	Slc7a10	412	Ermp1	653	Zfp787
172	Spdl1	413	Fcgr4	654	Cdc20
173	Tmed5	414	Shcbp1	655	Ripk3
174	Slc15a3	415	Knop1	656	Sdcbp2
175	Clec4d	416	Serpina12	657	Myo19
176	Serpinb9b	417	Larp1b	658	Tinagl1
177	Cux2	418	Thbs1	659	Tmem106a
178	Cdk18	419	Seh1l	660	Trim16
179	C6	420	Lgals3	661	5033430I15Rik
180	Lhfpl2	421	Nek6	662	AI606473
181	Scel	422	Ctse	663	Dolk
182	Glyctk	423	Hsd11b2	664	Laptm5
183	Mms22l	424	Itgb2	665	Lats2
184	Tcp11x2	425	Slamf7	666	Lbp
185	Cacna1e	426	3110027N22Rik	667	Ormdl3
186	Hipk2	427	Dmrt2	668	Pde1b
187	Ccl3	428	Hspb6	669	Prelp
188	Fabp12	429	Ptbp3	670	Serpina3c
189	Ncapg	430	Slc22a12	671	Hr
190	Pnpla2	431	Ttc7	672	Klhl25
191	Dppa3	432	Cenpi	673	Shb
192	Elovl3	433	Cxcl9	674	Vav1
193	Prss46	434	Itga7	675	6030422H21Rik
194	Mmp8	435	Lcn2	676	Ccdc86
195	Folh1	436	Pid1	677	Cenpp
196	Cenpf	437	Prc1	678	Gch1
197	Npy	438	1700112E06Rik	679	Ms4a6b

Table SIII. Continued.

Gene count	Gene symbol	Gene count	Gene symbol	Gene count	Gene symbol
198	Apol6	439	2010003K11Rik	680	Nlrc3
199	Rrbp1	440	Plekhg6	681	Gm9899
200	Pex5l	441	Kif22	682	Phtf2
201	F10	442	Ndc80	683	Tead4
202	Ccna2	443	Nlrp10	684	Tfcp2l1
203	Tmem135	444	Ptges3l	685	Tfpi2
204	Aspm	445	Sod3	686	Map2k5
205	Gm8350	446	Abhd15	687	Sh2b2
206	Nus1	447	Acsl1	688	Spint2
207	Tm4sf5	448	Ltc4s	689	Wdr62
208	Cdr2	449	Crk	690	4930511E03Rik
209	Aurkb	450	Naip2	691	B230307C23Rik
210	Lonrf3	451	Peg3	692	Cib2
211	Bcar3	452	4430402I18Rik	693	Olfm2
212	Dsg1a	453	Fgf21	694	Zfp655
213	Peg10	454	Lrrc28	695	Cenpk
214	Tmem38b	455	Plekhf2	696	Dgkd
215	Clec4e	456	Rad51ap1	697	Hspa12a
216	Galnt6	457	Sgol2a	698	Hspg2
217	Gys2	458	Ehd2	699	Morn5
218	Melk	459	St8sia4	700	Rbp7
219	Spag5	460	Dcbld1	701	Chpt1
220	Gsdma	461	Mtor	702	Ehd3
221	Glipr1	462	Plaur	703	Hk3
222	Pde7a	463	Akap2	704	LOC545086
223	Top2a	464	Ccnf	705	Mta3
224	Rab38	465	Lrr1	706	Spry4
225	Adh4	466	Nat1	707	Treml1
226	Cxcl10	467	Gm31718	708	Gpr65
227	Kif11	468	Kif20a	709	Rel
228	Hrasls	469	Optn	710	Stk17b
229	Kcnk3	470	Plod1	711	Zfp69
230	2810417H13Rik	471	Rad54b	712	Ccr7
231	1700029I15Rik	472	AU021933	713	Cenpn
232	Serpina3a	473	Ccrl2	714	Fbxo42
233	Lamb3	474	Piezo1	715	Ttpa
234	Plet1	475	Stab2	716	Vac14
235	Klb	476	C5ar1	717	Ncf1
236	Btc	477	Hgf	718	Ybx2
237	Ccdc125	478	Kbtbd12	719	Cd300ld
238	Rbpms	479	Map7	720	Gk
239	Mettl24	480	Rad18	721	Xrcc3
240	Tnc	481	Sdk2		
241	Tpcn2	482	Tlr8		
Downregulated					
1	March2	366	Tspan2	731	St6gal2
2	March4	367	Ttyh1	732	Sytl2
3	March5	368	Unc13a	733	Tnfrsf19
4	March6	369	Zfp612	734	Agr2
5	2900055J20Rik	370	1110002L01Rik	735	Bcan
6	Bcl11b	371	9330184L24Rik	736	C030034E14Rik
7	Cdk7	372	Aak1	737	Cntn2
8	Esr1	373	Adamtsl1	738	Dcdc2a
9	Gm13446	374	Aif1l	739	E130002L11Rik
10	Gpr85	375	Ank3	740	Fam131a
11	Hoxb9	376	Atl1	741	Fam167a
12	Htr7	377	B930095G15Rik	742	Fam169a
13	Kctd14	378	C030039L03Rik	743	Gap43
14	Mapk4	379	Cacnb3	744	Gng4
15	Ncdn	380	Calb2	745	Kcnd1
16	Osbpl3	381	Ccdc136	746	Krtdap
17	Pfn2	382	Cdh8	747	Lrrn1
18	Pou3f2	383	Clasp2	748	Lysmd4
19	Slc14a1	384	Dlg4	749	Mmd2
20	Tardbp	385	Epb41l4b	750	Nacad
21	4833423F13Rik	386	Fbxo30	751	Necab1

Table SIII. Continued.

Gene count	Gene symbol	Gene count	Gene symbol	Gene count	Gene symbol
22	Angel1	387	Gpr61	752	Nrxn1
23	BC030500	388	Itgb3bp	753	Nxpe3
24	Cacng4	389	Lcat	754	Parm1
25	Chd9	390	Lect1	755	Ptprt
26	Cst6	391	Magi1	756	Pvalb
27	Dpysl3	392	Meg3	757	Rem2
28	Ece1	393	Mmp9	758	Rps6ka6
29	Eif5a2	394	Neto2	759	Sphkap
30	Endod1	395	Otud7a	760	Syt11
31	Epha5	396	Phactr1	761	Th
32	Evi5	397	Prkcz	762	Thy1
33	Gjd2	398	Psd2	763	Tmem74
34	Gpr88	399	Rnf130	764	Trim37
35	Hs6st2	400	Sema3b	765	Tspan8
36	Htr1d	401	Sema4g	766	Wipf3
37	Ica1l	402	Slc2a3	767	Bves
38	Kalrn	403	Smr2	768	Ccdc92
39	Kcnmb2	404	Srr	769	Elfn1
40	Kcnv1	405	Trpm3	770	Erich3
41	Mag	406	Zfp385b	771	Galnt5
42	Nxph1	407	A830010M20Rik	772	Gca
43	Osbpl6	408	AI661384	773	Ggt7
44	Pax3	409	AI854703	774	Gria1
45	Pcdh9	410	AW046457	775	Hoxb5
46	Pcp4l1	411	Adam22	776	Kcnh1
47	Pter	412	B3gat1	777	Kcnip1
48	Rgs7	413	Baiap2l1	778	Kcnmb1
49	Scmh1	414	C530044C16Rik	779	Lrfn5
50	Slc1a6	415	Chrnb2	780	Mab21l2
51	Smco3	416	Cntnap5a	781	Necab3
52	Sostdc1	417	Cplx2	782	Nyap1
53	Stxbp1	418	Crh	783	Sptbn2
54	Stxbp5	419	Csdc2	784	Syn1
55	Tmem229b	420	Ctxn1	785	Tmem151a
56	Ube2e3	421	D2Ertd282e	786	Tmem25
57	Upp2	422	Dclk1	787	Tro
58	Zfp788	423	Eras	788	Trpa1
59	5330417C22Rik	424	Erich6	789	Agtr1b
60	A730089K16Rik	425	Gm36529	790	Calca
61	Abhd10	426	Greb1l	791	Camta1
62	Adgra1	427	Grm4	792	Crmp1
63	C79242	428	Hopx	793	Fam131b
64	Camk4	429	Mycn	794	Fam171b
65	Cep97	430	Nalcn	795	Gabra2
66	Cpsf2	431	Nebl	796	Kcnd3
67	Cpsf6	432	Nova1	797	Lmo3
68	Csmd3	433	Pcp4	798	Map3k9
69	Cyfip2	434	Plekha6	799	Mpped2
70	Eml2	435	Rab6b	800	Ngfr
71	Fat3	436	Rbfox3	801	Nmnat2
72	Fgf18	437	Rbm11	802	Prkar1b
73	Golga7b	438	Rgs8	803	Rims2
74	Gpr173	439	Rtn4	804	Rundc3b
75	Grin1	440	Sarm1	805	Scn4b
76	Hs3st1	441	Sema3e	806	Slc5a5
77	Irf4	442	Shisa4	807	Tesc
78	Klf12	443	Slc6a17	808	Trpv1
79	Lancl1	444	Slco1c1	809	Tst
80	Lrba	445	Synm	810	Ube2ql1
81	Lrrn4cl	446	Tubg2	811	Zfp365
82	Lrrtm4	447	Wdr17	812	Zfp804a
83	Nppb	448	9330182L06Rik	813	2700046A07Rik
84	Paqr5	449	Aifm3	814	AF529169
85	Plch1	450	Bhlha9	815	B3galt5
86	Prokr2	451	Cd200r3	816	Bean1
87	Prr5l	452	Cdh1	817	F2rl2

Table SIII. Continued.

Gene count	Gene symbol	Gene count	Gene symbol	Gene count	Gene symbol
88	R3hdm1	453	Chd5	818	Nrsn1
89	Runx1t1	454	Dgkg	819	Pcsk1
90	Sall4	455	E130309D14Rik	820	Pcyt1b
91	Slc29a4	456	Hapln2	821	Rnf157
92	Slc35f2	457	Myt1l	822	Serpini1
93	Trank1	458	Ntsr2	823	Slain1
94	Zdhhc18	459	Oprl1	824	Slc35f4
95	Zfp318	460	Prdm8	825	Slc4a10
96	Zfp37	461	Prr18	826	Vps13c
97	2900009J20Rik	462	Psmf1	827	Wt1
98	A930041H05Rik	463	Rab3a	828	Adamts16
99	Ak5	464	Rasgef1a	829	Ano3
100	Arg2	465	Rgmb	830	Arfgef3
101	Bank1	466	Rgs7bp	831	Arhgdig
102	Ccdc28a	467	Robo1	832	Cntn1
103	Cdkn1b	468	Rph3a	833	Ddx25
104	Clec2l	469	Slc2a12	834	Dzank1
105	Csmd1	470	Slc6a2	835	Fam19a3
106	Dip2a	471	Sstr4	836	Gprin2
107	Dlgap1	472	Syt7	837	Hsbp1l1
108	F5	473	Tdo2	838	Htr4
109	Fzd3	474	Tmem108	839	Jakmip1
110	Htr1a	475	Vwa5a	840	Jakmip2
111	Hunk	476	Zfr2	841	Klc1
112	Klhl32	477	9530077C05Rik	842	Lix1
113	L1cam	478	Acsl6	843	Maneal
114	Lrrtm2	479	Aqp4	844	Npy2r
115	Map6d1	480	Atcay	845	Rab3c
116	Mfsd6	481	Ccdc68	846	Reep2
117	Mrpl35	482	Cdk5r1	847	Rufy2
118	Nedd4l	483	Cgref1	848	Sh3gl2
119	Pcsk6	484	Cpb1	849	Vstm5
120	Plxnb1	485	Ctnnd2	850	1810041L15Rik
121	Ppp1r2	486	Cxxc4	851	A830039N20Rik
122	Rbm33	487	Dnah7a	852	Aldoc
123	Rfx4	488	Dzip3	853	Asic1
124	Sacs	489	Fndc4	854	BC059841
125	Serpina11	490	Fxyd7	855	Car10
126	Shd	491	Gabra5	856	Ccdc172
127	Tcte2	492	Glrb	857	Cldn10
128	Tia1	493	Lrch1	858	D130043K22Rik
129	Tox2	494	Mir124a-1hg	859	Gabrg2
130	Ttbk1	495	Ncam2	860	Gm16551
131	Ttc3	496	Plk5	861	Kcnip2
132	Vamp4	497	Pogz	862	Kcnip4
133	2900056L01Rik	498	Prox1	863	Kif3c
134	2900064F13Rik	499	Rasl10b	864	Mrgpra3
135	Arhgap20	500	Rnf208	865	Pappa2
136	Ccdc112	501	Scin	866	Rab39b
137	Cfap69	502	Scn8a	867	Rassf6
138	Cmtm5	503	Scrt1	868	Rbfox1
139	Dtna	504	Slitrk4	869	Rufy3
140	Dusp15	505	Susd5	870	Sez6l2
141	Ephx4	506	Tmem169	871	Soga3
142	Faim2	507	Tmem196	872	Stac
143	Gabrb3	508	Ttc39c	873	Sv2a
144	Galnt14	509	Tyrp1	874	Tmem179
145	Gm12371	510	Unc5c	875	Tspyl4
146	Gm13889	511	Vwc2l	876	Aplp1
147	Gprasp1	512	5930412G12Rik	877	Atp6v1g2
148	Hspa4l	513	Abcg4	878	Far2
149	Igsf11	514	Ache	879	Megf11
150	Itih3	515	Acsm3	880	Nsg2
151	Kcnip3	516	Arhgap12	881	Pclo
152	Kcnk1	517	Cabp7	882	Pou4f2
153	Lingo1	518	Ccdc30	883	Ptprn

Table SIII. Continued.

Gene count	Gene symbol	Gene count	Gene symbol	Gene count	Gene symbol
154	Mkx	519	Clip3	884	Rasgrp1
155	Nipa1	520	Clip4	885	Rit2
156	Phex	521	Dgkb	886	Slc1a2
157	Pnkd	522	Diras1	887	Them5
158	Ppm1l	523	Elovl2	888	Tmem151b
159	Spink10	524	Gm10700	889	Zwint
160	St3gal6	525	Gpr149	890	6430604M11Rik
161	St6galnac3	526	Has2	891	Bsn
162	Stk33	527	Hoxd10	892	C530008M17Rik
163	Tfap2a	528	Hs3st4	893	Cadps2
164	Wdr31	529	Iqsec3	894	Cbln2
165	4930519N06Rik	530	Kazn	895	Ctnna2
166	Acsbg1	531	Kcnf1	896	Cyp4x1
167	Akr1c18	532	Kif3a	897	Elavl3
168	Asxl3	533	Lepr	898	Fbxo2
169	Atad1	534	Lingo2	899	Gm10419
170	B3galt1	535	Mapt	900	Igfbp2
171	B630019K06Rik	536	Mycl	901	Jph3
172	Ccdc138	537	Neto1	902	Jph4
173	Cdr2l	538	Nipal3	903	Klhdc8a
174	Clec3b	539	Nwd2	904	Nrcam
175	Cyr61	540	Pdzd4	905	Ppap2c
176	Dhh	541	Plcxd3	906	Ppm1j
177	Edil3	542	Plp1	907	Ptgs2
178	Fign	543	Ppfia2	908	Tcte1
179	Gabbr1	544	Ptbp2	909	Tmem150c
180	Gabra1	545	Scrn1	910	Trim9
181	Gm13629	546	Slc25a18	911	Acpp
182	Gm5089	547	Slco5a1	912	Adgrb3
183	Gnaz	548	Svop	913	Anks1b
184	Gpr62	549	Syngr1	914	Ccdc184
185	Hcn1	550	Tmem246	915	Chga
186	Kcnk5	551	Tmem88b	916	Ckmt1
187	Kcnq5	552	Arpp21	917	Galnt13
188	Lrrc49	553	Atp1b1	918	Gng3
189	Mbp	554	Cd209g	919	Kcnab1
190	Pak1	555	Cda	920	Kcnc1
191	Pax9	556	Chst5	921	Kif5a
192	Pcdh10	557	Cnnm1	922	Napb
193	Praf2	558	Dleu2	923	Nrxn3
194	Prss12	559	Dscam	924	Ptgds
195	Ptchd2	560	Dusp26	925	Ptprn2
196	Rimklb	561	Hebp2	926	Rgs17
197	Sgtb	562	Il31ra	927	Tox3
198	Sh3d19	563	Lhfpl3	928	Uchl1
199	Slc16a9	564	Lrp8	929	Zmat4
200	Smpd3	565	Mfsd4	930	Csrnp3
201	Sorcs3	566	P2rx3	931	Dpp6
202	Stmn2	567	Pigz	932	Fam184b
203	Usp31	568	Pnma2	933	Gdap1
204	Vamp1	569	Rab39	934	Kctd8
205	Vat1l	570	Rell2	935	Nrg3
206	Zdbf2	571	Rlbp1	936	Rnf112
207	Aldh1a2	572	Sema4f	937	Syt2
208	Atp2b4	573	Slitrk5	938	Tmem200c
209	Cacnb4	574	Smarcal1	939	3632451O06Rik
210	Camk1g	575	Sntg1	940	9430021M05Rik
211	Chn1	576	Stmn3	941	AW060742
212	Dio3os	577	Susd4	942	Ank1
213	Fkbp1b	578	Tmem117	943	Asic3
214	Gjb1	579	Vwa7	944	Brsk2
215	Gna14	580	1700019D03Rik	945	Cldn11
216	Herc3	581	A2m	946	Faxc
217	Hnrnpr	582	Brsk1	947	Fstl5
218	Igsf1	583	C030011L09Rik	948	Lhfpl5
219	Irf6	584	Cabp1	949	Nptx2

Table SIII. Continued.

Gene count	Gene symbol	Gene count	Gene symbol	Gene count	Gene symbol
220	Ism1	585	Dok4	950	Pacsin1
221	Jam3	586	Epb41l3	951	Rims3
222	Klf7	587	Exph5	952	Rspo2
223	Ltbp1	588	Fez1	953	Rundc3a
224	Mapk8ip1	589	Fmn2	954	Scg5
225	Nek1	590	Gria2	955	Slc6a15
226	Nrip3	591	Kif5c	956	Srrm3
227	Phyhip	592	Mast1	957	St8sia3
228	Prepl	593	Ms4a3	958	Tram1l1
229	Rasgrf1	594	Ndrg4	959	Zswim5
230	Serpind1	595	Pirt	960	2900011O08Rik
231	Sox1	596	Prmt8	961	Astn1
232	Sox2ot	597	Rab33a	962	Atp2b2
233	Spock2	598	Rab37	963	Bend6
234	Susd2	599	Slc25a12	964	Bex2
235	Syndig1l	600	Srgap3	965	Cacna2d3
236	Zfhx2	601	Tmem163	966	Cckar
237	A730054J21Rik	602	Tmem79	967	Cend1
238	Adam11	603	Ttc9b	968	D930028M14Rik
239	Adcy1	604	4930524O07Rik	969	Dnm3
240	Adgrl3	605	A330050F15Rik	970	Fam155a
241	Ankrd13d	606	A330102I10Rik	971	Gnal
242	Apba1	607	Arhgap28	972	Ipw
243	Apcdd1	608	Arhgap44	973	Kcna4
244	B3gnt5	609	Celf4	974	Kcnj10
245	Bmp7	610	Cntnap4	975	Lsamp
246	Crym	611	Elovl7	976	Mapk8ip2
247	Dbndd2	612	Fcrls	977	Mtcl1
248	Eef1a2	613	Gpr37	978	Phf24
249	Fam81a	614	Grin3a	979	Snap25
250	Fbxl16	615	Ibsp	980	Tmem59l
251	Fbxo41	616	Ints6	981	Atp2b3
252	Flrt1	617	Lgi3	982	Col25a1
253	Gkn3	618	Lrrtm1	983	Dpysl5
254	Hey2	619	Magee1	984	Grip1
255	Kcnd2	620	Pcdh20	985	Hapln1
256	Kcng4	621	Plcxd2	986	Klk6
257	Lin7a	622	Plekhh1	987	Lhfpl4
258	Lrrtm3	623	Prkg2	988	Nap1l3
259	Ncam1	624	Prune2	989	Ppm1e
260	Nrsn2	625	Rcan2	990	Prph
261	Pak7	626	Scn2b	991	Rnf182
262	Pcolce2	627	Slc7a14	992	Rtn1
263	Ppp2r2c	628	Stx1b	993	Slc39a12
264	Prr15	629	Sult4a1	994	Tmem35
265	S100b	630	Syt14	995	Zcchc18
266	Samd14	631	Tmem132e	996	Ano4
267	Sh3gl3	632	Ubash3b	997	Arhgef7
268	Slc6a11	633	A830018L16Rik	998	BC048546
269	Trio	634	Adcy8	999	Gabrg1
270	2610100L16Rik	635	Cdh10	1000	Hecw1
271	AI846148	636	Ceacam10	1001	Insm2
272	Apbb1	637	Chrna6	1002	Map7d2
273	Ccl27a	638	Eno2	1003	Mog
274	Ccp110	639	Fgf4	1004	Pcsk2
275	Cd24a	640	Frrs1l	1005	Pgbd5
276	Clvs2	641	Gm5124	1006	Rprm
277	Cntn6	642	Gpr22	1007	Sgpp2
278	Cxcl13	643	Il1r2	1008	Slc17a7
279	Cytl1	644	Lancl3	1009	Slc26a7
280	Depdc5	645	Ogfrl1	1010	Spock1
281	Dkk2	646	Olfm3	1011	Adrb3
282	Gabrb2	647	Phactr3	1012	Akap6
283	Gm15663	648	Reep1	1013	C030017B01Rik
284	Hs3st2	649	Rgs4	1014	Calb1
285	Id4	650	Rimbp2	1015	Cpne4

Table SIII. Continued.

Gene count	Gene symbol	Gene count	Gene symbol	Gene count	Gene symbol
286	Il18	651	Skida1	1016	Dync1i1
287	Map1a	652	Slc6a1	1017	Isl1
288	Mllt11	653	Slitrk1	1018	Isl2
289	Nfasc	654	Tmem56	1019	Kndc1
290	Pak3	655	Trnp1	1020	Map4
291	Pgm2l1	656	Tspyl5	1021	Mapk10
292	Plcd4	657	Vstm2a	1022	Phyhipl
293	Rasal2	658	4832406H04Rik	1023	Pou4f1
294	Rltpr	659	A330068G13Rik	1024	Rims1
295	Sec62	660	Aard	1025	Sv2b
296	Snph	661	Acsl3	1026	Syt1
297	Stk32c	662	Atp8a2	1027	Syt4
298	Syngr3	663	Cacna1b	1028	Tubb4a
299	Tbc1d30	664	Cdh9	1029	Amph
300	Trim2	665	Ces1f	1030	Elavl4
301	1110032F04Rik	666	Col4a6	1031	Ermn
302	Ank2	667	Dner	1032	Gfap
303	Apc2	668	Fn3k	1033	Hoxd1
304	Apoh	669	Gm16532	1034	Mlc1
305	Asphd1	670	Itga8	1035	Mup10
306	BB319198	671	Kif1a	1036	Nrg1
307	Cacna2d2	672	L1td1	1037	Scn10a
308	Cadm3	673	Megf10	1038	Tagln3
309	Clgn	674	Mtus2	1039	Vgf
310	Cmah	675	Nipal2	1040	Add2
311	Ddn	676	Nrxn2	1041	Cdhr1
312	Dhrs2	677	Ntrk1	1042	Chrna7
313	Efcab1	678	Pcdh8	1043	Cpne6
314	Fam189a1	679	Pla2g3	1044	Dlg2
315	Gm32444	680	Rab9b	1045	Dpp10
316	Gpr158	681	Sowahb	1046	Fam19a4
317	Gpr75	682	Trpc3	1047	Grik1
318	Grm8	683	Trpc6	1048	Htr3a
319	Inadl	684	Tvp23a	1049	Plekhd1
320	Kcnq2	685	Vwa5b2	1050	Ppp1r1c
321	Kctd4	686	A730017C20Rik	1051	Ppp2r2b
322	Kif21a	687	Amer3	1052	Ralyl
323	Krt27	688	Arhgef4	1053	St8sia1
324	Lgi2	689	Arnt2	1054	Stmn4
325	Lonrf2	690	Ccser1	1055	Synpr
326	Lztfl1	691	Cntnap2	1056	2900052N01Rik
327	Mfsd2a	692	Cplx1	1057	Chgb
328	Mro	693	Crygs	1058	Fam19a2
329	Pcnxl2	694	Dock3	1059	Resp18
330	Prkg1	695	Dpp4	1060	Slc17a6
331	Srd5a1	696	Fam189b	1061	Spock3
332	Srsf12	697	Gdap1l1	1062	Vsnl1
333	Tmem231	698	Gm2115	1063	Nefl
334	Tnik	699	Gprasp2	1064	Scn9a
335	Trim36	700	Hoxb6	1065	Nts
336	Ttbk2	701	Lgi1	1066	Sult1e1
337	Aox3	702	Mobp	1067	Avil
338	Ccdc47	703	Mogat1	1068	2810037O22Rik
339	Celsr2	704	Mtmr7	1069	Nefh
340	Cldn9	705	Nkx2-2	1070	Cdk5r2
341	Dbndd1	706	Omg	1071	Ttc9
342	Esd	707	Pde1c	1072	Adcyap1
343	Fxyd3	708	Ptprz1	1073	Pon1
344	Greb1	709	Scn1a	1074	Slc24a2
345	Gria4	710	Slc35f3	1075	Nefm
346	Kcnn2	711	Spire2	1076	Panx2
347	Kcnt1	712	Stxbp5l	1077	Syt9
348	Lynx1	713	Tenm1	1078	Rimkla
349	Ndp	714	Timd4	1079	Gm2102
350	Nkain2	715	6330563C09Rik	1080	Scg2
351	Pi16	716	Ap3b2	1081	Tac1

Table SIII. Continued.

Gene count	Gene symbol	Gene count	Gene symbol	Gene count	Gene symbol
352	Pip5kl1	717	Arhgap36	1082	Prrxl1
353	Pla2g2d	718	Caln1	1083	AI593442
354	Ppl	719	Celf6	1084	Calcb
355	Prokr1	720	Cntn4	1085	Shh
356	Rab27b	721	Corin	1086	Tmem130
357	Rragd	722	Epb41	1087	Cyp2f2
358	Rsrp1	723	Fosb	1088	Snap91
359	Scrt2	724	Kcnj3	1089	Nap1l2
360	Slc35d3	725	Kcnk10	1090	Scn11a
361	Spink2	726	Lrrc75b	1091	Myt1
362	Stk39	727	Morn4	1092	Grm7
363	Synrg	728	Onecut2	1093	Tubb3
364	Tmem255a	729	Pcsk1n	1094	Cadps
365	Tshz2	730	Scg3		

decrease the likelihood of developing DPN (6). By contrast, for DPN in T2DM, not only glycemic control, but treatments for other risk factors including obesity may be equally critical in preventing DPN (6). Therefore, since the molecular mechanisms underlying the pathogenesis of DPN in each type of DM may differ, understanding the mechanisms may lead to novel therapeutic approaches for prevention or treatment.

In the present study, there were marked differences between the gene expression profiles, GO terms and KEGG pathways of DEGs in the sciatic nerves of T1- and T2DM mouse models. This was in accordance with previous studies revealing considerable alterations in global gene expression profiles of several tissues including skeletal muscles and adipose tissue (21), and organs such as the intestine (22), liver (23) and brain (24) in the two types of DM. It is established that T1DM is characterized by destruction of pancreatic islet cells by autoimmunity, with loss of pancreatic insulin production, while T2DM is a metabolic disease with high pancreatic insulin production in the setting of insulin resistance (6). Therefore, the different insulin level and insulin signaling pathways between the two types of DM may converge on and modulate the transcription of genes (25); it thus seemed reasonable to search for altered gene expression patterns in DPN between T1- and T2DM models characterized by absolute or relative insulin deficiency.

A number of DEGs unique to the sciatic nerve of T1DM mice were associated with cell proliferation, as well as the mitogen-activated protein kinase signaling pathway, which is a critical pathway for cell proliferation (26). In neuropathic pain, a correlation has been determined between the proliferation of nerve cells including microglia and astrocyte and the abnormal pain responses (27,28). In addition, previous study has demonstrated that the proliferation of glia cells including astrocyte was associated with structural changes in the nervous system, such as axonal growth (29). Furthermore, with loss of C-fibers, increased frequencies of denervated Schwann cells and regenerating fibers have been identified in T1DM mice but not in T2DM mice (8). Therefore, the DEGs associated with cell proliferation may serve a crucial role during the pathological changes of DPN in T1DM.

Insulin resistance is among the major factors that leads to the development and progression of complications in T2DM (30).

Table I. Top 20 coincident enriched GO terms in T1- and T2DM.

		T1DM		T2DM	
GO ID	GO term	Gene count	P-value	Gene count	P-value
GO:0005515 MF	Protein binding	57	3.1E-6	76	9.2E-20
GO:0005737 CC	Cytoplasm	21	6.7E-6	123	3.8E-14
GO:0001525 BP	Angiogenesis	14	9.6E-6	89	7.3E-18
GO:0000166 MF	Nucleotide binding	45	2.4E-5	46	5.5E-10
GO:0007399 BP	Nervous system development	21	3.2E-5	86	7.3E-11
GO:0008201 MF	Heparin binding	13	4.6E-5	57	5.9E-14
GO:0006468 BP	Protein phosphorylation	11	5.4E-5	61	4.3E-12
GO:0005578 CC	Proteinaceous extracellular matrix	24	5.5E-5	66	9.1E-20
GO:0016310 BP	Phosphorylation	13	6.2E-5	78	8.8E-16
GO:0009986 CC	Cell surface	12	6.5E-5	54	5.6E-17
GO:0016020 CC	Membrane	17	8.9E-5	23	3.2E-15
GO:0005794 CC	Golgi apparatus	12	2.4E-4	45	2.5E-17
GO:0004672 MF	Protein kinase activity	14	3.1E-4	24	4.2E-16
GO:0030335 BP	Positive regulation of cell migration	15	4.5E-4	19	8.5E-17
GO:0005783 CC	Endoplasmic reticulum	6	5.3E-4	32	5.2E-16
GO:0019933 BP	cAMP-mediated signaling	18	5.8E-4	30	7.5E-13
GO:0048471 CC	Perinuclear region of cytoplasm	16	6.3E-4	21	5.2E-12
GO:0016301 MF	Kinase activity	19	6.7E-4	26	7.1E-15
GO:0004674 MF	Protein serine/threonine kinase activity	32	1.3E-3	24	2.1E-18
GO:0006629 BP	Lipid metabolic process	22	1.6E-3	42	7.6E-22

GO, Gene ontology; BP, biological process; MF, molecular function; CC, cellular component; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus.

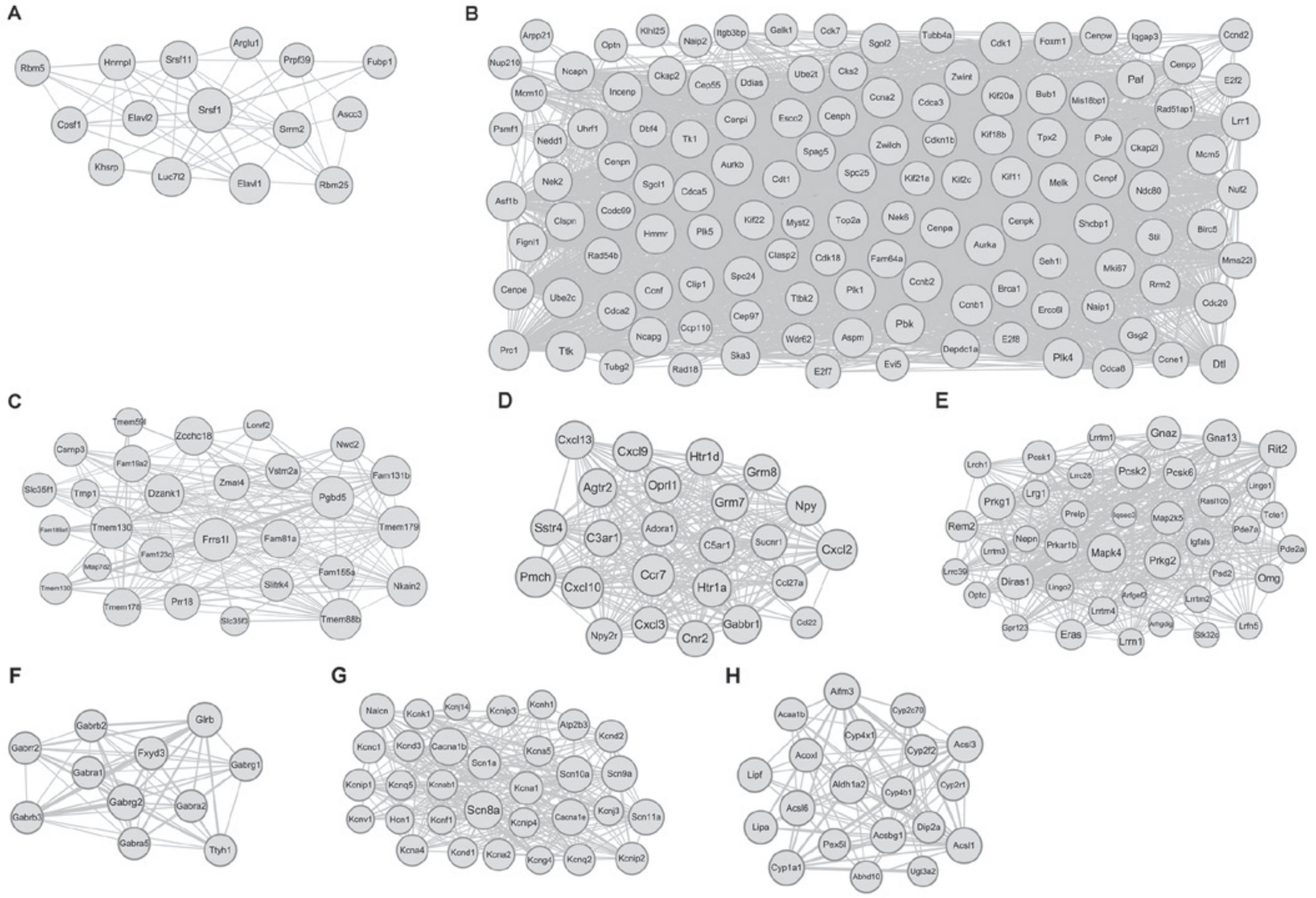

Figure 2. Protein modules in the PPI networks for T1- and T2DM. The size of a protein was determined by the degree of its connection to other proteins, and the width of the edge connecting two proteins by the combined score of those proteins. (A) Protein module in the PPI network for T1DM; (B-H) the 7 modules in the PPI network for T2DM. PPI, protein-protein interaction; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus.

Table II. Top 20 enriched GO terms for differentially expressed genes in the sciatic nerve of T1- and T2DM models, respectively.

GO ID	GO term	Gene count	P-value
T1DM			
GO:0005654 CC	Nucleoplasm	92	5.3E-7
GO:0070062 CC	Extracellular exosome	116	1.3E-6
GO:0005829 CC	Cytosol	84	2.8E-6
GO:0045893 BP	Positive regulation of transcription, DNA-templated	38	4.3E-6
GO:0050680 BP	Negative regulation of epithelial cell proliferation	12	6.0E-6
GO:0071560 BP	Cellular response to transforming growth factor β stimulus	11	8.3E-6
GO:0005604 CC	Basement membrane	13	1.7E-5
GO:0090090 BP	Negative regulation of canonical Wnt signaling pathway	13	3.5E-5
GO:0045165 BP	Cell fate commitment	11	3.7E-5
GO:0005925 CC	Focal adhesion	27	4.7E-5
GO:0030154 BP	Cell differentiation	43	6.9E-5
GO:0045944 BP	Positive regulation of transcription from RNA polymerase II promoter	50	1.6E-4
GO:0005634 CC	Nucleus	208	2.4E-4
GO:0009887 BP	Organ morphogenesis	12	2.9E-4
GO:0035925 MF	mRNA 3'-UTR AU-rich region binding	5	3.0E-4
GO:0008285 BP	Negative regulation of cell proliferation	25	3.1E-4
GO:0048709 BP	Oligodendrocyte differentiation	7	3.6E-4
GO:0000381 BP	Regulation of alternative mRNA splicing, via spliceosome	7	7.8E-4
GO:0000122 BP	Negative regulation of transcription from RNA polymerase II promoter	37	1.1E-3
GO:0031012 CC	Extracellular matrix	19	1.7E-3
T2DM			
GO:0030054 CC	Cell junction	147	1.4E-26
GO:0030424 CC	Axon	98	1.9E-26
GO:0043195 CC	Terminal bouton	46	8.7E-21
GO:0006811 BP	Ion transport	112	5.1E-18
GO:0005216 MF	Ion channel activity	48	1.8E-14
GO:0042734 CC	Presynaptic membrane	31	2.4E-14
GO:0034765 BP	Regulation of ion transmembrane transport	42	3.8E-14
GO:0008021 CC	Synaptic vesicle	39	3.6E-13
GO:0005244 MF	Voltage-gated ion channel activity	40	5.0E-13
GO:0005509 MF	Calcium ion binding	111	2.9E-12
GO:0045211 CC	Postsynaptic membrane	54	3.6E-13
GO:0005886 CC	Plasma membrane	509	3.5E-12
GO:0006810 BP	Transport	227	1.1E-11
GO:0007268 BP	Chemical synaptic transmission	44	1.4E-11
GO:0008076 CC	Voltage-gated potassium channel complex	27	2.2E-10
GO:0007269 BP	Neurotransmitter secretion	17	3.6E-11
GO:0000775 CC	Chromosome, centromeric region	38	7.1E-11
GO:0006813 BP	Potassium ion transport	34	1.1E-9
GO:0005267 MF	Potassium channel activity	26	1.4E-9
GO:0005887 CC	Integral component of plasma membrane	150	5.7E-10

GO, gene ontology; BP, biological process; MF, molecular function; CC, cellular component; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus.

Table III. Coincident enriched Kyoto Encyclopedia of Genes and Genomes pathways in T1- and T2DM.

	T1DM		T2DM	
Term	Gene count	P-value	Gene count	P-value
mmu04010:MAPK signaling pathway	19	7.5E-4	29	3.2E-2
mmu04512:ECM-receptor interaction	10	1.4E-3	15	6.9E-3
mmu04390:Hippo signaling pathway	11	1.8E-2	24	1.2E-3
mmu04360:Axon guidance	9	4.5E-2	17	3.8E-2

T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus.

Table IV. Enriched Kyoto Encyclopedia of Genes and Genomes pathways in T1- and T2DM, respectively.

Term	Gene count	P-value
T1DM		
mmu04010:MAPK signaling pathway	19	7.5E-4
mmu04512:ECM-receptor interaction	10	1.4E-3
mmu05202:Transcriptionalmisregulation in cancer	14	1.7E-3
mmu05200:Pathways in cancer	24	2.5E-3
mmu05205:Proteoglycans in cancer	15	3.8E-3
mmu04310:Wnt signaling pathway	11	1.1E-2
mmu05214:Glioma	7	1.4E-2
mmu05222:Small cell lung cancer	8	1.4E-2
mmu04015:Rap1 signaling pathway	14	1.4E-2
mmu04330:Notch signaling pathway	6	1.7E-2
mmu04914:Progesterone-mediated oocyte maturation	8	1.7E-2
mmu04390:Hippo signaling pathway	11	1.8E-2
mmu00100:Steroid biosynthesis	4	1.9E-2
mmu05218:Melanoma	7	2.1E-2
mmu04614:Renin-angiotensin system	5	2.2E-2
mmu04520:Adherens junction	7	2.3E-2
mmu04510:Focal adhesion	13	2.5E-2
mmu04913:Ovarian steroidogenesis	6	3.0E-2
mmu04360:Axon guidance	9	4.5E-2
mmu05210:Colorectal cancer	6	4.6E-2
mmu05212:Pancreatic cancer	6	4.9E-2
T2DM		
mmu05033:Nicotine addiction	19	1.6E-10
mmu04080:Neuroactive ligand-receptor interaction	49	1.4E-7
mmu04723:Retrograde endocannabinoid signaling	23	8.5E-6
mmu04721:Synaptic vesicle cycle	17	1.2E-5
mmu05032:Morphine addiction	20	6.7E-5
mmu04514:Cell adhesion molecules (CAMs)	27	2.4E-4
mmu04724:Glutamatergic synapse	21	4.3E-4
mmu04024:cAMP signaling pathway	30	4.9E-4
mmu04923:Regulation of lipolysis in adipocytes	13	1.1E-3
mmu04390:Hippo signaling pathway	24	1.2E-3
mmu04020:Calcium signaling pathway	26	2.7E-3
mmu04972:Pancreatic secretion	17	3.8E-3
mmu00561:Glycerolipid metabolism	12	4.2E-3
mmu04911:Insulin secretion	15	5.6E-3
mmu04727:GABAergic synapse	15	6.2E-3
mmu04512:ECM-receptor interaction	15	6.9E-3
mmu04261:Adrenergic signaling in cardiomyocytes	20	2.1E-2
mmu04022:cGMP-PKG signaling pathway	22	2.2E-2
mmu04810:Regulation of actin cytoskeleton	26	2.3E-2
mmu04726:Serotonergic synapse	18	2.4E-2
mmu04725:Cholinergic synapse	16	2.6E-2
mmu04728:Dopaminergic synapse	18	2.8E-2
mmu04610:Complement and coagulation cascades	12	3.0E-2
mmu04010:MAPK signaling pathway	29	3.2E-2
mmu04970:Salivary secretion	12	3.3E-2
mmu04360:Axon guidance	17	3.8E-2
mmu04062:Chemokine signaling pathway	23	4.6E-2

T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus.

Table V. Top 10 proteins with relatively high connectivity degrees in the protein-protein interaction networks for T1- and T2DM.

T1DM			T2DM		
Rank	Protein	Degree	Rank	Protein	Degree
1	Lrrk1	76	1	Top2a	171
2	Trp53	65	2	Cdk1	144
3	Actb	60	3	Plk1	126
4	Actr1b	42	4	Aurkb	120
5	Fn1	40	5	Plk4	116
6	Yes1	38	6	Ccnb1	115
7	Mapk12	38	7	Aurka	114
8	Prkacb	33	8	Mki67	113
9	Pten	32	9	Kif11	112
10	Ywhaz	28	10	Cdc20	111

T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus.

Regarding DPN, it has been suggested that perturbation of insulin receptor signaling due to insulin resistance may cause neurons to become more vulnerable to metabolic insults and contribute to the pathogenesis of neuropathy (31). However, how gene expression is altered under the insulin-resistant state in nerve tissue remains unclear for T2DM. In the present study, a number of unique GO terms and signaling pathways were determined for the sciatic nerve profile of T2DM mice, which may result from an insulin-resistant state. For instance, a majority of the GO terms among the top 20 enriched terms unique to T2DM were related to the biological processes associated with cell junctions, ion activity and membrane activity. Previous studies indicated that the insulin-resistant state induced phosphorylation and downregulated of the expression of certain connexin (Cx) proteins including Cx43, which may constitute a potential mechanism underlying the pathogenesis of insulin resistance and its complications (32,33). Furthermore, it was demonstrated that Ca^{2+} overload in the mitochondria caused production of superoxide and functional impairment of multiple tissues, which may result in β-cell failure and insulin resistance in target tissues, further aggravating the complications of diabetes (34). Therefore, it may be speculated that the impairment of nerve tissues under the insulin-resistant state is attributable to these DEGs in the aforementioned biological processes in T2DM.

In addition, it was apparent that the efficacy of different treatment strategies for the two types of DM may be attributed to certain DEGs. For example, treatment of obesity appeared as critical as glycemic control for preventing the development of DPN in T2DM (5). In the present study, C-C chemokine receptor 7 (Ccr7), which was among the proteins with the highest degrees of connectivity in the PPI network for T2DM, could interact with the chemokine ligand 19 (Ccl19). The Ccl19-Ccr7 pathway may serve an important role in development of high-fat-induced obesity and subsequent insulin resistance (35). Therefore, it may be suggested that a potential treatment strategy is through Ccr7 targeting to alleviate insulin resistance and neuropathy in T2DM.

Table VI. Information on the modules of the protein-protein interaction networks in T1- and T2DM.

Module	Node number	P-value	Protein with highest connectivity degree (degree)	GO term number	KEGG pathway number
T1DM					
1	15	9.4E-5	Srsf1 (22)	18	0
T2DM					
1	125	4.2E-14	Top2a (171)	151	8
2	28	2.9E-10	Frrs1l (28)	2	0
3	24	8.3E-8	Ccr7 (46)	79	5
4	41	1.0E-4	Mapk4 (72)	40	4
5	11	2.8E-4	Gabrg2 (25)	37	5
6	32	3.4E-4	Scn8a (52)	74	4
7	20	6.0E-4	Aldh1a2 (30)	34	9

T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus.

Limitation of the current study included the data being obtained from online databases, meaning the genetic backgrounds of the mice could vary substantially. Further genetic analyses are therefore warranted to identify genes and determine the molecular differences in neuropathy between the two types of DM based on different strains of mice.

In conclusion, the present study revealed the gene expression profiles and signaling pathways associated with the sciatic nerve in T1- and T2DM mouse models. The DEGs and signaling pathways may indicate unique biological processes and treatment strategies for the two types of DM. Further molecular biological experiments are required to validate the function of the DEGs and signaling pathways in DPN.

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Availability of data and materials

All data used and/or analyzed during this study are included in this published article.

Authors' contributions

XL designed the study and aided in drafting of the manuscript. YG and ZLQ performed the bioinformatics analysis and drafted the manuscript. DZL and GLS analyzed the data. ZQH and YCG interpreted the results and prepared the figures. XL and ZQH edited and revised manuscript. All authors approved the final version of the manuscript to be published.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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