Supplementary Table 1. Characteristics of Japanese CD patients who received prophylaxis.

	Type I Paneth cell phenotype	**Type II Paneth cell phenotype**	***P value***
N	24	52	
Sex (male)	18/24 (75.0%)	38/52 (73.1%)	1.000
Mean disease duration (years)	17.0 (13.7-20.3)	17.1 (14.8-19.3)	0.962
Mean age at onset	23.2 (20.7-25.6)	23.1 (21.4-24.7)	0.941
Disease Onset			
A1	4/24 (16.7%)	9/52 (17.3%)	1.000
A2	20/24 (83.3%)	43/52 (82.7%)	1.000
A3	0	0	NA
Disease Location			
L1	3/24 (12.5%)	6/52 (11.5%)	1.000
L2	0	0	NA
L3	21/24 (87.5%)	46/52 (88.5%)	1.000
Disease Behavior			
B1	0	0	NA
B2	21/24 (87.5%)	50/52 (96.2%)	0.318
B3	14/24 (58.3%)	21/52 (40.4%)	0.216
Perianal disease	19/24 (79.2%)	40/52 (78.4%)	1.000
Current smoking	6/18 (33.3%)	11/37 (29.7%)	1.000
Previous resection	15/24 (62.5%)	37/52 (71.2%)	0.596
Treatment received prior to surgery			
Biologics (Bio)	9/24 (37.5%)	19/52 (36.5%)	1.000
Immunomodulator (IM)	5/24 (20.8%)	5/52 (9.6%)	0.272
Elemental diet (ED)	9/24 (37.5%)	15/52 (28.9%)	0.596
Pre-surgery treatment combination			
Only Bio	3/24 (12.5%)	11/52 (21.2%)	0.528
Only IM	0	0	NA
Only ED	4/24 (16.7%)	11/52 (21.2%)	0.763
Bio+IM	1/24 (4.2%)	4/52 (7.7%)	1.000
Bio+ED	1/24 (4.2%)	3/52 (5.8%)	1.000
ED+IM	0	0	NA
Bio+IM+ED	4/24 (16.7%)	1/52 (1.3%)	0.036
Postoperative therapy			
Bio	16/24 (66.7%)	35/52 (67.3%)	1.000
First use of Bio	10/24 (41.7%)	20/52 (38.5%)	0.806
IM	6/24 (25.0%)	12/52 (23.1%)	1.000
ED	13 /24(54.2%)	26/52 (50.0%)	0.808
Postoperative treatment combination			
Only Bio	9/24 (37.5%)	17/52 (32.7%)	0.796
Only IM	1/24 (4.2%)	2/52 (3.9%)	1.000

Only ED	5/24 (20.8%)	14/52 (26.9%)	0.777
Bio+IM	1/24 (4.2%)	7/52 (13.5%)	0.423
Bio+ED	4/24 (16.7%)	9/52 (17.3%)	1.000
ED+IM	2/24 (8.3%)	1/52 (1.9%)	0.233
Bio+IM+ED	2/24 (8.3%)	2/52 (3.9%)	0.587

Bio: biologics (infliximab or adalimumab), IM: immunomodulator, ED: elemental diet, PC: Paneth cell

Supplementary Table 2. Univariate and multivariate association analyses of recurrence after surgery in Japanese CD cohort. Biologics includes infliximab and adalimumab.

		Univariate		Multivariate	
	N	*P* value	hazard ratio	*P* value	hazard ratio
Disease Onset					
A1	13/76 (17%)	0.893			
A2	63/76 (83%)	0.893			
A3	0	NA			
Disease Location					
L1	9/76 (12%)	0.173			
L2	0	NA			
L3	67/76 (88%)	0.173			
Disease Behavior					
B1	0	NA			
B2	71/76 (93%)	0.463			
B3	35/76 (46%)	0.611			
Perianal disease	59/76 (78%)	0.398			
Current smoker	17/55 (31%)	0.047	1.94(0.91-2.14)		
Previous resection	52/76 (68%)	0.600	1.22(0.61-2.45)		
Postoperative therapy					
Elemental diet (ED)	39/76 (51%)	0.318			
Immunomodulator (IM)	18/76 (24%)	0.043	1.91(0.88-4.12)	0.108	
Biologics (Bio)	51/76 (67%)	0.463			
Bio+IM	12/76 (16%)	0.273			
First use of bio	30/76 (39%)	0.071	0.55(0.30-1.02)	0.028	0.47(0.23-0.93)
***LRRK2* M2397T (0 or 1, 2)**	8/67 (12%)	0.100	0.44(0.20-0.95)		
Type I Paneth cell phenotype	24/76 (32%)	0.013	2.10(1.04-4.24)	0.007	2.56(1.31-4.96)

Supplementary Table 3. Association between known CD susceptible loci or genes known to affect Paneth cell function and Paneth cell defect in Japanese CD.

CHR	Position (bp)*	dbSNP ID	A1	A2	Risk for CD	Gene	A1F	Beta	P values	Source
1	63049593	rs1748195	G	C	G	*USP1*	28.6%	-1.60	7.69E-02	(5)
1	67648596	rs76418789	A	G	G	*IL23R*	4.6%	-0.77	6.86E-01	(22)
1	120451190	rs3897478	C	T	T	*ADAM3*	2.0%	-1.89	4.49E-01	(3)
1	172862234	rs9286879	A	G	G	*FASLG,TNFSF18*	3.1%	0.20	9.39E-01	(3)
1	186875459	rs10798069	T	G	G	*PTGS2,PLA2G 4A*	43.2%	-1.05	2.72E-01	(5)
2	27635463	rs1728918	A	G	A	*UCN*	25.5%	-0.55	5.44E-01	(3)
2	62551472	rs10865331	A	G	A		30.1%	0.77	4.25E-01	(3)
2	234183368	rs2241880	G	A	G	*ATG16L1*	23.5%	1.25	1.98E-01	(27)
2	241570249	rs3749172	A	C	A	*GPR35*	30.1%	-1.54	9.96E-02	(28)
2	242737341	rs35320439	C	T	C	*PDCD1,ATG4B*	38.3%	0.60	4.74E-01	(5)
3	57414434	rs4462937	G	A	A	*DNAH12*	39.2%	1.52	8.31E-02	(22)
3	141105570	rs724016	G	A	G		48.0%	0.42	6.22E-01	(5)
4	38335823	rs1487630	T	C	T	*(4p14)*	32.7%	0.38	6.66E-01	(21)
4	48363983	rs6837335	G	A	G	*TXK,TEC,SLC1A4*	38.8%	0.38	6.98E-01	(3)
5	55438851	rs10065637	T	C	C	*IL6ST,IL31RA*	2.6%	-2.96	2.85E-01	(3)
5	72551134	rs7702331	G	A	A		15.8%	-0.83	4.45E-01	(3)
5	173337853	rs17695092	G	T	T	*CPEB4*	8.7%	0.58	6.83E-01	(3)
6	382559	rs7773324	A	G	A	*IRF4,DUSP22*	24.0%	0.05	9.67E-01	(5)
6	3420406	rs13204048	C	T	T		50.6%	-1.97	1.74E-02	(5)
6	31274380	rs9264942	C	T	C	*HLA-C,PSORS1C1,NFKBIL1,MICB*	33.7%	-0.42	6.23E-01	(3)
6	32370816	rs28362680	A	G	A	*BTNL2*	42.9%	-0.83	3.33E-01	(22)
6	32373232	rs10947261	T	G	T	*BTNL2*	42.9%	-0.83	3.33E-01	(28)
6	32713030	rs3208181	T	C	C	*HLA-DQA2*	19.4%	0.62	5.78E-01	(22)
6	33764033	rs751728	C	T	T	*ITPR3, MIF1, IP6K3, LEMD2, MLN*	21.9%	-0.89	3.36E-01	(28)
6	127456122	rs9491697	A	G	G		50.5%	0.76	3.79E-01	(3)

6	167371110	rs2149085	C	T	T	*RNASET2, FGFR1OP, CCR6, MIR3939*	45.4%	-0.46	6.14E-01	(28)
7	26892440	rs10486483	A	G	A		16.8%	-0.49	6.78E-01	(3)
7	28180556	rs864745	C	T	T	*CREB5,JAZF1*	18.9%	-2.48	1.12E-02	(3)
8	90875918	rs7015630	C	T	T	*RIPK2*	21.1%	-1.29	2.42E-01	(3)
8	129567181	rs6651252	C	T	T		2.0%	-1.77	5.67E-01	(3)
9	117568766	rs6478109	A	G	G	*TNFSF15*	27.0%	-0.31	7.27E-01	(21)
9	117665187	rs3181374	A	G	G	*TNFSF8*	41.3%	-0.58	4.78E-01	(22)
10	64477836	rs224143	A	G	G	*ZNF365*	38.8%	-0.13	8.95E-01	(28)
10	81045207	rs1250569	C	T	T	*ZMIZI*	39.4%	0.34	7.00E-01	(28)
10	101295863	rs888208	G	A	A	*NKX2-3*	40.6%	0.29	7.17E-01	(22)
10	112186148	rs11195128	T	C	T	*SMNDC1-DUSP5*	25.5%	0.24	8.02E-01	(28)
11	72533536	rs11235604	T	C	T	*ATG16L2*	13.8%	2.00	1.06E-01	(28)
11	72863697	rs11235667	G	A	G	*ATG16L2-FCHSD2*	14.3%	1.76	1.51E-01	(28)
12	6491125	rs7954567	A	G	A	*CD27,TNFRSF 1A,LTBR*	4.1%	1.16	6.03E-01	(5)
12	40758652	rs3761863	C	T	T	*LRRK2*	39.3%	3.28	3.62E-04	(29)
13	41558110	rs7329174	G	A	G	*ELF1*	31.6%	0.42	6.74E-01	(21)
13	43018030	rs9525625	C	T	T	*AKAP1, TFSF11*	16.8%	-2.06	6.96E-02	(5)
13	44457925	rs3764147	G	A	G	*LACC1*	37.8%	0.47	6.05E-01	(3)
14	35870798	rs2273650	T	C	C	*NFKBIA*	18.9%	-0.92	3.80E-01	(22)
15	38899190	rs16967103	C	T	C	*RASGRP1,SPRED1*	6.1%	-2.97	8.00E-02	(3)
17	25843643	rs2945412	A	G	A	*LGALS9,NOS2*	25.5%	-1.38	1.34E-01	(3)
17	40466092	rs1053004	G	A	A	*STAT3*	35.9%	2.04	3.81E-02	(22)
17	54880993	rs3853824	T	C	C		26.5%	-0.63	4.97E-01	(5)
18	12854072	rs514000	C	T	C	*PTPN2*	38.8%	-1.17	1.74E-01	(28)
18	56879827	rs9319943	C	T	C		11.3%	1.00	4.49E-01	(5)
19	1124031	rs2024092	A	G	A	*GPX4,HMHA1*	19.4%	0.53	6.47E-01	(3)
19	46849806	rs4802307	T	G	G		5.1%	2.17	2.81E-01	(3)
21	16784706	rs2823256	A	G	G	*NRIP1, USP25*	23.2%	-0.47	6.40E-01	(28)
21	34776695	rs2284553	A	G	G	*IFNGR2,IFNAR1,IFNAR2,IL1RB,GART,TMEM5B*	22.5%	-1.36	1.64E-01	(3)
22	29145539	rs5997391	T	C	C	*XBP1*	13.3%	-2.31	5.29E-02	(17)

22	41867377	rs727563	C	T	C	*TEF, NHP2L1, PMM1, L3MBTL2, CHADL*	38.7%	0.38	7.22E-01		(5)

*Positions are based on the Genome Reference Consortium human build 37 (GRCh37).

A1F: Allele 1 frequencies.

Supplementary Table 4. Candidate non-synonymous SNPs and genes associated with Paneth cell defect in Japanese CD by GWAS ($P \leq 5 \times 10^{-4}$).

dbSNP	Chr	Position* (bp)	Allele1/2	MAF in Japanese database	MAF in our cohort	P-value	Beta	Gene	Location
rs2296441	10	100144782	C/T	40.9%	41.5%	1.34×10^{-5}	−4.046	*PYROXD2*	Ala533Thr
rs28364680	3	158520011	C/T	17.3%	14.8%	1.91×10^{-5}	−4.799	*MFSD1*	Pro73Ser
rs12224646	11	125708293	T/G	21.4%	19.4%	4.45×10^{-5}	−4.23	*PATE4*	Cys90Gly
rs3742076	12	2968169	A/G	26.6%	30.1%	1.42×10^{-4}	−3.288	*FOXM1*	Ser627Pro
rs4841399	8	10467124	G/C	37.4%	28.4%	1.49×10^{-4}	−3.367	*RP1L1*	Pro1495Arg
rs3732675	3	12858028	T/C	47.7%	44.8%	2.44×10^{-4}	−3.024	*CAND2*	Ser533Pro
rs2282542	18	13056682	G/A	25.4%	23.0%	3.61×10^{-4}	−3.671	*CEP192*	Val1365Met

MAF: Minor allele (Allele 2) frequencies. *Positions are based on the Genome Reference Consortium human build 37 (GRCh37).

Supplementary Table 5. Functional annotation clusters identified by DAVID.

Category	Term	Count	%	P Value	Genes	List Total	Pop Hits	Pop Total	Fold Enrichment	Bonferroni	Benjamini	FDR
Annotation Cluster 1	Enrichment Score: 3.5887324933722864											
GOTERM_MF_FAT	GO:0008092~cytoskeletal protein binding	20	0.878	6.78E-05	*PHACTR1, MYO1D, MYO3B, KATNB1, SYNPO2, ACTN2, PALLD, GAS7, CAPZB, GPR98, SYNPO2L, TNKS1BP1, FMN2, MYO18B, SORBS1, SORBS2, PAFAH1B1, SPTB, PARVA, SNTG2*	180	504	12983	2.862	3.10E-02	3.10E-02	0.10
GOTERM_MF_FAT	GO:0003779~actin binding	15	0.659	1.70E-04	*PHACTR1, MYO1D, MYO3B, SYNPO2, ACTN2, PALLD, CAPZB, GAS7, SYNPO2L, FMN2, MYO18B, SORBS1, SPTB, PARVA, SNTG2*	180	326	12983	3.319	7.60E-02	3.87E-02	0.24
GOTERM_CC_FAT	GO:0015629~actin cytoskeleton	14	0.615	2.03E-04	*MYO1D, MYO3B, SYNPO2, ACTN2, PALLD, CAPZB, GAS7, CTNNA3, FMN2, MYO18B, SORBS1, SORBS2, CLIC5, SPTB*	192	269	12782	3.465	5.71E-02	5.71E-02	0.27
SP_PIR_KEYWORDS	actin-binding	12	0.527	4.05E-04	*PHACTR1, MYO18B, MYO3B, MYO1D, SYNPO2, ACTN2, PALLD, CAPZB, SYNPO2L, SPTB, PARVA, SNTG2*	251	247	19235	3.723	1.12E-01	3.87E-02	0.54
GOTERM_CC_FAT	GO:0005856~cytoskeleton	36	1.581	1.20E-03	*SGCZ, KATNB1, CHEK1, CEP55, CAPZB, SYNPO2L, CDC45, SORBS1, SORBS2, PAFAH1B1, LRRFIP1, MYOF, DISC1, ANKS1B, CEP192, MYO1D, MYO3B, SYNPO2, ACTN2, PLEKHH1, PALLD, LRRC49, GAS7, GRM1, ARHGAP26, CTNNA3, FMN2, MYO18B, UACA, SEPT7P2, CLIC5, JAK2, SPTB, PARVA, SNTG2, KIF26B*	192	1381	12782	1.735	2.95E-01	1.10E-01	1.59
Annotation Cluster 2	Enrichment Score: 2.937621133530258											
GOTERM_MF_FAT	GO:0046983~protein dimerization activity	19	0.834	4.99E-04	*JDP2, CADM1, KATNB1, DSCAML1, CREB5, ACTN2, ZBTB16, FOXP1, ABCG1, CDH13, CRYL1, SLC24A2, P2RX3, CHRNA7, PAFAH1B1, LRRK2, EXT1, PON3, ALX1*	180	542	12983	2.528	2.07E-01	7.45E-02	0.71
GOTERM_MF_FAT	GO:0042802~identical protein binding	20	0.878	1.34E-03	*UPF2, CADM1, PFKFB3, CLDN5, DSCAML1, ACTN2, ZBTB16, ABCG1, FOXP1, ATXN1, CDH13, CRYL1, P2RX3, CMYA5, COL1A2, CHRNA7, PAFAH1B1, LRRK2, EXT1, PON3*	180	640	12983	2.254	4.63E-01	1.44E-01	1.89
GOTERM_MF_FAT	GO:0042803~protein homodimerization activity	13	0.571	2.30E-03	*CDH13, CRYL1, CADM1, P2RX3, DSCAML1, PAFAH1B1, CHRNA7, ZBTB16, LRRK2, EXT1, ABCG1, FOXP1, PON3*	180	334	12983	2.807	6.58E-01	1.93E-01	3.23
Annotation Cluster 3	Enrichment Score: 2.4242046946842724											
GOTERM_BP_FAT	GO:0007155~cell adhesion	21	0.922	1.27E-03	*CADM1, CLSTN2, CNTNAP5, NRXN3, COL22A1, CLSTN1, CLDN5, COL15A1, DSCAML1, CPXM2, SPOCK1, ACTN2, GPR98, CTNNA3, CDH13, COL14A1, COL6A6, SORBS1, TNR, PARVA, ALX1*	184	700	13528	2.206	8.50E-01	4.68E-01	2.09
GOTERM_BP_FAT	GO:0022610~biological adhesion	21	0.922	1.29E-03	*CADM1, CLSTN2, CNTNAP5, NRXN3, COL22A1, CLSTN1, CLDN5, COL15A1, DSCAML1, CPXM2, SPOCK1, ACTN2, GPR98, CTNNA3, CDH13, COL14A1, COL6A6, SORBS1, TNR, PARVA, ALX1*	184	701	13528	2.203	8.54E-01	3.82E-01	2.13
SP_PIR_KEYWORDS	cell adhesion	13	0.571	9.50E-03	*CADM1, CLSTN2, CNTNAP5, NRXN3, CLSTN1, COL15A1, DSCAML1, CTNNA3, CDH13, COL14A1, COL6A6, TNR, PARVA*	251	422	19235	2.361	9.38E-01	2.07E-01	11.93

GOTERM_BP_FAT	GO:0016337~cell-cell adhesion	10	0.439	1.29E-02	*CDH13, COL14A1, CADM1, CLSTN2, CLSTN1, CLDN5, DSCAML1, GPR98, CTNNA3, ALX1*	184	276	13528	2.664	1.00E+00	7.99E-01	19.33
Annotation Cluster 4	Enrichment Score: 2.349548248314411											
GOTERM_CC_FAT	GO:0015629~actin cytoskeleton	14	0.615	2.03E-04	*MYO1D, MYO3B, SYNPO2, ACTN2, PALLD, CAPZB, GAS7, CTNNA3, FMN2, MYO18B, SORBS1, SORBS2, CLIC5, SPTB*	192	269	12782	3.465	5.71E-02	5.71E-02	0.27
SP_PIR_KEYWORDS	cytoskeleton	20	0.878	6.86E-04	*SGCZ, CEP192, MYO3B, KATNB1, CHEK1, CEP55, PALLD, CAPZB, LRRC49, ARHGAP26, CTNNA3, SYNPO2L, UACA, SORBS1, CLIC5, PAFAH1B1, DISC1, SPTB, PARVA, SNTG2*	251	636	19235	2.410	1.81E-01	4.88E-02	0.91
GOTERM_CC_FAT	GO:0005856~cytoskeleton	36	1.581	1.20E-03	*SGCZ, KATNB1, CHEK1, CEP55, CAPZB, SYNPO2L, CDC45, SORBS1, SORBS2, PAFAH1B1, LRRFIP1, MYOF, DISC1, ANKS1B, CEP192, MYO1D, MYO3B, SYNPO2, ACTN2, PLEKHH1, PALLD, LRRC49, GAS7, GRM1, ARHGAP26, CTNNA3, FMN2, MYO18B, UACA, SEPT7P2, CLIC5, JAK2, SPTB, PARVA, SNTG2, KIF26B*	192	1381	12782	1.735	2.95E-01	1.10E-01	1.59
GOTERM_CC_FAT	GO:0044430~cytoskeletal part	23	1.010	2.71E-02	*ANKS1B, CEP192, MYO1D, MYO3B, KATNB1, CHEK1, ACTN2, CEP55, PALLD, GAS7, GRM1, CAPZB, LRRC49, CDC45, MYO18B, SORBS1, SEPT7P2, CLIC5, PAFAH1B1, MYOF, DISC1, SPTB, KIF26B*	192	952	12782	1.608	1.00E+00	3.92E-01	30.55
GOTERM_CC_FAT	GO:0043228~non-membrane-bounded organelle	50	2.196	4.20E-02	*BTD, HIRA, SYNPO2L, TOP1, CDC45, SEH1L, LRRFIP1, DISC1, ALX1, NOL6, ANKS1B, MYO3B, TRPA1, ACTN2, PLEKHH1, PALLD, GRM1, CTNNA3, ARHGAP26, FMN2, MYO18B, NAV2, CLIC5, SPTB, KIF26B, PARVA, SNTG2, SGCZ, KATNB1, AHCTF1, CHEK1, CEP55, ZBTB16, CAPZB, SORBS1, SORBS2, PAFAH1B1, MYOF, CEP192, MYO1D, SYNPO2, CPS1, GAS7, LRRC49, FOXP1, ATXN1, TNKS1BP1, UACA, SEPT7P2, JAK2*	192	2596	12782	1.282	1.00E+00	4.32E-01	43.51
GOTERM_CC_FAT	GO:0043232~intracellular non-membrane-bounded organelle	50	2.196	4.20E-02	*BTD, HIRA, SYNPO2L, TOP1, CDC45, SEH1L, LRRFIP1, DISC1, ALX1, NOL6, ANKS1B, MYO3B, TRPA1, ACTN2, PLEKHH1, PALLD, GRM1, CTNNA3, ARHGAP26, FMN2, MYO18B, NAV2, CLIC5, SPTB, KIF26B, PARVA, SNTG2, SGCZ, KATNB1, AHCTF1, CHEK1, CEP55, ZBTB16, CAPZB, SORBS1, SORBS2, PAFAH1B1, MYOF, CEP192, MYO1D, SYNPO2, CPS1, GAS7, LRRC49, FOXP1, ATXN1, TNKS1BP1, UACA, SEPT7P2, JAK2*	192	2596	12782	1.282	1.00E+00	4.32E-01	43.51
Annotation Cluster 5	Enrichment Score: 1.808780874062325											
GOTERM_CC_FAT	GO:0045202~synapse	14	0.615	2.63E-03	*PHACTR1, ANKS1B, CADM1, CLSTN2, RIMBP2, CLSTN1, GRM1, GRM8, GRM7, OTOF, CHRNA7, ERC1, LRRK2, GAP43*	192	355	12782	2.625	5.34E-01	1.42E-01	3.44
SP_PIR_KEYWORDS	cell junction	12	0.527	1.57E-02	*NOX4, ANKS1B, PHACTR1, SORBS1, OTOF, CLSTN1, RIMBP2, CLDN5, CHRNA7, GAP43, ARHGAP26, PARVA*	251	399	19235	2.305	9.90E-01	2.81E-01	18.99
GOTERM_CC_FAT	GO:0030054~cell junction	15	0.659	2.35E-02	*NOX4, PHACTR1, ANKS1B, CADM1, CLDN5, RIMBP2, CLSTN1, ACTN2, ARHGAP26, CTNNA3, SORBS1, OTOF, CHRNA7, GAP43, PARVA*	192	518	12782	1.928	9.99E-01	3.69E-01	27.12
SP_PIR_KEYWORDS	synapse	7	0.307	6.00E-02	*ANKS1B, PHACTR1, OTOF, CLSTN1, RIMBP2, CHRNA7, GAP43*	251	213	19235	2.518	1.00E+00	5.44E-01	56.08

Annotation Cluster 6	Enrichment Score: 1.7852952536854563											
GOTERM_CC_FAT	GO:0045202~synapse	14	0.615	2.63E-03	*PHACTR1, ANKS1B, CADM1, CLSTN2, RIMBP2, CLSTN1, GRM1, GRM8, GRM7, OTOF, CHRNA7, ERC1, LRRK2, GAP43*	192	355	12782	2.625	5.34E-01	1.42E-01	3.44
GOTERM_CC_FAT	GO:0044456~synapse part	10	0.439	1.17E-02	*ANKS1B, CADM1, CLSTN2, GRM8, GRM7, CLSTN1, CHRNA7, ERC1, LRRK2, GRM1*	192	246	12782	2.706	9.67E-01	3.47E-01	14.45
GOTERM_CC_FAT	GO:0045211~postsynaptic membrane	5	0.220	1.44E-01	*ANKS1B, CLSTN2, GRM7, CLSTN1, CHRNA7*	192	135	12782	2.466	1.00E+00	6.94E-01	87.28
Annotation Cluster 7	Enrichment Score: 1.747108846856024											
GOTERM_CC_FAT	GO:0043005~neuron projection	13	0.571	5.33E-03	*ANKS1B, CDH13, CADM1, GRM8, TACR1, GRM7, P2RX3, KATNB1, PAFAH1B1, ACTN2, LRRK2, GRM1, GAP43*	192	342	12782	2.531	7.88E-01	2.28E-01	6.86
GOTERM_CC_FAT	GO:0042995~cell projection	19	0.834	1.67E-02	*ANKS1B, CADM1, TACR1, CLSTN1, KATNB1, ACTN2, CAPZB, GRM1, GAS7, CTNNA3, CDH13, GRM8, CLIC5, P2RX3, GRM7, PAFAH1B1, LRRK2, GAP43, PARVA*	192	697	12782	1.815	9.92E-01	3.34E-01	20.03
GOTERM_CC_FAT	GO:0030424~axon	7	0.307	3.21E-02	*CADM1, GRM7, P2RX3, KATNB1, LRRK2, GRM1, GAP43*	192	159	12782	2.931	1.00E+00	4.27E-01	35.23
GOTERM_CC_FAT	GO:0030425~dendrite	7	0.307	3.60E-02	*ANKS1B, CADM1, TACR1, GRM7, ACTN2, LRRK2, GRM1*	192	163	12782	2.859	1.00E+00	4.12E-01	38.55
Annotation Cluster 8	Enrichment Score: 1.7084036327548526											
GOTERM_BP_FAT	GO:0030030~cell projection organization	14	0.615	1.51E-03	*PRKCA, NRXN3, DSCAML1, ACTN2, CAPZB, GAS7, GPR98, CDH13, TNR, CLIC5, PAFAH1B1, JAK2, UNC5C, GAP43*	184	368	13528	2.797	8.94E-01	3.61E-01	2.47
GOTERM_BP_FAT	GO:0048667~cell morphogenesis involved in neuron differentiation	9	0.395	7.59E-03	*PRKCA, NRXN3, TNR, CLIC5, DSCAML1, PAFAH1B1, JAK2, UNC5C, GAP43*	184	209	13528	3.166	1.00E+00	8.02E-01	11.88
GOTERM_BP_FAT	GO:0048812~neuron projection morphogenesis	9	0.395	8.46E-03	*PRKCA, NRXN3, TNR, DSCAML1, PAFAH1B1, JAK2, UNC5C, GAS7, GAP43*	184	213	13528	3.107	1.00E+00	7.94E-01	13.16
GOTERM_BP_FAT	GO:0000902~cell morphogenesis	12	0.527	9.16E-03	*PRKCA, NOX4, NRXN3, TNR, CLIC5, DSCAML1, PAFAH1B1, JAK2, UNC5C, UPK3A, GAS7, GAP43*	184	356	13528	2.478	1.00E+00	7.82E-01	14.16
GOTERM_BP_FAT	GO:0007409~axonogenesis	8	0.351	1.60E-02	*PRKCA, NRXN3, TNR, DSCAML1, PAFAH1B1, JAK2, UNC5C, GAP43*	184	193	13528	3.048	1.00E+00	7.77E-01	23.52
GOTERM_BP_FAT	GO:0048666~neuron development	11	0.483	1.71E-02	*PRKCA, NRXN3, TNR, CLIC5, DSCAML1, PAFAH1B1, JAK2, UNC5C, GAS7, GAP43, GPR98*	184	339	13528	2.386	1.00E+00	7.78E-01	24.85
GOTERM_BP_FAT	GO:0000904~cell morphogenesis involved in differentiation	9	0.395	1.80E-02	*PRKCA, NRXN3, TNR, CLIC5, DSCAML1, PAFAH1B1, JAK2, UNC5C, GAP43*	184	244	13528	2.712	1.00E+00	7.58E-01	25.98
GOTERM_BP_FAT	GO:0048858~cell projection morphogenesis	9	0.395	1.84E-02	*PRKCA, NRXN3, TNR, DSCAML1, PAFAH1B1, JAK2, UNC5C, GAS7, GAP43*	184	245	13528	2.701	1.00E+00	7.48E-01	26.50
GOTERM_BP_FAT	GO:0032989~cellular component morphogenesis	12	0.527	1.93E-02	*PRKCA, NOX4, NRXN3, TNR, CLIC5, DSCAML1, PAFAH1B1, JAK2, UNC5C, UPK3A, GAS7, GAP43*	184	397	13528	2.222	1.00E+00	7.48E-01	27.59
GOTERM_BP_FAT	GO:0031175~neuron projection development	9	0.395	2.32E-02	*PRKCA, NRXN3, TNR, DSCAML1, PAFAH1B1, JAK2, UNC5C, GAS7, GAP43*	184	256	13528	2.585	1.00E+00	7.82E-01	32.32
GOTERM_BP_FAT	GO:0032990~cell part morphogenesis	9	0.395	2.32E-02	*PRKCA, NRXN3, TNR, DSCAML1, PAFAH1B1, JAK2, UNC5C, GAS7, GAP43*	184	256	13528	2.585	1.00E+00	7.82E-01	32.32
GOTERM_BP_FAT	GO:0030182~neuron differentiation	11	0.483	7.41E-02	*PRKCA, NRXN3, TNR, CLIC5, DSCAML1, PAFAH1B1, JAK2, UNC5C, GAS7, GAP43, GPR98*	184	438	13528	1.846	1.00E+00	9.39E-01	72.16
GOTERM_BP_FAT	GO:0006928~cell motion	11	0.483	1.11E-01	*PRKCA, CDH13, NRXN3, TNR, ATP1A4, PAFAH1B1, SPOCK1, JAK2, UNC5C, CAPZB, GAP43*	184	475	13528	1.703	1.00E+00	9.41E-01	85.82

GOTERM_BP_FAT	GO:0007411~axon guidance	4	0.176	1.77E-01	*NRXN3, TNR, UNC5C, GAP43*	184	107	13528	2.748	1.00E+00	9.40E-01	96.03
Annotation Cluster 9	Enrichment Score: 1.5406287959155505											
INTERPRO	IPR000162:GPCR, family 3, metabotropic glutamate receptor	3	0.132	4.70E-03	*GRM8, GRM7, GRM1*	223	8	16659	28.014	9.22E-01	7.21E-01	6.63
GOTERM_CC_FAT	GO:0042734~presynaptic membrane	4	0.176	9.02E-03	*GRM8, GRM7, ERC1, GRM1*	192	29	12782	9.182	9.28E-01	3.13E-01	11.35
INTERPRO	IPR011500:GPCR, family 3, nine cysteines region	3	0.132	1.45E-02	*GRM8, GRM7, GRM1*	223	14	16659	16.008	1.00E+00	8.62E-01	19.14
INTERPRO	IPR000337:GPCR, family 3	3	0.132	1.88E-02	*GRM8, GRM7, GRM1*	223	16	16659	14.007	1.00E+00	8.72E-01	24.11
INTERPRO	IPR017979:GPCR, family 3, conserved site	3	0.132	3.43E-02	*GRM8, GRM7, GRM1*	223	22	16659	10.187	1.00E+00	9.57E-01	39.84
INTERPRO	IPR017978:GPCR, family 3, C-terminal	3	0.132	4.03E-02	*GRM8, GRM7, GRM1*	223	24	16659	9.338	1.00E+00	9.39E-01	45.04
GOTERM_MF_FAT	GO:0008066~glutamate receptor activity	3	0.132	6.77E-02	*GRM8, GRM7, GRM1*	180	31	12983	6.980	1.00E+00	8.70E-01	63.20
INTERPRO	IPR001828:Extracellular ligand-binding receptor	3	0.132	8.29E-02	*GRM8, GRM7, GRM1*	223	36	16659	6.225	1.00E+00	9.73E-01	71.65
KEGG_PATHWAY	hsa04080:Neuroactive ligand-receptor interaction	7	0.307	1.53E-01	*ADORA3, GRM8, TACR1, GRM7, P2RX3, GRM1, ADRA1D*	73	256	5085	1.905	1.00E+00	8.10E-01	83.55
Annotation Cluster 10	Enrichment Score: 1.5317650008320958											
GOTERM_CC_FAT	GO:0005626~insoluble fraction	22	0.966	1.39E-02	*PRKCA, SLC13A5, CADM1, SPHK2, SLC22A8, ACSBG2, MME, TSPAN9, GRM1, POR, STT3A, ACSL1, UACA, CLIC5, SLC24A2, IGF2R, OTOF, JAK2, PAFAH1B1, LRRK2, PON3, ATP8B3*	192	839	12782	1.746	9.83E-01	3.63E-01	16.97
GOTERM_CC_FAT	GO:0005624~membrane fraction	20	0.878	3.36E-02	*PRKCA, CADM1, SPHK2, SLC22A8, ACSBG2, MME, TSPAN9, GRM1, POR, STT3A, ACSL1, UACA, SLC24A2, IGF2R, OTOF, JAK2, PAFAH1B1, LRRK2, PON3, ATP8B3*	192	809	12782	1.646	1.00E+00	4.07E-01	36.53
GOTERM_CC_FAT	GO:0000267~cell fraction	24	1.054	5.44E-02	*PRKCA, SLC13A5, CADM1, SPHK2, BTC, SLC22A8, ACSBG2, MME, TSPAN9, GRM1, POR, FBLN1, STT3A, ACSL1, UACA, CLIC5, SLC24A2, IGF2R, OTOF, JAK2, PAFAH1B1, LRRK2, PON3, ATP8B3*	192	1083	12782	1.475	1.00E+00	4.91E-01	52.45
Annotation Cluster 11	Enrichment Score: 1.521405906636893											
INTERPRO	IPR008160:Collagen triple helix repeat	7	0.307	8.96E-04	*COL4A4, COL14A1, COL6A6, COL22A1, COL1A2, COL15A1, WDR33*	223	84	16659	6.225	3.85E-01	3.85E-01	1.30
GOTERM_CC_FAT	GO:0005578~proteinaceous extracellular matrix	14	0.615	1.05E-03	*COL4A4, ADAMTS17, LTBP1, SPOCK3, COL22A1, COL15A1, SPOCK1, FBLN1, COL14A1, COL6A6, NAV2, TNR, GPC6, COL1A2*	192	320	12782	2.913	2.62E-01	1.41E-01	1.38
SP_PIR_KEYWORDS	extracellular matrix	11	0.483	1.26E-03	*COL4A4, ADAMTS17, FBLN1, COL14A1, COL6A6, SPOCK3, TNR, COL22A1, COL1A2, COL15A1, SPOCK1*	251	241	19235	3.498	3.09E-01	5.13E-02	1.67
SP_PIR_KEYWORDS	collagen	7	0.307	1.50E-03	*COL4A4, COL14A1, COL6A6, COL22A1, COL1A2, COL15A1, WDR33*	251	95	19235	5.647	3.56E-01	5.35E-02	1.98
GOTERM_CC_FAT	GO:0031012~extracellular matrix	14	0.615	2.04E-03	*COL4A4, ADAMTS17, LTBP1, SPOCK3, COL22A1, COL15A1, SPOCK1, FBLN1, COL14A1, COL6A6, NAV2, TNR, GPC6, COL1A2*	192	345	12782	2.702	4.47E-01	1.38E-01	2.68
SP_PIR_KEYWORDS	hydroxylation	6	0.264	2.31E-03	*COL4A4, LTBP1, COL14A1, COL6A6, COL1A2, COL15A1*	251	71	19235	6.476	4.91E-01	7.23E-02	3.03

GOTERM_CC_FAT	GO:0005581~collagen	4	0.176	1.51E-02	*COL4A4, COL14A1, COL1A2, COL15A1*	192	35	12782	7.608	9.88E-01	3.57E-01	18.35
GOTERM_MF_FAT	GO:0005201~extracellular matrix structural constituent	5	0.220	3.10E-02	*COL4A4, FBLN1, COL14A1, COL1A2, COL15A1*	180	86	12983	4.193	1.00E+00	8.03E-01	36.14
INTERPRO	IPR003129:Laminin G, thrombospondin-type, N-terminal	3	0.132	3.43E-02	*COL14A1, COL22A1, COL15A1*	223	22	16659	10.187	1.00E+00	9.57E-01	39.84
UP_SEQ_FEATURE	domain:TSP N-terminal	3	0.132	3.60E-02	*COL14A1, COL22A1, COL15A1*	251	23	19113	9.932	1.00E+00	9.62E-01	44.24
SMART	SM00210:TSPN	3	0.132	4.34E-02	*COL14A1, COL22A1, COL15A1*	139	22	9079	8.907	9.98E-01	9.98E-01	40.67
SP_PIR_KEYWORDS	trimer	3	0.132	4.46E-02	*COL4A4, COL14A1, COL1A2*	251	26	19235	8.842	1.00E+00	4.54E-01	45.48
SP_PIR_KEYWORDS	hydroxylysine	3	0.132	6.11E-02	*COL4A4, COL14A1, COL1A2*	251	31	19235	7.416	1.00E+00	5.36E-01	56.81
SP_PIR_KEYWORDS	triple helix	3	0.132	6.11E-02	*COL4A4, COL14A1, COL1A2*	251	31	19235	7.416	1.00E+00	5.36E-01	56.81
GOTERM_CC_FAT	GO:0044421~extracellular region part	21	0.922	8.16E-02	*COL4A4, ADAMTS17, LTBP1, SPOCK3, BTD, BTC, COL22A1, COL15A1, SPOCK1, CCL26, CDH13, FBLN1, COL14A1, COL6A6, SFRP1, NAV2, GPC6, TNR, SULF1, COL1A2, PON3*	192	960	12782	1.456	1.00E+00	5.86E-01	67.75
SP_PIR_KEYWORDS	hydroxyproline	3	0.132	8.33E-02	*COL4A4, COL14A1, COL1A2*	251	37	19235	6.214	1.00E+00	6.23E-01	68.57
INTERPRO	IPR002035:von Willebrand factor, type A	4	0.176	8.86E-02	*COL14A1, COL6A6, COL22A1, CACNA2D3*	223	79	16659	3.782	1.00E+00	9.73E-01	74.11
UP_SEQ_FEATURE	short sequence motif:Cell attachment site	4	0.176	1.08E-01	*COL4A4, LTBP1, COL14A1, COL6A6*	251	88	19113	3.461	1.00E+00	9.87E-01	83.95
KEGG_PATHWAY	hsa04512:ECM-receptor interaction	4	0.176	1.15E-01	*COL4A4, COL6A6, TNR, COL1A2*	73	84	5085	3.317	1.00E+00	7.94E-01	73.68
SMART	SM00327:VWA	4	0.176	1.19E-01	*COL14A1, COL6A6, COL22A1, CACNA2D3*	139	79	9079	3.307	1.00E+00	9.15E-01	77.32
GOTERM_CC_FAT	GO:0044420~extracellular matrix part	4	0.176	2.55E-01	*COL4A4, COL14A1, COL1A2, COL15A1*	192	117	12782	2.276	1.00E+00	8.25E-01	97.99
GOTERM_MF_FAT	GO:0005198~structural molecule activity	12	0.527	2.59E-01	*COL4A4, CLTA, FBLN1, COL14A1, SORBS2, COL22A1, CLDN5, COL1A2, COL15A1, ACTN2, CTNNA3, SPTB*	180	634	12983	1.365	1.00E+00	9.49E-01	98.61
SP_PIR_KEYWORDS	Secreted	26	1.142	2.77E-01	*ADAMTS17, LTBP1, BTD, SPOCK3, BTC, SPOCK1, CCL26, COL6A6, GPC6, TNR, DEFB1, COL4A4, TUB, PATE1, COL22A1, COL15A1, CPXM2, FBLN1, COL14A1, SFRP1, COL1A2, MUC19, PATE2, CHGB, PON3, PATE4*	251	1689	19235	1.180	1.00E+00	8.43E-01	98.65
GOTERM_CC_FAT	GO:0005576~extracellular region	31	1.361	5.34E-01	*ADAMTS17, LTBP1, BTD, SPOCK3, BTC, SPOCK1, CCL26, COL6A6, TNR, GPC6, DEFB1, COL4A4, PATE1, COL22A1, COL15A1, CPXM2, ACTN2, CDH13, FBLN1, UACA, COL14A1, SFRP1, NAV2, SULF1, COL1A2, MUC19, CHGB, SSC5D, PATE2, PON3, PATE4*	192	2010	12782	1.027	1.00E+00	9.33E-01	100.00
Annotation Cluster 12	Enrichment Score: 1.4274713832542512											
GOTERM_CC_FAT	GO:0044459~plasma membrane part	46	2.020	1.52E-02	*SGCZ, CLTA, ADORA3, SLC13A5, CADM1, TACR1, CLSTN1, CLDN5, MME, TSPAN9, IL17RA, ACBD3, SORBS1, GPC6, CHRNA7, GNG2, GOLM1, RHOH, NOX4, ANKS1B, PHACTR1, NRXN3, SLC22A8, RIMBP2, TRPA1, ATP1A4, ACTN2, UPK3A, GRM1, ABCG1, ARHGAP26, CTNNA3, CDH13, RAB31, GRM8,*	192	2203	12782	1.390	9.88E-01	3.31E-01	18.37

					IGF2R, OTOF, GRM7, P2RX3, JAK2, ADRA1D, GAP43, PLA2G4E, SPTB, PARVA, SNTG2							
SP_PIR_KEYWORDS	cell membrane	40	1.757	2.65E-02	*SGCZ, ADORA3, CADM1, CLSTN2, TACR1, CLSTN1, OR1J1, CLDN5, BTC, OR4K17, MME, STOML3, MREG, LPHN3, SORBS1, GPC6, CHRNA7, GNG2, MYOF, RHOH, PRKCA, NOX4, GPR97, TUB, ANKS1B, SLC22A8, RIMBP2, GRM1, GPR98, CDH13, RAB31, GRM8, OTOF, GRM7, ANXA13, TREML2, GAP43, ADRA1D, PARVA, SNTG2*	251	2194	19235	1.397	1.00E+00	3.24E-01	30.02
GOTERM_CC_FAT	GO:0005886~plasma membrane	65	2.855	1.30E-01	*FHIT, CLTA, ADCY1, ADORA3, SLC13A5, CLSTN2, CADM1, TACR1, CLSTN1, CLDN5, OR1J1, BTC, OR4K17, STOML3, TSPAN9, IL17RA, ACBD3, LPHN3, GPC6, GNG2, CHRNA7, GOLM1, RHOH, PRKCA, GPR97, ANKS1B, NRXN3, SLC22A8, TRPA1, RIMBP2, ACTN2, GRM1, ARHGAP26, CTNNA3, GPR98, GRM8, IGF2R, OTOF, GRM7, COL1A2, LRRK2, GAP43, SPTB, SNTG2, PARVA, SGCZ, MME, ZBTB16, MREG, ACSL1, SORBS1, MYOF, NOX4, PHACTR1, ATP1A4, UPK3A, ABCG1, CDH13, RAB31, P2RX3, ANXA13, JAK2, TREML2, ADRA1D, PLA2G4E*	192	3777	12782	1.146	1.00E+00	6.75E-01	84.33

Supplementary Table 6. Protein-protein interaction (PPI) network for the top 288 annotated genes.

node1	**node2**	**node1 string_id**	**node2 string_id**	**node1_external_id**	**node2_external_id**	**neighborhood**	**fusion**	**cooccurence**	**homology**	**coexpression**	**experimental**	**knowledge**	**textmining**	**combined score**
EXT1	ANXA13	1856833	1845095	ENSP00000367446	ENSP00000262219	0	0	0	0	0	0	0	0.744	0.744
RAB39A	UACA	1850467	1849718	ENSP00000322594	ENSP00000314556	0	0	0	0	0	0	0	0.956	0.957
PDE7B	LINGO2	1849328	1849261	ENSP00000310661	ENSP00000310126	0	0	0	0	0	0.203	0	0.412	0.511
ADRA1D	PLCB4	1857034	1851676	ENSP00000368766	ENSP00000334105	0	0	0	0	0	0.08	0.9	0	0.904
ESRRG	MED1	1859115	1848202	ENSP00000386171	ENSP00000300651	0	0	0	0	0	0	0.9	0.191	0.915
CEP192	PAFAH1B1	1861712	1858470	ENSP00000427550	ENSP00000380378	0	0	0	0	0	0	0.9	0	0.9
ARNTL	MED1	1857849	1848202	ENSP00000374357	ENSP00000300651	0	0	0	0	0	0	0.9	0.24	0.92
CDC45	CEP55	1860553	1855493	ENSP00000405726	ENSP00000360540	0	0	0	0	0.112	0.359	0	0.213	0.512
P2RX3	TRPA1	1845329	1845090	ENSP00000263314	ENSP00000262209	0	0	0	0	0	0	0	0.662	0.662
OR4K17	OR1J1	1850124	1844685	ENSP00000319197	ENSP00000259357	0	0	0	0.882	0	0	0.9	0	0.9
STT3A	PUS3	1858037	1843115	ENSP00000376472	ENSP00000227474	0	0	0	0	0	0	0	0.483	0.483
ADRA1D	GRM1	1857034	1846816	ENSP00000368766	ENSP00000282753	0	0	0	0	0	0	0.9	0.089	0.905
CHEK2	FOXM1	1857546	1852579	ENSP00000372023	ENSP00000342307	0	0	0	0	0.072	0.576	0	0.858	0.939
DISC1	ACTN2	1854415	1854402	ENSP00000355593	ENSP00000355537	0	0	0	0	0	0.484	0	0.311	0.629
CHEK2	KPNA3	1857546	1844961	ENSP00000372023	ENSP00000261667	0	0	0	0	0.065	0.293	0	0.414	0.578
PRKCA	JAK2	1860737	1857411	ENSP00000408695	ENSP00000371067	0	0	0	0.617	0	0.101	0.9	0.289	0.915
GAS7	MOB2	1860671	1851066	ENSP00000407552	ENSP00000328694	0	0	0	0	0	0.332	0	0.141	0.401
CCDC39	LRRC49	1860550	1844783	ENSP00000405708	ENSP00000260382	0	0	0	0	0	0	0	0.404	0.404
CHEK2	TOP1	1857546	1854138	ENSP00000372023	ENSP00000354522	0	0	0	0	0	0	0	0.684	0.684
ATP1A4	PLCB4	1854723	1851676	ENSP00000357060	ENSP00000334105	0	0	0	0	0	0	0	0.706	0.706
PATE4	PATE1	1860919	1848925	ENSP00000411439	ENSP00000307164	0	0	0	0	0	0	0	0.413	0.412
CPS1	CWC27	1860357	1857330	ENSP00000402608	ENSP00000370460	0	0	0	0	0.078	0.285	0	0.182	0.413
CSMD1	SGCZ	1862182	1857476	ENSP00000441462	ENSP00000371512	0	0	0	0	0	0	0	0.5	0.499

RHOH	ARHGAP26	1857435	1846390	ENSP00000371219	ENSP00000274498	0	0	0	0	0	0.109	0.9	0.045	0.907
IGF2R	CLTA	1853441	1843621	ENSP00000349437	ENSP00000242285	0	0	0	0	0	0.084	0.36	0.101	0.426
PLCB4	GRM1	1851676	1846816	ENSP00000334105	ENSP00000282753	0	0	0	0	0	0	0.9	0.264	0.923
PLA2G4E	PAFAH1B1	1858733	1858470	ENSP00000382434	ENSP00000380378	0	0	0	0	0	0	0.9	0	0.9
CHRNA7	JAK2	1860670	1857411	ENSP00000407546	ENSP00000371067	0	0	0	0	0	0	0.8	0.162	0.825
SGCZ	SNTG2	1857476	1849468	ENSP00000371512	ENSP00000311837	0	0	0	0	0	0	0.72	0.162	0.755
P2RX3	ASIC2	1845329	1843054	ENSP00000263314	ENSP00000225823	0	0	0	0	0	0	0	0.508	0.508
PATE4	DDX25	1860919	1845369	ENSP00000411439	ENSP00000263576	0	0	0	0	0	0	0	0.407	0.407
LRRK2	STK32B	1848005	1846824	ENSP00000298910	ENSP00000282908	0	0	0	0.621	0	0.353	0	0.345	0.43
SPTB	CAPZB	1857851	1845501	ENSP00000374372	ENSP00000264202	0	0	0	0	0	0.424	0	0.125	0.474
TRPA1	ASIC2	1845090	1843054	ENSP00000262209	ENSP00000225823	0	0	0	0	0	0	0	0.499	0.499
PRKCA	ARNTL	1860737	1857849	ENSP00000408695	ENSP00000374357	0	0	0	0	0	0.063	0	0.845	0.849
DNAJC6	EPN2	1858290	1850258	ENSP00000378735	ENSP00000320543	0	0	0	0	0	0	0	0.558	0.558
ZNF454	ADCY1	1850812	1847854	ENSP00000326249	ENSP00000297323	0	0	0	0	0.157	0.085	0	0.33	0.438
CDH13	FHIT	1860733	1852550	ENSP00000408632	ENSP00000342087	0	0	0	0	0	0	0	0.566	0.566
PRKCA	LRRK2	1860737	1848005	ENSP00000408695	ENSP00000298910	0	0	0	0.617	0	0.353	0	0.351	0.433
LPHN3	GRM8	1861567	1852779	ENSP00000422533	ENSP00000344173	0	0	0	0	0	0	0	0.601	0.601
COL4A4	COL14A1	1858410	1847909	ENSP00000379866	ENSP00000297848	0	0	0	0	0	0	0.9	0.075	0.903
ADORA3	GRM8	1855085	1852779	ENSP00000358730	ENSP00000344173	0	0	0	0	0	0	0.9	0.056	0.901
PRKCA	BTC	1860737	1858326	ENSP00000408695	ENSP00000379092	0	0	0	0	0	0	0	0.805	0.805
CHEK1	SFRP1	1859362	1842801	ENSP00000388648	ENSP00000220772	0	0	0	0	0	0.566	0	0.047	0.568
GRM8	GRM1	1852779	1846816	ENSP00000344173	ENSP00000282753	0	0	0	0.902	0	0	0.9	0.837	0.908
ASB2	JAK2	1862769	1857411	ENSP00000451575	ENSP00000371067	0	0	0	0	0	0.583	0	0.092	0.605
GRM1	KPNA3	1846816	1844961	ENSP00000282753	ENSP00000261667	0	0	0	0	0	0.567	0	0	0.567
GNG2	TACR1	1851723	1848544	ENSP00000334448	ENSP00000303522	0	0	0	0	0	0	0.9	0	0.9

ADORA3	ADCY1	1855085	1847854	ENSP00000358730	ENSP00000297323	0	0	0	0	0	0	0.9	0.043	0.9
PRKCA	PLA2G4E	1860737	1858733	ENSP00000408695	ENSP00000382434	0	0	0	0	0	0.087	0.8	0	0.809
CPS1	JAK2	1860357	1857411	ENSP00000402608	ENSP00000371067	0	0	0	0	0	0.101	0	0.399	0.436
GRM7	GRM1	1853578	1846816	ENSP00000350348	ENSP00000282753	0	0	0	0.902	0	0	0.9	0.886	0.908
CES1	COL14A1	1854024	1847909	ENSP00000353720	ENSP00000297848	0	0	0	0	0	0	0	0.472	0.472
PRKCA	GRM7	1860737	1853578	ENSP00000408695	ENSP00000350348	0	0	0	0	0	0.576	0	0.312	0.695
GAS7	MYO18B	1860671	1851736	ENSP00000407552	ENSP00000334563	0	0	0	0	0	0.406	0	0.617	0.763
SPTB	CTNNA3	1857851	1855980	ENSP00000374372	ENSP00000362849	0	0	0	0	0	0.102	0	0.487	0.52
ATP8B3	MS4A14	1849407	1848159	ENSP00000311336	ENSP00000300187	0	0	0	0	0	0	0	0.501	0.501
KATNB1	HIATL1	1857071	1856280	ENSP00000368982	ENSP00000364493	0	0	0	0	0	0	0	0.486	0.485
CDH13	CADM1	1860733	1859861	ENSP00000408632	ENSP00000395359	0	0	0	0	0	0	0	0.458	0.457
DNAJC6	SRBD1	1858290	1845406	ENSP00000378735	ENSP00000263736	0	0	0	0	0.495	0	0	0	0.495
ADORA3	GNG2	1855085	1851723	ENSP00000358730	ENSP00000334448	0	0	0	0	0	0	0.9	0.071	0.903
JAK2	SPHK2	1857411	1843751	ENSP00000371067	ENSP00000245222	0	0	0	0	0	0	0.9	0.116	0.907
PRKCA	CHEK1	1860737	1859362	ENSP00000408695	ENSP00000388648	0	0	0	0.656	0	0.17	0.9	0.181	0.917
PLCB4	TACR1	1851676	1848544	ENSP00000334105	ENSP00000303522	0	0	0	0	0	0	0.9	0.12	0.908
SLC35F2	SLC25A1	1859730	1842516	ENSP00000393571	ENSP00000215882	0	0	0	0	0	0	0	0.431	0.431
JAK2	DAB2IP	1857411	1844688	ENSP00000371067	ENSP00000259371	0	0	0	0	0	0	0	0.809	0.809
EXT1	GPC6	1856833	1856600	ENSP00000367446	ENSP00000366246	0	0	0	0	0	0	0.9	0.541	0.952
ACTN2	MYO18B	1854402	1851736	ENSP00000355537	ENSP00000334563	0	0	0	0	0.07	0.153	0	0.369	0.459
FBLN1	TNR	1851357	1845363	ENSP00000331544	ENSP00000263525	0	0	0	0	0	0	0	0.608	0.608
PLA2G4E	MBOAT1	1858733	1850697	ENSP00000382434	ENSP00000324944	0	0	0	0	0	0.149	0.9	0.089	0.915
PAFAH1B1	DISC1	1858470	1854415	ENSP00000380378	ENSP00000355593	0	0	0	0	0	0.306	0	0.564	0.684
PRKCA	RHOH	1860737	1857435	ENSP00000408695	ENSP00000371219	0	0	0	0	0	0.302	0	0.444	0.595
GRM7	ADCY1	1853578	1847854	ENSP00000350348	ENSP00000297323	0	0	0	0	0	0	0.9	0.106	0.906

CACNA2D3	ATP11A	1861397	1846860	ENSP00000419101	ENSP00000283558	0	0	0	0	0	0	0	0.419	0.419
MED1	ACSL1	1848202	1846727	ENSP00000300651	ENSP00000281455	0	0	0	0	0	0	0.9	0	0.9
COL22A1	COL14A1	1848499	1847909	ENSP00000303153	ENSP00000297848	0	0	0	0.63	0	0	0.9	0.234	0.907
PALLD	ACTN2	1861658	1854402	ENSP00000425556	ENSP00000355537	0	0	0	0	0	0.576	0	0	0.576
CDK12	CREB5	1860122	1853582	ENSP00000398880	ENSP00000350359	0	0	0	0	0	0.572	0	0	0.572
FAM155A	FAM189A1	1856404	1844878	ENSP00000365080	ENSP00000261275	0	0	0	0	0	0	0	0.544	0.544
CTNNA3	ACTN2	1855980	1854402	ENSP00000362849	ENSP00000355537	0	0	0	0	0	0.102	0.8	0.757	0.952
KCNK10	TRPA1	1849312	1845090	ENSP00000310568	ENSP00000262209	0	0	0	0	0	0	0	0.416	0.416
COL1A2	MITF	1847845	1847592	ENSP00000297268	ENSP00000295600	0	0	0	0	0	0	0	0.495	0.495
LTBP1	ADORA3	1859086	1855085	ENSP00000386043	ENSP00000358730	0	0	0	0	0	0	0	0.609	0.609
PATE4	PATE2	1860919	1853698	ENSP00000411439	ENSP00000351325	0	0	0	0	0	0	0	0.725	0.725
COL4A4	COL22A1	1858410	1848499	ENSP00000379866	ENSP00000303153	0	0	0	0.611	0	0	0.9	0.139	0.903
PRKCA	ADCY1	1860737	1847854	ENSP00000408695	ENSP00000297323	0	0	0	0	0	0.15	0	0.427	0.492
PALLD	SORBS2	1861658	1846926	ENSP00000425556	ENSP00000284776	0	0	0	0	0	0.576	0	0	0.576
MYO3B	MYO18B	1859134	1851736	ENSP00000386213	ENSP00000334563	0	0	0	0.622	0.289	0	0	0.657	0.461
PDE7B	LRRK2	1849328	1848005	ENSP00000310661	ENSP00000298910	0	0	0	0	0	0.311	0	0.206	0.429
JAK2	TUB	1857411	1848730	ENSP00000371067	ENSP00000305426	0	0	0	0	0	0.57	0	0.083	0.588
CSMD1	SLC35F2	1862182	1859730	ENSP00000441462	ENSP00000393571	0	0	0	0	0	0	0	0.526	0.526
PRKCA	GNG2	1860737	1851723	ENSP00000408695	ENSP00000334448	0	0	0	0	0	0	0.9	0.062	0.902
CDC45	CHEK2	1860553	1857546	ENSP00000405726	ENSP00000372023	0	0	0	0	0.288	0.211	0	0.727	0.833
CDC45	TOP1	1860553	1854138	ENSP00000405726	ENSP00000354522	0	0	0	0	0	0.506	0	0.632	0.81
CRYL1	ACSBG2	1847940	1844148	ENSP00000298248	ENSP00000252669	0.282	0	0	0	0	0	0	0.201	0.401
BCL11A	FOXP1	1852138	1850093	ENSP00000338774	ENSP00000318902	0	0	0	0	0	0.102	0	0.363	0.404
GRM7	GRM8	1853578	1852779	ENSP00000350348	ENSP00000344173	0	0	0	0.983	0	0	0.9	0.871	0.901
DNAJC6	CLTA	1858290	1843621	ENSP00000378735	ENSP00000242285	0	0	0	0	0	0.575	0	0.873	0.944

ADORA3	GRM7	1855085	1853578	ENSP00000358730	ENSP00000350348	0	0	0	0	0	0	0.9	0.126	0.908
PATE2	PUS3	1853698	1843115	ENSP00000351325	ENSP00000227474	0	0	0	0	0	0	0	0.47	0.47
PAFAH1B1	AHCTF1	1858470	1854384	ENSP00000380378	ENSP00000355465	0	0	0	0	0	0	0.9	0.043	0.9
COL4A4	COL15A1	1858410	1856217	ENSP00000379866	ENSP00000364140	0	0	0	0	0	0	0.9	0.187	0.915
GNG2	PLCB4	1851723	1851676	ENSP00000334448	ENSP00000334105	0	0	0	0	0	0	0.9	0	0.9
CPS1	UPF2	1860357	1853334	ENSP00000402608	ENSP00000348708	0	0	0	0	0	0.617	0	0.09	0.636
SEH1L	AHCTF1	1858770	1854384	ENSP00000382779	ENSP00000355465	0	0	0	0	0	0.491	0	0.58	0.777
WRNIP1	NMNAT3	1857283	1852338	ENSP00000370150	ENSP00000340523	0.073	0	0	0	0	0.59	0	0.049	0.606
MME	FOXP1	1854017	1850093	ENSP00000353679	ENSP00000318902	0	0	0	0	0	0	0	0.506	0.506
ACRV1	PATE4	1861923	1860919	ENSP00000432816	ENSP00000411439	0	0	0	0	0	0	0	0.503	0.503
MYO18B	CAPZB	1851736	1845501	ENSP00000334563	ENSP00000264202	0	0	0	0	0	0.22	0	0.416	0.525
GRM7	GNG2	1853578	1851723	ENSP00000350348	ENSP00000334448	0	0	0	0	0	0	0.9	0	0.9
EPN2	CLTA	1850258	1843621	ENSP00000320543	ENSP00000242285	0	0	0	0	0	0.376	0	0.417	0.621
CCDC135	ACSBG2	1854055	1844148	ENSP00000353942	ENSP00000252669	0	0	0	0	0	0	0	0.635	0.635
COL15A1	COL1A2	1856217	1847845	ENSP00000364140	ENSP00000297268	0	0	0	0.613	0	0	0.9	0.617	0.923
ERC1	RAB6B	1854082	1846951	ENSP00000354158	ENSP00000285208	0	0	0	0	0	0.576	0	0.754	0.891
ADRA1D	TACR1	1857034	1848544	ENSP00000368766	ENSP00000303522	0	0	0	0.646	0	0	0.9	0.142	0.903
NMNAT3	BTD	1852338	1848848	ENSP00000340523	ENSP00000306477	0.281	0	0	0	0	0	0	0.281	0.46
ERC1	NRXN3	1854082	1852100	ENSP00000354158	ENSP00000338349	0	0	0	0	0	0	0	0.794	0.795
DDX25	PUS3	1845369	1843115	ENSP00000263576	ENSP00000227474	0	0	0	0	0	0.094	0	0.674	0.692
HYLS1	PUS3	1853354	1843115	ENSP00000348815	ENSP00000227474	0	0	0	0	0	0	0	0.639	0.639
ARNTL	TOP1	1857849	1854138	ENSP00000374357	ENSP00000354522	0	0	0	0	0	0	0	0.813	0.813
PDE7B	ADCY1	1849328	1847854	ENSP00000310661	ENSP00000297323	0	0	0	0	0.238	0.297	0.9	0.492	0.969
ADRA1D	GNG2	1857034	1851723	ENSP00000368766	ENSP00000334448	0	0	0	0	0	0	0.9	0.104	0.906
ACRV1	PATE2	1861923	1853698	ENSP00000432816	ENSP00000351325	0	0	0	0	0	0	0	0.5	0.499

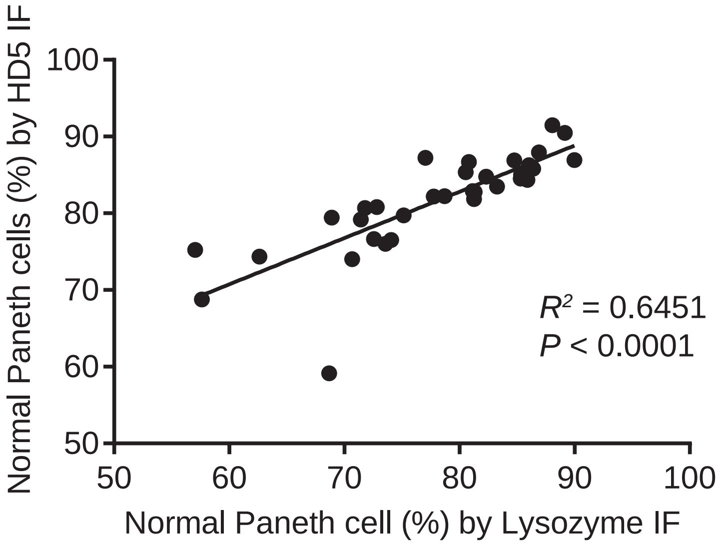
CDC45	CHEK1	1860553	1859362	ENSP00000405726	ENSP00000388648	0	0	0	0	0.127	0.821	0.9	0.807	0.996
PATE2	DDX25	1853698	1845369	ENSP00000351325	ENSP00000263576	0	0	0	0	0	0	0	0.507	0.507
TACR1	GRM1	1848544	1846816	ENSP00000303522	ENSP00000282753	0	0	0	0	0	0	0.9	0.181	0.914
PRKCA	PLCB4	1860737	1851676	ENSP00000408695	ENSP00000334105	0	0	0	0	0	0.149	0.8	0.374	0.884
COL15A1	COL14A1	1856217	1847909	ENSP00000364140	ENSP00000297848	0	0	0	0	0	0	0.9	0.424	0.939
COL4A4	COL1A2	1858410	1847845	ENSP00000379866	ENSP00000297268	0	0	0	0.638	0	0	0.9	0.346	0.911
ACTN2	CAPZB	1854402	1845501	ENSP00000355537	ENSP00000264202	0	0	0	0	0	0.424	0	0.125	0.474
CDC45	UFD1L	1860553	1845303	ENSP00000405726	ENSP00000263202	0	0	0	0	0	0	0	0.634	0.634
CEP55	FOXM1	1855493	1852579	ENSP00000360540	ENSP00000342307	0	0	0	0	0.112	0	0	0.889	0.897
GRM8	ADCY1	1852779	1847854	ENSP00000344173	ENSP00000297323	0	0	0	0	0	0	0.9	0.143	0.91
CHEK1	CHEK2	1859362	1857546	ENSP00000388648	ENSP00000372023	0	0	0	0.704	0.124	0.722	0	0.991	0.82
KATNB1	CCDC135	1857071	1854055	ENSP00000368982	ENSP00000353942	0	0	0	0	0	0	0	0.65	0.65
COL15A1	COL22A1	1856217	1848499	ENSP00000364140	ENSP00000303153	0	0	0	0.609	0	0	0.9	0.335	0.912
FBXO32	DAB2IP	1861731	1844688	ENSP00000428205	ENSP00000259371	0	0	0	0	0	0	0	0.419	0.419
HYLS1	DDX25	1853354	1845369	ENSP00000348815	ENSP00000263576	0	0	0	0	0	0	0	0.881	0.881
GRM8	GNG2	1852779	1851723	ENSP00000344173	ENSP00000334448	0	0	0	0	0	0	0.9	0.042	0.9
GNG2	ADCY1	1851723	1847854	ENSP00000334448	ENSP00000297323	0	0	0	0	0	0	0.9	0.4	0.937
PRKCA	CREB5	1860737	1853582	ENSP00000408695	ENSP00000350359	0	0	0	0	0	0.149	0.8	0.128	0.838
ADCY1	ATP11A	1847854	1846860	ENSP00000297323	ENSP00000283558	0	0	0	0	0.106	0	0	0.378	0.42
UPF2	MSI2	1853334	1846883	ENSP00000348708	ENSP00000284073	0	0	0	0	0	0.304	0	0.196	0.416
CPS1	SEPSECS	1860357	1857481	ENSP00000402608	ENSP00000371535	0	0	0	0	0.069	0.465	0	0.11	0.517
STT3A	DDX25	1858037	1845369	ENSP00000376472	ENSP00000263576	0	0	0	0	0.112	0	0	0.451	0.492
COL14A1	COL1A2	1847909	1847845	ENSP00000297848	ENSP00000297268	0	0	0	0	0	0	0.9	0.321	0.929
GAS7	TUB	1860671	1848730	ENSP00000407552	ENSP00000305426	0	0	0	0	0	0	0	0.564	0.564
MUC19	LRRK2	1859854	1848005	ENSP00000395253	ENSP00000298910	0	0	0	0	0	0	0	0.473	0.473

PATE4	PUS3	1860919	1843115	ENSP00000411439	ENSP00000227474	0	0	0	0	0	0	0	0.472	0.472
ACTN2	SYNPO2	1854402	1848802	ENSP00000355537	ENSP00000306015	0	0	0	0	0	0.576	0	0.126	0.613
STT3A	HYLS1	1858037	1853354	ENSP00000376472	ENSP00000348815	0	0	0	0	0	0	0	0.43	0.431
STOML3	ASIC2	1857064	1843054	ENSP00000368952	ENSP00000225823	0	0	0	0	0	0.096	0	0.551	0.577
JAK2	NOX4	1857411	1845330	ENSP00000371067	ENSP00000263317	0	0	0	0	0	0	0	0.866	0.866
GNG2	GRM1	1851723	1846816	ENSP00000334448	ENSP00000282753	0	0	0	0	0	0	0.9	0	0.9
CLDN5	SLC25A1	1858954	1842516	ENSP00000384554	ENSP00000215882	0	0	0	0	0	0	0	0.608	0.608
CHEK1	TOP1	1859362	1854138	ENSP00000388648	ENSP00000354522	0	0	0	0	0	0.3	0	0.744	0.813
PRKCA	SPHK2	1860737	1843751	ENSP00000408695	ENSP00000245222	0	0	0	0	0	0	0.8	0.117	0.815
CLSTN2	NMNAT3	1860345	1852338	ENSP00000402460	ENSP00000340523	0	0	0	0	0	0	0	0.867	0.867
TOP1	CES1	1854138	1854024	ENSP00000354522	ENSP00000353720	0	0	0	0	0	0	0	0.658	0.658
MYO3B	RHOH	1859134	1857435	ENSP00000386213	ENSP00000371219	0	0	0	0	0	0.23	0	0.369	0.493
SPTB	COL14A1	1857851	1847909	ENSP00000374372	ENSP00000297848	0	0	0	0	0	0	0	0.421	0.421
PRKCA	GRM1	1860737	1846816	ENSP00000408695	ENSP00000282753	0	0	0	0	0	0.576	0	0.126	0.613
CRYL1	ACSL1	1847940	1846727	ENSP00000298248	ENSP00000281455	0.282	0	0	0	0	0	0	0.201	0.401
MME	TACR1	1854017	1848544	ENSP00000353679	ENSP00000303522	0	0	0	0	0	0	0	0.45	0.45
CDH13	SFRP1	1860733	1842801	ENSP00000408632	ENSP00000220772	0	0	0	0	0	0	0	0.474	0.474
DUSP7	HOXA10	1861273	1846874	ENSP00000417183	ENSP00000283921	0	0	0	0	0	0	0	0.603	0.603
COL22A1	COL1A2	1848499	1847845	ENSP00000303153	ENSP00000297268	0	0	0	0.644	0	0	0.9	0.284	0.909
SGCZ	LINGO2	1857476	1849261	ENSP00000371512	ENSP00000310126	0	0	0	0	0	0	0	0.5	0.499
ARNTL	NOX4	1857849	1845330	ENSP00000374357	ENSP00000263317	0	0	0	0	0	0	0	0.803	0.803
CMYA5	ACTN2	1859827	1854402	ENSP00000394770	ENSP00000355537	0	0	0	0	0.112	0	0	0.561	0.593
SGPP2	SPHK2	1849763	1843751	ENSP00000315137	ENSP00000245222	0.254	0	0	0	0	0.202	0.9	0.698	0.979
FOXM1	ALX1	1852579	1849786	ENSP00000342307	ENSP00000315417	0	0	0	0	0	0.086	0	0.373	0.402
CSMD1	LINGO2	1862182	1849261	ENSP00000441462	ENSP00000310126	0	0	0	0	0	0	0	0.435	0.435

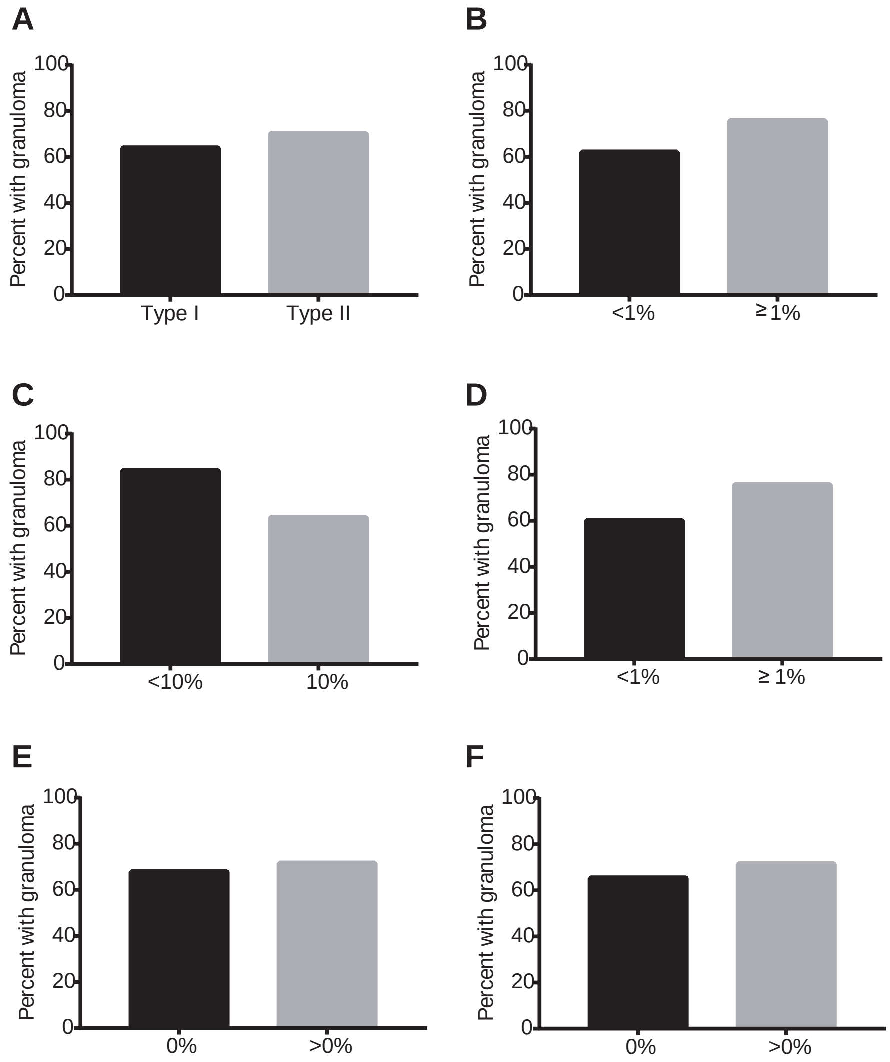
Supplementary Table 7. Potential pathways associated with Paneth cell defect in Japanese CD.

Term	Number of genes	*P* value	*P* value (FDR)
Protein digestion and absorption	7	1.10×10^{-4}	3.14×10^{-2}
Glutamatergic synapse	7	5.48×10^{-4}	7.86×10^{-2}
Calcium signaling pathway	8	1.99×10^{-3}	1.91×10^{-1}
Cholinergic synapse	6	2.71×10^{-3}	1.95×10^{-1}
Long-term depression	4	6.75×10^{-3}	3.38×10^{-1}
Inflammatory mediator regulation of TRP channels	5	7.56×10^{-3}	3.38×10^{-1}
Retrograde endocannabinoid signaling	5	8.25×10^{-3}	3.38×10^{-1}
Amoebiasis	5	1.14×10^{-2}	4.10×10^{-1}
Leukocyte transendothelial migration	5	1.59×10^{-2}	4.73×10^{-1}
Focal adhesion	7	1.65×10^{-2}	4.73×10^{-1}
Endocrine and other factor-regulated calcium reabsorption	3	2.17×10^{-2}	5.05×10^{-1}
Dopaminergic synapse	5	2.28×10^{-2}	5.05×10^{-1}
Neuroactive ligand-receptor interaction	8	2.44×10^{-2}	5.05×10^{-1}
ECM-receptor interaction	4	2.46×10^{-2}	5.05×10^{-1}
Adrenergic signaling in cardiomyocytes	5	3.67×10^{-2}	7.03×10^{-1}
VEGF signaling pathway	3	4.11×10^{-2}	7.37×10^{-1}

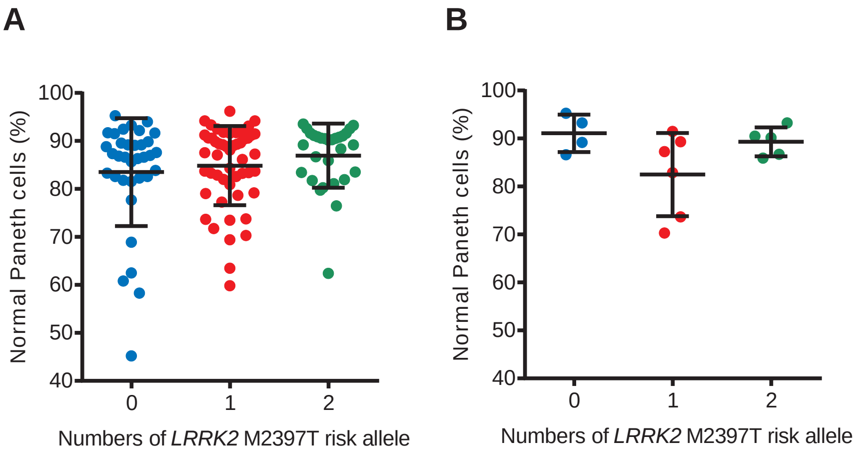
Supplementary Figure 1



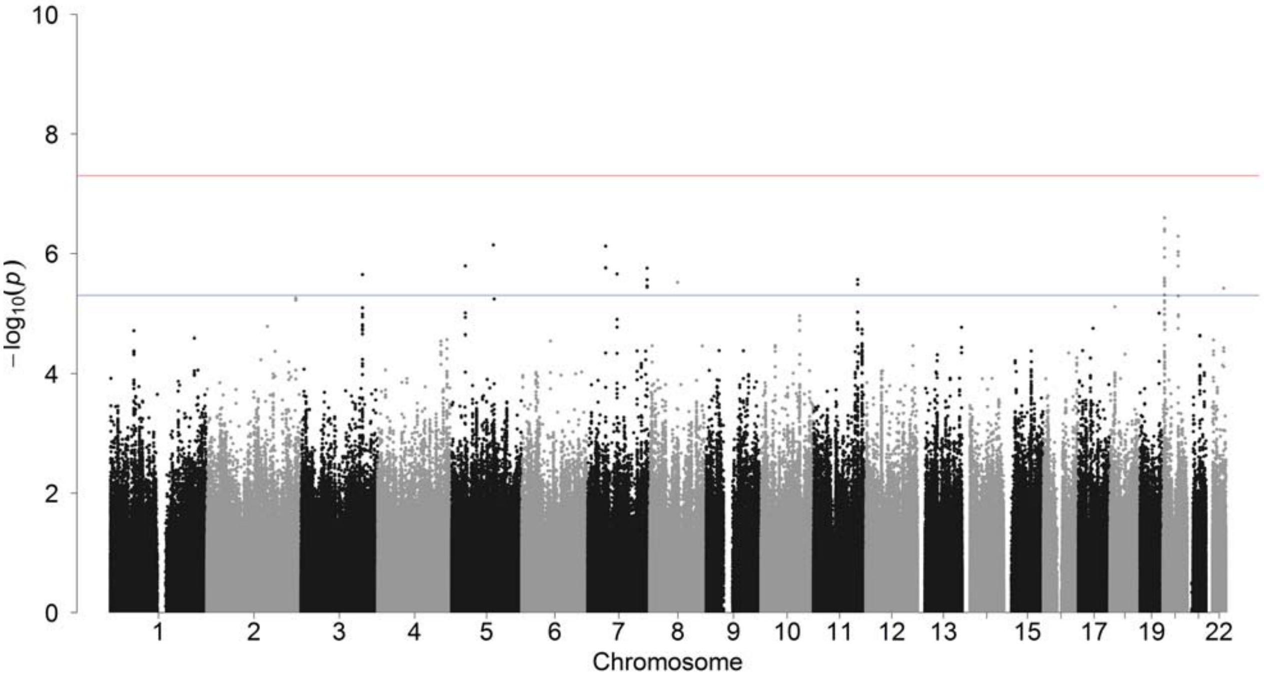
Supplementary Figure 2



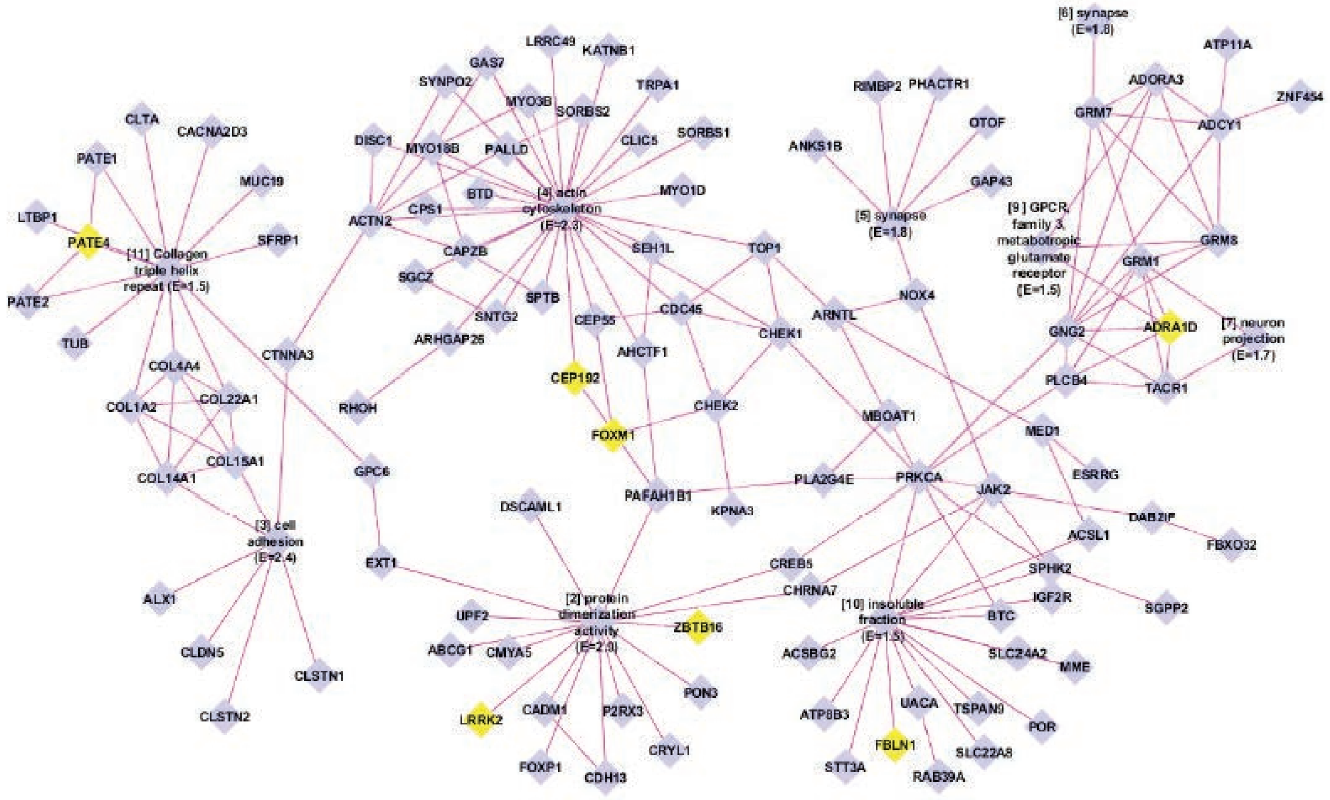
Supplementary Figure 3



Supplementary Figure 4



Supplementary Figure 5



Supplementary Figure legend:

Supplementary Figure 1. Determination of percentage of normal Paneth cells obtained by Defensin-5 (HD5) immunofluorescence strongly correlated with that obtained by lysozyme immunofluorescence. A series of 33 Japanese Crohn's disease cases were co-stained with both HD5 and lysozyme immunofluorescence ($R^2 = 0.6451$; $P < 0.0001$ by linear regression).

Supplementary Figure 2. Correlation of Paneth cell phenotype and presence of granuloma in the Japanese Crohn's disease cohort. No significant difference was seen when the presence of granuloma was correlated with (A) Type I vs. Type II Paneth cell phenotype ($P = 0.6469$); (B) Percentage of disordered (D1) Paneth cells ($P = 0.1249$); (C) Percentage of diminished (D2) Paneth cells ($P = 0.0506$); (D) Percentage of diffuse (D3) Paneth cells ($P = 0.0992$); (E) Percentage of excluded (D4) Paneth cells ($P = 0.7152$); (F) Percentage of enlarged (D5) Paneth cells ($P = 0.5396$). Statistical analysis was performed using Fisher's exact test.

Supplementary Figure 3. The numbers of *LRRK2* M2397T allele did not correlate with the percentage of normal Paneth cells in North American Crohn's disease (CD) patients with (A) either *ATG16L1* T300A or *NOD2* risk alleles ($R^2 = 0.01998$ and $P = 0.13$ by linear regression) or (B) no risk alleles for *ATG16L1* T300A or *NOD2* ($R^2 = 0.003903$ and $P = 0.82$ by linear regression). Error bars represent ± SEM.

Supplementary Figure 4. Manhattan plot for 4,198,245 SNPs from the genome-wide association analysis for Paneth cell phenotype. Single nucleotide polymorphisms are plotted according to chromosomal location, with the -log10(P) calculated by the linear regression test. The red line indicates the threshold for the genome-wide significance ($P = 5 \times 10^{-8}$). The blue line indicates the threshold for the nominal significance ($P = 5 \times 10^{-6}$).

Supplementary Figure 5. Network annotation of pathway analysis. Genes associated with the candidate single nucleotide polymorphismsare highlighted in yellow.