Supplementary data

Table S1: 101 targeted region genes

ADO
AK3
APOBEC3B;Alias=APOBEC3A
APOBEC3C
APOBEC3D
APOBEC3F
APOBEC3G
APOBEC3H
ATF4
ATG16L1
C11orf30
C16orf74
C1orf141
C5orf56
C5orf62
C7
C9orf163
CARD6
CARD9
CBX7
CNTN1
COX4I1
COX4NB
CYLD
DGKD
DKFZP434A062
DNLZ
EGR2
FLJ30679
FOXC2
FOXF1
FOXL1
GINS2
GLS
GPSM1
GPX3
GUCY2E
IL12B
IL12RB2
IL23R
IL5
INPP5E
INSL4
INSL6
IPO11
IRF1
IRF8
IRGM
JAK2
KIAA0182
LOC553103

LOC732275
LRRC32
LRRC70
LRRK2
MGAT3
MIR3936
MST1R
MTHFSD
MTHFSD_DUP_01
NOD2
NOTCH1
NRBF2
PDGFB
PMPCA
PRKAA1
PRKRIR
PTGER4
RCL1
RNF145
RNU86
RPL3
RPL37
RTKN2
SAG
SCARNA5
SCARNA6
SDCCAG3
SEC16A
SLC22A4
SLC22A5
SLC2A13
SMCR7L
SNAPC4
SNORD43
SNORD72
SNORD83A
SNORD83B
STAT1
STAT3
STAT4
SYNGR1
TAB1
TNIP1
TSKU
TTC33
UBLCP1
USP40
ZNF300
ZNF300P1
ZNF365

Table S2: 63 testable genes for multiple test correction

ADO
AK3
APOBEC3D
APOBEC3F
APOBEC3G
APOBEC3H
ATF4
ATG16L1
C11orf30
C16orf74
C1orf141
C5orf62
C7
CARD6
CARD9
CNTN1
COX4I1
DGKD
DNLZ
FOXC2
FOXL1
GPSM1
IL12B
IL12RB2
IL23R
INPP5E
IPO11
IRF1
IRF8
IRGM
JAK2
KIAA0182
LRRC32
LRRC70
LRRK2
MGAT3
MST1R
MTHFSD_DUP_01
NOD2
NOTCH1
NRBF2
PDGFB
PMPCA
PRKRIR
PTGER4
RCL1
RNF145
RTKN2
SAG
SDCCAG3
SEC16A
SLC22A4
SLC22A5
SLC2A13

SMCR7L
SNAPC4
STAT4
TAB1
TNIP1
TSKU
USP40
ZNF300
ZNF365

Table S3. VAAST results for genes with p-value less than 0.05

Gene	VAAST p-value	VAAST p-value after Bonferroni correction	Variant coordinates (hg19)	Amino acid substitution	Control reference allele count	Control alternate allele count	Case reference allele count	Case alternate allele count
NOD2	1.53×10^{-5}	0.00096	chr16:50745926	R702W	379	21	369	41
			chr16:50756540	G908R	396	4	390	20
			ins-chr16-50763778	L1007fs	390	10	373	37
			chr16:50733465	S47L	400	0	409	1
			chr16:50733485	E54K	400	0	409	1
			chr16:50744694	D291G	400	0	409	1
			del-chr16-50745826	P668fs	400	0	409	1
			chr16:50744999	R393C	400	0	409	1
			chr16:50745114	S431L	400	0	409	1
			chr16:50745081	R420H	400	0	409	1
			chr16:50746194	R791Q	400	0	408	2
			chr16:50750524	R830L	400	0	409	1
			chr16:50750559	C842R	400	0	409	1
			chr16:50759434	C973R	400	0	409	1
RTKN2	0.00165	0.10395	del-chr10-63976913	A328fs	377	23	361	49
			chr10:63957780	G573S	400	0	408	2
MGAT3	0.0147	0.9361	chr22:39884847	D499H	400	0	407	3
			chr22:39884925	R525W	400	0	409	1
			chr22:39883837	R162Q	400	0	409	1

Table S4. The list of meta-analyses and odds ratios used for R702W in *NOD2*

Study	Year	OR	Lower bound	Upper bound
Karban,A,	2005	5.58	0.23	137.89
Kugathasan,S,	2005	0.44	0.02	7.89
Kugathasan,S,	2005	0.53	0.06	4.8
Zouiten-Mekki,L,	2005	3.51	0.41	30.3
Ince,AT,	2008	0.16	0.02	1.26
Tukel,T,	2004	6.71	1.04	43.16
Qzen,SC	2006	0.75	0.14	4.17
Vavassori,P,	2004	1.52	0.28	8.37
Torkvist,L,	2006	6.68	1.52	29.31
Canto,E,	2007	6.59	1.52	28.55
Gazouli,M,	2004	11	2.57	47.14
Tomer,G,	2003	5.47	1.48	20.16
Jess,T	2005	3.76	1.11	12.8
Zaahl,MG	2005	2.1	0.62	7.08
Crawford,NPS	2007	5.5	1.67	18.18
Bene,J	2006	1.89	0.58	6.1
Derakhshan,F	2008	9.51	3	30.16
Economou,M	2007	3.85	1.25	11.93
Karban,A	2004	4.13	1.38	12.34
Buhner,S	2006	3.15	1.06	9.32
Karban,A	2005	4.24	1.46	12.3
Rigoli,L	2008	4.36	1.64	11.55
Lappalainen,M	2008	2.15	0.83	5.55
Vind,I	2005	1.01	0.41	2.49
Vermeire,S	2002	3.38	1.43	8.01
Ferraris,A	2006	4.51	1.91	10.64
Tukel,T	2004	2.11	0.92	4.84
Nagy,Z	2005	2.3	1	5.27
van,der,Linde,K	2007	1.53	0.68	3.45
Cottone,M	2006	2.98	1.33	6.7
Rodrigo,L	2007	0.79	0.36	1.72
Magyari,L	2009	1.41	0.66	3.03
Helio,T	2003	1.84	0.86	3.93
Buning,C	2005	2.81	1.33	5.92
Hugot,JP	2001	3.06	1.47	6.39
Heresbach,D	2004	2.6	1.25	5.43
Mendoza,JL	2003	3.52	1.7	7.26
Cukovic-Cavak,S	2006	2.79	1.35	5.76
Russel,RK	2005	1.19	0.58	2.43
Zhou,Z	2002	1.13	0.56	2.26

Diego,CD	2006	2.29	1.15	5.43
Braat,H	2005	2.89	1.47	5.65
Bianchi,V	2007	1.79	0.94	3.42
Nunez,C	2004	1.17	0.62	2.2
Baptista,ML	2008	3.77	2	7.1
Lakatos,PL	2005	2.55	1.37	4.73
Gearry,RB	2007	2.59	1.41	4.76
Leung,E	2005	1.47	0.8	2.69
Giachino,D	2004	1.56	0.89	2.76
Annese,V	2005	2.2	1.26	3.85
Newman,B	2004	2.26	1.31	3.9
Arnot,IDR	2004	1.48	0.88	2.51
Vermeire,S	2004	2.94	1.74	4.96
Brant,SR	2007	3.49	2.08	5.86
Protic,MB	2007	1.5	0.9	2.5
de,Ridder,L	2007	2.96	1.77	4.93
Cuthbert,AP	2002	2.72	1.64	4.5
Kugathasan,S	2005	1.26	0.76	2.07
Cucchiara,S	2007	3.01	1.83	4.95
Esters,N	2004	2.42	1.48	3.97
Ferreira,AC	2005	3.31	2.03	5.38
Sugimura,K	2003	1.73	1.1	2.73
Bonen,DK	2003	1.95	1.26	3.04
Hradsky,O	2008	1.48	0.95	2.3
Oostenbrug,LE	2006	1.88	1.21	2.92
Riss,L	2007	2.31	1.5	3.57
Ahmad,T	2002	2.63	1.71	4.04
Mascheretti,S	2002	2.05	1.33	3.14
Ernst,A	2002	2.02	1.32	3.09
cavanaugh,JA	2003	2.35	1.56	3.56
Hampe,J,	2002	2.72	1.92	3.84
Weersma,RK	2009	1.65	1.33	2.04
D'Addabbo,A	2009	1.99	0.85	4.65
Schoultz,I	2009	2.43	1.49	3.97
Csongei,V	2010	2.13	1.19	3.8
Dassopoulos,T	2010	1.59	0.39	6.48
Gazouli,M.	2010	1.54	0.89	2.66
Gazouli,M.	2010	1.72	1.2	2.48
Glas,J.	2010	2.07	1.53	2.79
Lacher,M	2010	3.8	2.2	6.58
Sventoraityte,J.	2010	0.71	0.15	3.33
Naderi,N.	2011	12.15	3.6	41.05
Adeyanju,O.	2012	1.08	0.53	2.22

Azzam,N.	2012	7.71	2.87	20.71
Hama,I.	2012	2.38	0.89	6.4
Kanaan,Z.	2012	4.36	1.77	10.7
Akyuz,F.	2013	0.56	0.02	13.89
Boukercha,A.	2015	3.67	0.48	4.87
Meddour,Y.	2014	11.64	2.7	50.2

Table S5. The list of meta-analyses and odds ratios used for R908W in *NOD2*

Study	Year	OR	Lower bound	Upper bound
Zaahi,MG	2005	0.81	0.03	19.99
Lappalainen,M	2008	3.98	0.19	83.06
Kugathasan,S	2005	0.96	0.05	18.98
Helio,T,	2003	7.79	0.04	151.18
Canto,E	2007	5.83	0.32	106.57
Russel,RK	2005	11.2	0.64	197.01
Torkvist,L	2006	12.3	0.7	216.21
Protic,MB	2007	20.6	1.22	347.57
Ince,AT	2008	0.65	0.06	7.21
Bene,J	2006	6.28	0.78	50.38
van,der,Linde,K	2007	9.88	1.29	75.93
Arnot,IDR	2004	7.1	0.93	54.19
Vermeire,S	2002	7.73	1.04	57.63
Jess,T	2005	2.31	0.38	14.24
Ozen,SC	2005	2.3	0.38	13.94
Derakhshan,F	2008	5.21	0.94	29.04
Karban,A	2005	1.87	0.37	9.39
Rodrigo,L	2007	1.2	0.24	5.99
Buhner,S	2006	2.63	0.57	12.19
Nagy,Z	2005	1.95	0.43	8.86
Cukovic-Cavak,S	2006	4.15	0.92	18.78
Vind,I	2005	3.11	0.69	14.06
Magyari,L	2009	8.2	1.83	36.73
Hugot,JP	2001	6.49	1.57	26.82
Tukel,T	2004	7.52	1.9	29.85
Crawford,NPS	2007	2.3	0.66	8.06
Heresbach,D	2004	2.37	0.68	8.28
Nunez,C	2004	5.19	1.49	18.1
Bianchi,V	2007	4.79	1.37	16.71
Cuthbert,AP	2002	6.71	2.03	22.14
Queiroz,DM	2009	5.23	1.61	17.04
Diego,CD	2006	2.63	0.83	8.35
Buning,C	2005	2.58	0.85	7.77
Ferraris,A	2006	6.89	2.33	20.32
Mendoza,JL	2003	4.64	1.62	13.25
Zouiten-Mekki,L	2005	1.99	0.7	5.63
Baptista,ML	2008	1.2	0.43	3.33
Giachino,D	2004	3.17	1.15	8.76
Vavassori,P	2004	2.66	0.97	7.31

VermeireS	2004	2.1	0.81	5.42
Gearry,RB	2007	2.21	0.86	5.65
Cavanaugh,JA	2003	2.13	0.85	5.33
Cottone,M	2006	4.01	1.61	9.99
Ferreira,AC	2005	2.19	0.9	5.33
Rigoli,L	2008	1.03	0.43	2.5
Brant,SR	2007	4.06	1.69	9.73
Leung,E	2005	1.48	0.62	3.5
Esters,N	2004	3.43	1.47	7.97
Gazouli,M	2004	2.55	1.97	10.51
Riss,L	2007	1.21	0.53	2.76
Lakators,PL	2005	1.76	0.77	4.02
Karban,A	2004	7	3.12	15.69
Karban,A	2005	5.75	2.59	12.81
Ahmad,T	2002	2.33	1.05	5.18
Economou,M	2007	0.84	0.39	1.79
Ernst,A	2007	1.55	0.73	3.29
Tomer,G	2003	1.96	0.98	3.93
Hampe,J	2002	5.72	2.91	11.25
Annese,V	2005	2.85	1.46	5.56
Kugathasan,S	2005	4.27	2.23	8.17
Tukel,T	2004	2.5	1.3	4.78
Newman,B	2004	1.52	0.8	2.91
Braat,H	2005	1.11	0.59	2.09
Zhou,Z	2002	3.31	1.8	6.1
Bonen,Dk	2003	3.31	1.8	6.1
Cucchiara,S	2007	2.97	1.63	5.42
Hradsky,O	2008	2.82	1.55	5.12
Mascheretti,S	2002	2.52	1.41	4.51
Oostenbrug,LE	2006	1.41	0.83	2.45
de,Ridder,L	2007	1.31	0.78	2.22
Sugimura,K	2003	1.58	0.95	2.63
Weersma,K	2003	2.05	1.49	2.82
D'Addabbo,A	2009	2.7	1.06	6.89
Schoultz,I	2009	4.59	1.66	12.7
Csongei,V	2010	1.62	0.71	3.89
Dassopoulos,T	2010	3.95	0.19	82.99
Gazouli,M.	2010	2.97	1.7	5.18
Gazouli,M.	2010	3.14	2.09	4.71
Glas,J.	2010	1.72	1.14	2.6
Lacher,M	2010	6.96	2.99	16.18
Sventoraityte,J.	2010	1.06	0.28	3.97
Naderi,N.	2011	1.04	0.23	4.71

Adeyanju,O.	2012	2.83	0.33	24.4
Azzam,N.	2012	9.42	3.43	25.9
Hama,I.	2012	5.35	0.26	112.1
Kanaan,Z.	2012	4.07	2.29	7.23
Akyuz,F.	2013	15.76	0.84	295.37
Boukercha,A.	2015	2.72	0.31	23.69
Meddour,Y.	2014	6.22	1.37	28.15
Salkic,N.,N.	2014	0.48	0.09	2.66

Table S6. The list of meta-analyses and odds ratios used for L1007fs in *NOD2*

Study	Year	OR	Lower bound	Upper bound
Karban,A	2005	5.58	0.23	137.89
Tukel,T	2004	49.85	2.29	1082.74
Ozen,SC	2006	7.67	0.37	161
Zouiten-Mekki,L	2005	4.91	0.25	95.57
Guo,QS	2004	11.83	0.72	194.03
Protic,MB	2007	64.25	3.92	1052.26
Kugathasan,S	2005	7.06	0.43	115.39
Ince,AT	2008	1.3	0.08	20.99
Kugathasan,S	2005	2.15	0.13	34.64
Zaahi,MG	2005	0.3	0.04	2.41
Canto,E	2007	4.26	0.53	34.53
Buhner,S	2006	18.74	2.53	138.87
Vermeire,S	2002	16.35	2.24	119.53
Derakhshan,F	2008	2.54	0.35	18.34
Roussomoustakaki,M	2003	1.82	0.3	11.07
Jess,T	2005	1.13	0.24	5.23
Queiroz,DM	2009	26.98	6.62	109.87
Rodrigo,L	2007	1.75	0.49	6.21
Russel,RK	2005	3.51	1	12.37
Nunez,C	2004	5.19	1.49	18.1
Bene,J	2006	5.24	1.52	18.07
Bianchi,V	2007	5.8	1.69	19.89
Murillo,L	2002	9.27	2.74	31.36
van,der,Linde,K	2007	6.12	1.81	20.64
Leung,E	2005	10.91	3.3	36.08
Vacassori,P	2004	10.4	3.17	34.13
Annese,V	2005	13.97	4.35	44.87
Torkvist,L	2006	1.13	0.35	3.59
Baptista,ML	2008	4.56	1.47	14.08
Ferraris,A	2006	6.18	2.08	18.4
Radimayr,M	2002	9.54	3.28	27.77
Nagy,Z	2005	4.03	1.4	11.55
Arnot,IDR	2004	3.86	1.35	11.03
Gearry,RB	2007	4.17	1.5	11.57
Hugot,JP	2001	6.86	2.5	18.83
Crawford,NPS	2007	2.95	1.13	7.72
Karban,A	2004	3.22	1.28	8.08
Lappalainen,M	2008	3.14	1.26	7.78
Rigoli,L	2008	3.61	1.46	8.95
Karban,A	2005	3.17	1.3	7.73

Diego,CD	2006	2.35	0.96	5.73
Vind,I	2005	2.63	1.1	6.32
Cottone,M	2006	4.26	1.82	9.98
Magyari,L	2009	5.1	2.18	11.94
Giachino,D	2004	2.88	1.27	6.53
Vermeire,S	2004	6.41	2.87	14.31
Cukovic-Cavak,S	2006	2.9	1.3	6.45
Heresbach,D	2004	2.26	1.03	4.95
Cavanaugh,JA	2003	7.54	3.48	16.32
Buning,C	2005	5.48	2.57	11.67
Braat,H	2005	2.34	1.1	4.98
Zhou,Z	2002	1.73	0.82	3.68
Tomer,G	2003	5.46	2.59	11.49
Helio,T	2003	2.97	1.42	6.22
Mendoza,JL	2003	3.66	1.78	7.55
Ferreira,AC	2005	4.49	2.18	9.22
Cucchiara,S	2007	4.53	2.23	9.26
Economou,M	2007	7.06	3.47	14.37
Tukel,T	2004	4.18	2.09	8.37
Gazoli,M	2004	3.42	1.75	6.69
Ahmad,T	2002	6.5	3.33	12.68
Esters	2004	3.01	1.55	5.84
Lakatos,PL	2005	4.78	2.48	9.21
Sugimura,K	2003	3.56	1.87	6.77
Cuthbert,AP	2002	3.23	1.72	6.1
Newan,B	2004	1.76	0.95	3.26
Riss,L	2007	2.13	1.15	3.92
Brant,SR	2007	2.96	1.66	5.3
Ernst,A	2007	5.7	3.34	9.74
Oostenbrug,LE	2006	2.87	1.71	4.83
de,Ridder,L	2007	1.7	1.02	2.82
Kugathasan,S	2005	6.82	4.12	11.29
Ogura,Y	2001	2.13	1.31	3.46
Mascheretti,S	2002	2.82	1.75	4.55
Bonen,DK	2003	2.45	1.53	3.92
Hampe,J	2001	4.11	2.59	6.54
Hampe,J	2002	4.73	3.26	6.86
Hradsky,O	2008	4.76	3.39	6.69
Weersma,RK	2009	3.69	2.73	4.98
D'Addabbo,A	2009	2.32	1.01	5.34
Schoultz,I	2009	3.83	1.99	7.38
Csongei,V	2010	2.57	1.51	4.36
Dassopoulos,T	2010	12.2	0.69	215.34

Gazouli,M.	2010	5.5	3.39	8.94
Gazouli,M.	2010	2.95	1.95	4.44
Glas,J.	2010	5.03	3.54	7.15
Lacher,M	2010	22.44	9.99	50.43
Sventoraityte,J.	2010	5.54	2.85	10.75
Naderi,N.	2011	2.02	0.33	12.2
Adeyanju,O.	2012	12.5	0.73	213.07
Azzam,N.	2012	19	6.2	58.21
Hama,I.	2012	1.06	0.07	17.06
Kanaan,Z.	2012	4.4	2.18	8.87
Akyuz,F.	2013	0.85	0.08	9.43
Boukercha,A.	2015	1.07	0.19	5.9
Salkic,N.,N.	2014	6.92	3.19	15.02

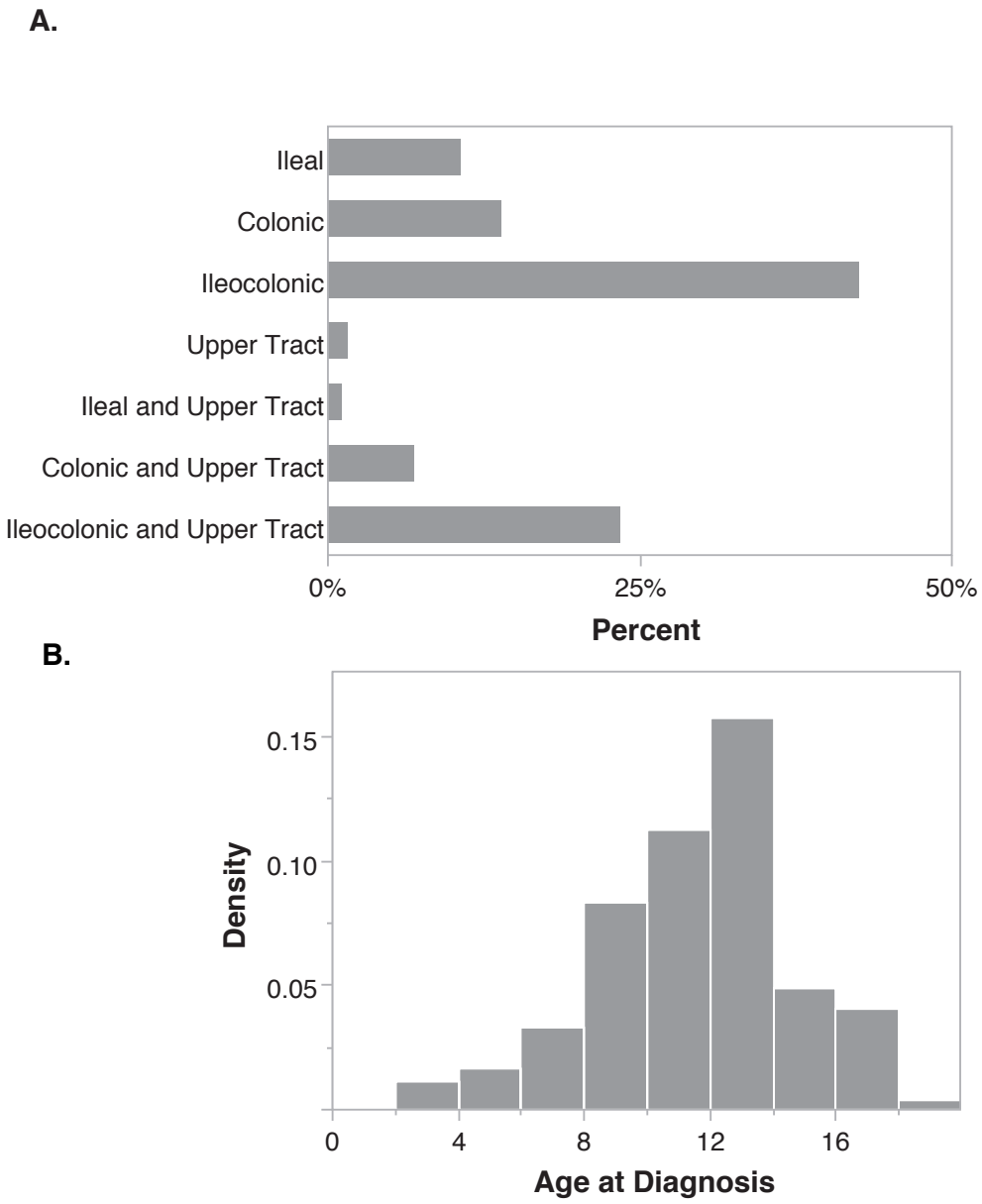

Figure S1. Clinical characteristics of cases. (A) Disease location. (B) Distribution of age at diagnosis.

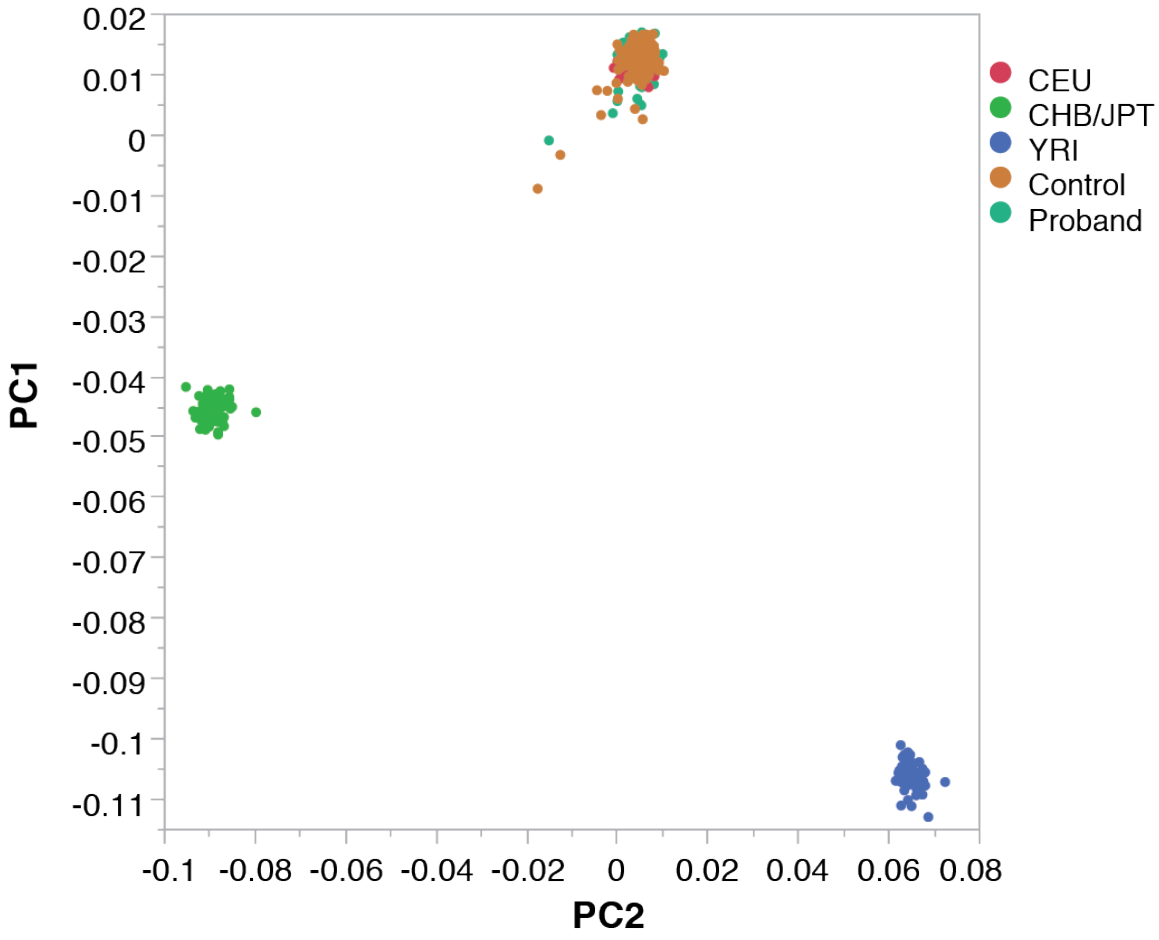

Figure S2. PCA plot of cases and controls superimposed on HapMap samples. CEU=Utah residents with Northern and Western European ancestry; YRI=Yoruba in Ibadan, Nigeria. CHB=Han Chinese in Beijing, China; JPT=Japanese in Tokyo, Japan.