Letter to the Editor

Whole-exome sequencing of Ethiopian patients with ichthyosis vulgaris and atopic dermatitis

To the Editor:

Ichthyosis vulgaris (IV) is a common skin disease characterized by palmar hyperlinearity, excess scaling, and keratosis pilaris. The underlying genetic cause of IV is haploinsufficiency of the filaggrin gene *(FLG)* because of loss-of-function mutations,[1] leading to early termination of profilaggrin and loss of filaggrin expression. Atopic dermatitis (AD) is a common complex inflammatory skin disorder with a high prevalence (20%) among children of Western countries.[2] In Ethiopia, contrasting frequencies of AD have been reported, ranging from 1.2% to 19%.[2] AD and IV show phenotypically overlapping features. The most significant genetic susceptibility factor to AD in European populations is truncating loss-of-function mutations of *FLG*, although with a reduced penetrance compared with IV.[1] Even though few studies have been performed in African populations, we and others reported either absence or very low frequency of *FLG* mutations, suggesting another cause for IV/AD.[2-4] In contrast, a recent publication by Polcari et al[3] reported *FLG* mutations in 22.2% of African Americans with IV/AD, but here the possibility of genetic admixture must be taken into account.

Given previous findings, in this study we set out to identify other underlying genetic factors in this population.[2] Assuming that IV is a monogenic disease with an effect on AD susceptibility, we selected 22 Ethiopian patients (18 unrelated subjects and 2 parent-child pairs) manifesting both IV and AD for whole-exome sequencing (WES). The diagnosis was based on clinical findings done by the same dermatologist (K.D.B.), and the UK Working Party's diagnostic criteria were applied for AD. All patients were recruited in Gondar, Ethiopia. Their median age was 9 years (range, 1-31 years), 50% were female, and 73% had severe AD (SCORAD score >40). All patients had keratosis pilaris, palmar hyperlinearity, and xerosis and had negative results for *FLG* mutations, as reported previously.[2] A larger IV/AD cohort (n = 155) and matched control subjects (n = 192) from the same region were included to evaluate the frequencies of 7 single nucleotide variants (SNVs) identified in patients undergoing WES.

WES was performed at SciLifeLab (Stockholm, Sweden). Libraries were prepared with the SureSelect Human All Exon V4 or V5 kit (Agilent Technologies, Santa Clara, Calif) and sequenced on the HiSeq 2000 (Illumina, San Diego, Calif) to a minimum sequence depth of 87×. The data were analyzed with in-house pipelines. A minor allele frequency (MAF) of 5% for African populations was applied to the 1000 Genomes Project (1000Goct2014) and the Exome Aggregation Consortium (ExAC 0.2) data set to exclude common variants. Less stringent filtering parameters were additionally applied to identify relatively common nonsense variants. On average, each patient showed 1364 (1234-1486) nonsynonymous exonic variants. Seven SNVs were assayed by using Custom TaqMan SNP Genotyping Assays (Life Technologies, Grand Island, NY) with a QuantStudio 7 FLEX instrument (Life Technologies). Significance was evaluated by using the Fisher exact test ($P \leq .05$ was considered significant).

In accordance with our previous Sanger sequencing data, we did not identify any loss-of-function mutations in *FLG*. The coverage of the coding part was almost complete, with a read depth of between 61× and 296×.

We were particularly interested in genes clustered on chromosome band 1q21 (epidermal differentiation complex [EDC]) because they encode proteins that have structural and functional similarities to filaggrin and are abundant in the upper epidermis. We identified 3 nonsense variants in the EDC genes. Among them, we observed *FLG2* S2377X in 12 samples (10 heterozygous and 2 homozygous samples), with a rather high MAF of 0.29 in 1000 Genomes Project African populations. It is already known that S2377X is a very common variant, and according to HapMap data, the MAF for T (giving the premature stop) is close to 50% in Asian populations and 30% in those of African ancestry reported from the United States. Alas, it is common to be a homozygous carrier of the stop mutation in the general population, and therefore we find it unlikely that *FLG2* variants are associated with IV/AD. Furthermore, *FLG2* variants have been tested and found not to be associated with AD in Europe.[4]

We detected 2 other heterozygous nonsense SNVs in the EDC genes *TCHH* (E207X) and *TCHHL1* (Q294X; Table I). *TCHH* E207X has not been reported before. *TCHHL1* Q294X is a single nucleotide polymorphism formerly reported in an African American AD cohort with an MAF of 0.017.[5] Moreover, we detected

TABLE I. Variants identified in EDC locus genes

Chromosome	Position (hg19)	Gene	Nucleotide and amino acid change	Type of variation	MAF in 1000G (African)	MAF in ExAC (African)	dbSNP no.
1	152085074	*TCHH*	NM_007113:exon3:c.619G>T:p.E207X	Nonsense	—	—	—
1	152059278	*TCHHL1*	NM_001008536:exon3:c.880C>T:p.Q294X	Nonsense	0.0204	0.0160	rs61749316
1	152323132	*FLG2*	NM_001014342:exon3:c.7130C>A:p.S2377X	Nonsense	—	—	rs12568784
1	152383382	*CRNN*	NM_016190:exon3:c.G176A:p.R59H	Missense	0.0106	0.0056	rs145120458
1	152191822	*HRNR*	NM_001009931:exon3:c.A2283C:p.Q761H	Missense	—	—	—
1	152191419	*HRNR*	NM_001009931:exon3:c.C2686T:p.R896C	Missense	—	—	—
1	152190027	*HRNR*	NM_001009931:exon3:c.C4078T:p.P1360S	Missense	—	—	—
1	152192605	*HRNR*	NM_001009931:exon3:c.G1500C:p.Q500H	Missense	—	—	—
1	152192541	*HRNR*	NM_001009931:exon3:c.T1564A:p.S522T	Missense	—	—	—

A complete list of genes is given in Table E1.

CRNN, Cornulin; *dbSNP*, Single Nucleotide Polymorphism database; *ExAC*, Exome Aggregation Consortium; *FLG2*, filaggrin family 2; *1000G*, 1000 Genomes Project; *HRNR*, hornerin; *TCHH*, trichohyalin; *TCHHL1*, trichohyalin-like 1.

TABLE II. Variants identified in non-EDC locus genes

Chromosome	Position (hg19)	Gene	Nucleotide and amino acid change	Type of variation	MAF in 1000G (African)	MAF in ExAC (African)	dbSNP no.
20	3654244	*ADAM33*	NM_001282447:exon10:c.G967T:p.E323X	Nonsense	—	—	—
18	28971048	*DSG4*	NM_001134453:exon7:c.G692A:p.S231N	Missense	—	—	—
18	28968349	*DSG4*	NM_001134453:exon4:c.C236T:p.S79L	Missense	0.0061	0.0046	rs36040686
18	28979427	*DSG4*	NM_001134453:exon9:c.G1198A:p.G400R	Missense	0.0061	0.0045	rs35378785
17	74004853	*EVPL*	NM_001988:exon22:c.C4433T:p.T1478M	Missense	—	—	—
17	74003539	*EVPL*	NM_001988:exon22:c.C5747T:p.S1916L	Missense	—	—	—
6	158613020	*GTF2H5*	NM_207118:exon3:c.T47G:p.M16R	Missense	—	—	—
17	5462548	*NLRP1*	NM_001033053:exon4:c.T1468G:p.F490V	Missense	—	—	—
5	147449998	*SPINK5*	NM_001127698:exon3:c.C194T:p.T65M	Missense	—	—	—
5	147469114	*SPINK5*	NM_001127698:exon7:c.G532A:p.E178K	Missense	—	0.0001	—
5	147480955	*SPINK5*	NM_001127698:exon14:c.A1258G:p.K420E	Missense	0.1989	0.2433	rs2303067
5	147481363	*SPINK5*	NM_001127698:exon15:c.G1322A:p.R441H	Missense	0.0219	0.0243	rs34393923
5	147496004	*SPINK5*	NM_001127698:exon22:c.2087_2089del: p.696_697del	Nonframeshift deletion	0.0219	0.0238	rs111662216

A complete list of genes is given in Table E2.

ADAM33, ADAM metallopeptidase domain 33; *dbSNP*, Single Nucleotide Polymorphism Database; *DSG4*, desmoglein 4; *EVPL*, envoplakin; *ExAC*, Exome Aggregation Consortium; *1000G*, 1000 Genomes Project; *GTF2H5*, general transcription factor IIH, polypeptide 5; *NLRP1*, NLR family, pyrin domain containing 1; *SPINK5*, serine peptidase inhibitor, Kazal type 5.

missense variants in previously described candidate genes, such as cornulin *(CRNN)* and hornulin (*HRNR*; Table I). In total, we detected 72 variants in EDC genes (see Table E1 in this article's Online Repository at www.jacionline.org).

Next, we extended our analysis beyond the EDC locus. In total, we found 4 stopgain variants, 12 indels, and 236 nonsynonymous SNVs (see Table E2 in this article's Online Repository at www.jacionline.org). In *SPINK5* we found a known missense variant, K420E, in 8 cases (5 heterozygous and 3 homozygous cases). *SPINK5* encodes the protein LEKTI, and 420K and 420E LEKTI display different proteolytic activities, affecting downstream profilaggrin processing.[6] Although mutations of SPINK5 cause Netherton disease, this variant has previously been reported as a susceptibility factor for AD in European and Japanese populations.[7] However, its frequency is high in the general population (1000 Genomes Project: 0.43) and also in investigated African populations (1000 Genomes Project African population: 0.19) and for that reason was less likely to be important in the development of IV/AD.

We also detected novel missense variants in SPINK5 (T65M and E187K; Table II) and GTF2H5 (M16R; Table II) genes. GTF2H5 gene is associated with a rare autosomal recessive disease, trichothiodystrophy, characterized by ichthyotic skin and asthma with many other clinical features. Their contribution to the patient's phenotype remains an interesting open question. However, based on the present data, neither *SPINK5* nor *GTF2H5* could be considered a recurrently hit gene generally explaining the incidence of IV/AD in Ethiopia but might support a more heterogeneous genetic susceptibility pattern of IV/AD in African populations. More such variants in candidate genes are listed in Table II and Table E2.

A set of 7 SNVs was selected and tested with TaqMan assays. No significant differences in allele frequencies between cases and control subjects were detected (see Table E3 in this article's Online Repository at www.jacionline.org), indicating population-specific variation rather than disease-associated variants.

In conclusion, we present the first study that uses WES in Ethiopian patients with IV/AD. It is important to remember that mutations in regulatory or noncoding regions cannot be excluded with this method and to remember the relatively small number of patients analyzed. However, our data suggest, as is the case with *FLG* mutations in IV/AD patients of European origin, there is no single recurrent gene, which is likely to be causative for the disease in Ethiopian population. Instead, we revealed several rare variants in both previously described and new candidate genes, suggesting a heterogeneous disease pathogenesis among Ethiopian patients.

Web resources for this work include http://github.com/dnil/etiologica, http://mip-api.readthedocs.org, http://www.openbioinformatics.org/annovar/, and http://exac.broadinstitute.org.

We thank all the participating patients. We also acknowledge support from Science for Life Laboratory, the National Genomics Infrastructure, and UPPMAX under projects b2012235 and b2012244 for providing assistance in massive parallel sequencing and computational infrastructure.

Fulya Taylan, PhD[a,b]
Daniel Nilsson, PhD[a,b]
Samina Asad, PhD[a]
Agne Lieden, PhD[a]
Carl-Fredrik Wahlgren, MD, PhD[c]
Mårten C. G. Winge, MD, PhD[a]
Kassahun Desalegn Bilcha, MD[d]
Magnus Nordenskjöld, MD, PhD[a]
Maria Bradley, MD, PhD[a,c]

From [a]the Department of Molecular Medicine & Surgery and the Center for Molecular Medicine and [c]the Dermatology Unit, Department of Medicine Solna, Karolinska Institutet, Karolinska University Hospital Solna, Stockholm, Sweden; [b]the Science for Life Laboratory, Karolinska Institutet Science Park, Solna, Sweden; and [d]the Department of Dermatovenereology, Faculty of Medicine, Gondar University, Gondar, Ethiopia. E-mail: fulya.taylan@ki.se.

Supported by Edward Welander Foundation (2206) and the Swedish Asthma and Allergy Association's Research Foundation (2013040) and through the regional agreement on medical training and clinical research (ALF) between Stockholm County Council and Karolinska Institutet.

REFERENCES

1. Smith FJD, Irvine AD, Terron-Kwiatkowski A, Sandilands A, Campbell LE, Zhao Y, et al. Loss-of-function mutations in the gene encoding filaggrin cause ichthyosis vulgaris. Nat Genet 2006;38:337-42.

2. Winge MC, Bilcha KD, Liedén A, Shibeshi D, Sandilands A, Wahlgren CF, et al. Novel filaggrin mutation but no other loss-of-function variants found in Ethiopian patients with atopic dermatitis. Br J Dermatol 2011;165:1074-80.
3. Polcari I, Becker L, Stein SL, Smith MS, Paller AS. Filaggrin gene mutations in African Americans with both ichthyosis vulgaris and atopic dermatitis. Pediatr Dermatol 2014;31:489-92.
4. Marenholz I, Rivera VA, Esparza-Gordillo J, Bauerfeind A, Lee-Kirsch MA, Ciechanowicz A, et al. Association screening in the epidermal differentiation complex (EDC) identifies an SPRR3 repeat number variant as a risk factor for eczema. J Invest Dermatol 2011;131:1644-9.
5. Margolis DJ, Gupta J, Apter AJ, Hoffstad O, Papadopoulos M, Rebbeck TR, et al. Exome sequencing of filaggrin and related genes in African-American children with atopic dermatitis. J Invest Dermatol 2014;134:2272-4.
6. Fortugno P, Furio L, Teson M, Berretti M, El Hachem M, Zambruno G, et al. The 420K LEKTI variant alters LEKTI proteolytic activation and results in protease deregulation: implications for atopic dermatitis. Hum Mol Genet 2012;21:4187-200.
7. Kato A, Fukai K, Oiso N, Hosomi N, Murakami T, Ishii M. Cutaneous biology association of SPINK5 gene polymorphisms with atopic dermatitis in the Japanese population. Br J Dermatol 2003;148:665-9.

http://dx.doi.org/10.1016/j.jaci.2015.02.010

ARTICLE IN PRESS

TABLE E1. Variants identified in the EDC locus (chromosome 1q21.3) genes

No. of cases	Start	End	Reference allele	Alternative allele	Function	Exonic function	Gene	Amino acid change	ExAC_ALL	ExAC_AFR	1000g2014 oct_all	1000g2014 oct_afr	dbSNP accession no.	caddgt10 (raw, scaled)
6	152383382	152383382	C	T	Exonic	Nonsynonymous SNV	*CRNN*	CRNN:NM_016190:exon3:c.G176A:p.R59H	1.938e-03	0.0056	0.00419329	0.0106	rs145120458	
1	152382885	152382885	C	G	Exonic	Nonsynonymous SNV	*CRNN*	CRNN:NM_016190:exon3:c.G673C:p.E225Q	7.888e-04	0.0080	0.00299521	0.0091	rs35492900	
1	152283820	152283822	TGG	—	Exonic	Nonframeshift deletion	*FLG*	FLG:NM_002016:exon3:c.3540_3542del:p.1180_1181del						
1	152283649	152283649	T	C	Exonic	Nonsynonymous SNV	*FLG*	FLG:NM_002016:exon3:c.A3713G:p.H1238R	8.132e-06	0				
1	152283530	152283530	T	C	Exonic	Nonsynonymous SNV	*FLG*	FLG:NM_002016:exon3:c.A3832G:p.R1278G	1.016e-03	0.0033	0.00199681	0.003	rs111626670	
1	152276908	152276908	G	A	Exonic	Nonsynonymous SNV	*FLG*	FLG:NM_002016:exon3:c.C10454T:p.A3485V	7.321e-05	0.0002	0.000599042		rs200036291	1.481525,10.90
1	152276159	152276159	G	C	Exonic	Nonsynonymous SNV	*FLG*	FLG:NM_002016:exon3:c.C11203G:p.Q3735E	1.220e-04	0.0014	0.000599042	0.0023	rs143135026	
1	152283926	152283926	G	T	Exonic	Nonsynonymous SNV	*FLG*	FLG:NM_002016:exon3:c.C3436A:p.H1146N	1.789e-04	9.454e-05	0.000199681	0.0008		
1	152283472	152283472	G	T	Exonic	Nonsynonymous SNV	*FLG*	FLG:NM_002016:exon3:c.C3890A:p.S1297Y	3.497e-04	0.0008	0.000599042	0.0008	rs147367657	
1	152279816	152279816	G	C	Exonic	Nonsynonymous SNV	*FLG*	FLG:NM_002016:exon3:c.C7546G:p.Q2516E						
2	152279642	152279642	G	C	Exonic	Nonsynonymous SNV	*FLG*	FLG:NM_002016:exon3:c.C7720G:p.Q2574E	0.020	0.0097	0.0121805	0.0151	rs149024902	
1	152277449	152277449	G	A	Exonic	Nonsynonymous SNV	*FLG*	FLG:NM_002016:exon3:c.C9913T:p.R3305C						1.634128,11.42
2	152276671	152276671	C	A	Exonic	Nonsynonymous SNV	*FLG*	FLG:NM_002016:exon3:c.G10691T:p.R3564L	0.033		0.0163738	0.0083	rs7518080	
1	152276144	152276144	C	T	Exonic	Nonsynonymous SNV	*FLG*	FLG:NM_002016:exon3:c.G11218A:p.E3740K	5.692e-05	0	0.000199681			2.244786,13.46
1	152287069	152287069	C	G	Exonic	Nonsynonymous SNV	*FLG*	FLG:NM_002016:exon3:c.G293C:p.G98A						
1	152283533	152283533	C	G	Exonic	Nonsynonymous SNV	*FLG*	FLG:NM_002016:exon3:c.G3829C:p.E1277Q	8.213e-04	0.0014	0.00159744	0.0023	rs139456266	
2	152282080	152282080	C	A	Exonic	Nonsynonymous SNV	*FLG*	FLG:NM_002016:exon3:c.G5282T:p.R1761L						
1	152279896	152279896	C	A	Exonic	Nonsynonymous SNV	*FLG*	FLG:NM_002016:exon3:c.G7466T:p.G2489V	3.497e-04	0.0008	0.000599042	0.0008	rs138270516	
1	152277797	152277797	C	G	Exonic	Nonsynonymous SNV	*FLG*	FLG:NM_002016:exon3:c.G9565C:p.A3189P	2.188e-03	0.0094	0.00579073	0.0144	rs142839051	
1	152275193	152275193	A	G	Exonic	Nonsynonymous SNV	*FLG*	FLG:NM_002016:exon3:c.T12169C:p.Y4057H						
1	152286951	152286951	A	T	Exonic	Nonsynonymous SNV	*FLG*	FLG:NM_002016:exon3:c.T411A:p.N137K	1.626e-05	0				
1	152331324	152331324	C	A	Exonic	Nonsynonymous SNV	*FLG2*	FLG2:NM_001014342:exon2:c.G37T:p.D13Y	5.693e-05	0.0003				3.051947,16.19
1	152328883	152328883	G	A	Exonic	Nonsynonymous SNV	*FLG2*	FLG2:NM_001014342:exon3:c.C1379T:p.S460L	8.132e-06	0				2.089726,12.94
1	152327404	152327404	G	A	Exonic	Nonsynonymous SNV	*FLG2*	FLG2:NM_001014342:exon3:c.C2858T:p.S953L	1.903e-03	0.0215	0.00519169	0.0182	rs116751426	
12	152323132	152323132	G	T	Exonic	Stop gain	*FLG2*	FLG2:NM_001014342:exon3:c.C7130A:p.S2377X	0.232	0.2706	0.316893	0.2905	rs12568784	11.361751,45
1	152326769	152326769	C	A	Exonic	Nonsynonymous SNV	*FLG2*	FLG2:NM_001014342:exon3:c.G3493T:p.G1165C	1.903e-03	0.0215	0.00519169	0.0182	rs78418747	2.445864,14.14
2	152324239	152324239	C	G	Exonic	Nonsynonymous SNV	*FLG2*	FLG2:NM_001014342:exon3:c.G6023C:p.G2008A	1.139e-04	0.0012	0.000798722	0.003	rs140302446	
2	152324032	152324032	C	G	Exonic	Nonsynonymous SNV	*FLG2*	FLG2:NM_001014342:exon3:c.G6230C:p.G2077A	1.626e-04	0.0017	0.000798722	0.0015	rs145838203	
7	152327405	152327405	A	G	Exonic	Nonsynonymous SNV	*FLG2*	FLG2:NM_001014342:exon3:c.T2857C:p.S953P	1.659e-03	0.0052	0.00419329	0.0106	rs138718549	
1	152326290	152326290	A	T	Exonic	Nonsynonymous SNV	*FLG2*	FLG2:NM_001014342:exon3:c.T3972A:p.H1324Q	1.626e-05	0				
1	152191822	152191822	T	G	Exonic	Nonsynonymous SNV	*HRNR*	HRNR:NM_001009931:exon3:c.A2283C:p.Q761H						
2	152191698	152191698	T	C	Exonic	Nonsynonymous SNV	*HRNR*	HRNR:NM_001009931:exon3:c.A2407G:p.S803G	2.147e-03	0.0235	0.00738818	0.025	rs111789738	
1	152191712	152191712	G	T	Exonic	Nonsynonymous SNV	*HRNR*	HRNR:NM_001009931:exon3:c.C2393A:p.T798K	1.391e-03	0.0155	0.00419329	0.0144	rs77898999	
1	152191419	152191419	G	A	Exonic	Nonsynonymous SNV	*HRNR*	HRNR:NM_001009931:exon3:c.C2686T:p.R896C	1.220e-04	0	0.000599042			
1	152193780	152193780	G	T	Exonic	Nonsynonymous SNV	*HRNR*	HRNR:NM_001009931:exon3:c.C325A:p.Q109K	6.506e-05	0			rs139222671	2.006277,12.67
2	152193720	152193720	G	A	Exonic	Nonsynonymous SNV	*HRNR*	HRNR:NM_001009931:exon3:c.C385T:p.H129Y	3.253e-05	0.0002			rs148822876	
1	152190027	152190027	G	A	Exonic	Nonsynonymous SNV	*HRNR*	HRNR:NM_001009931:exon3:c.C4078T:p.P1360S						
1	152192882	152192882	C	T	Exonic	Nonsynonymous SNV	*HRNR*	HRNR:NM_001009931:exon3:c.G1223A:p.R408H	3.171e-04	0	0.000399361		rs142030922	
1	152192605	152192605	C	G	Exonic	Nonsynonymous SNV	*HRNR*	HRNR:NM_001009931:exon3:c.G1500C:p.Q500H	8.132e-06	0				
1	152193390	152193390	C	G	Exonic	Nonsynonymous SNV	*HRNR*	HRNR:NM_001009931:exon3:c.G715C:p.G239R	1.789e-04	9.452e-05	0.000199681	0.0008	rs187389918	
1	152193177	152193177	C	T	Exonic	Nonsynonymous SNV	*HRNR*	HRNR:NM_001009931:exon3:c.G928A:p.V310I	1.870e-04	0.0004			rs148892565	
1	152192541	152192541	A	T	Exonic	Nonsynonymous SNV	*HRNR*	HRNR:NM_001009931:exon3:c.T1564A:p.S522T						
2	152883317	152883317	G	T	Exonic	Nonsynonymous SNV	*IVL*	IVL:NM_005547:exon2:c.G1044T:p.Q348H	1.925e-04	0.0029	0.00119808	0.0045	rs182325885	2.210168,13.35
2	152883155	152883155	G	T	Exonic	Nonsynonymous SNV	*IVL*	IVL:NM_005547:exon2:c.G882T:p.K294N	1.481e-04	0.0029	0.00119808	0.0045	rs184389068	
2	152785170	152785170	G	A	Exonic	Nonsynonymous SNV	*LCE1B*	LCE1B:NM_178349:exon1:c.G248A:p.R83H	0.025	0.0049	0.0141773		rs56056379	
1	152770446	152770446	A	C	Exonic	Nonsynonymous SNV	*LCE1D*	LCE1D:NM_178352:exon2:c.A176C:p.N59T						
1	152770403	152770403	G	A	Exonic	Nonsynonymous SNV	*LCE1D*	LCE1D:NM_178352:exon2:c.G133A:p.G45R	1.917e-03	0.0204	0.0061901	0.0227	rs150172690	
1	152748914	152748928	AAGTGC CCCAC ACCG	—	Exonic	Nonframeshift deletion	*LCE1F*	LCE1F:NM_178354:exon1:c.67_81del:p.23_27del	1.708e-03	0.0184	0.00579073	0.0212		
1	152671437	152671437	C	—	Exonic	Frameshift deletion	*LCE2A*	LCE2A:NM_178428:exon2:c.60delC:p.C20fs						
1	152659554	152659554	C	G	Exonic	Nonsynonymous SNV	*LCE2B*	LCE2B:NM_014357:exon2:c.C235G:p.R79G						
1	152552171	152552171	C	A	Exonic	Nonsynonymous SNV	*LCE3D*	LCE3D:NM_032563:exon2:c.G242T:p.G81V	3.058e-03	0.0359	0.0105831	0.0401	rs57201979	
1	152484216	152484216	T	G	Exonic	Nonsynonymous SNV	*LCE5A*	LCE5A:NM_178438:exon2:c.T206G:p.L69R						1.645049,11.46
2	153279696	153279696	C	T	Exonic	Nonsynonymous SNV	*PGLYRP3*	PGLYRP3:NM_052891:exon2:c.G103A:p.A35T	0.041	0.0110	0.0185703	0.0045	rs55991125	

1	153276449	153276449	T	C	Exonic	Nonsynonymous SNV	*PGLYRP3*	PGLYRP3:NM_052891:exon4:c.A413G:p.E138G	0.021	0.0288	0.0405351	0.0371	rs41264632	2.059855,12.84
2	153276333	153276333	C	G	Exonic	Nonsynonymous SNV	*PGLYRP3*	PGLYRP3:NM_052891: exon4:c.G529C:p.V177L	2.358e-04	0.0025	0.000599042	0.0023	rs146895196	1.575394,11.22
1	153317723	153317723	T	C	Exonic	Nonsynonymous SNV	*PGLYRP4*	PGLYRP4:NM_020393: exon4:c.A275G:p.Q92R	0.042	0.0084	0.0209665	0.003	rs3006453	
3	152127663	152127663	A	G	Exonic	Nonsynonymous SNV	*RPTN*	RPTN:NM_001122965:exon3:c.T1912C:p.S638P	1.090e-03	0.0092	0.00359425	0.0129	rs77415490	
2	153604205	153604205	T	C	Exonic	Nonsynonymous SNV	*S100A1*	S100A1:NM_006271:exon3:c.T173C:p.V58A						3.684716,18.72
1	152005145	152005145	C	T	Exonic	Nonsynonymous SNV	*S100A11*	S100A11:NM_005620:exon3:c.G311A:p.R104Q	4.879e-05	0.0003	0.000399361	0.0015	rs200047972	1.796464,11.97
6	153507176	153507176	C	T	Exonic	Nonsynonymous SNV	*S100A6*	S100A6:NM_014624:exon3:c.G269A:p.G90D	2.399e-03	0.0261	0.00738818	0.0265	rs2228293	3.521573,17.98
1	153391726	153391726	G	C	Exonic	Nonsynonymous SNV	*S100A7A*	S100A7A:NM_176823:exon3:c.G247C:p.A83P	8.132e-06					1.913755,12.36
1	153410682	153410682	T	C	Exonic	Nonsynonymous SNV	*S100A7L2*	S100A7L2:NM_001045479:exon2:c.A157G:p.N53D	4.416e-03	0.0468	0.0115815	0.0416	rs61743588	2.908039,15.69
1	153409689	153409689	C	T	Exonic	Nonsynonymous SNV	*S100A7L2*	S100A7L2:NM_001045479:exon3:c.G184A:p.D62N						1.496955,10.95
1	152957939	152957939	C	T	Exonic	Nonsynonymous SNV	*SPRR1A*	SPRR1A:NM_001199828:exon2:c.C233T:p.T78I, SPRR1A:NM_005987:exon2:c.C233T:p.T78I	8.132e-06	0				
1	152957839	152957839	G	A	Exonic	Nonsynonymous SNV	*SPRR1A*	SPRR1A:NM_001199828:exon2:c.G133A:p.V45M, SPRR1A:NM_005987:exon2:c.G133A:p.V45M						3.663854,18.62
1	152957924	152957924	G	T	Exonic	Nonsynonymous SNV	*SPRR1A*	SPRR1A:NM_001199828:exon2:c.G218T:p.C73F, SPRR1A:NM_005987:exon2:c.G218T:p.C73F						3.352803,17.29
1	152081272	152081272	T	A	Exonic	Nonsynonymous SNV	*TCHH*	TCHH:NM_007113:exon3:c.A4421T:p.E1474V						
1	152084732	152084732	T	C	Exonic	Nonsynonymous SNV	*TCHH*	TCHH:NM_007113:exon3:c.A961G:p.R321G						1.350244,10.44
1	152080066	152080066	C	T	Exonic	Nonsynonymous SNV	*TCHH*	TCHH:NM_007113:exon3:c.G5627A:p.R1876Q	1.036e-03	0.0003	0.000199681		rs140720320	1.555567,11.16
1	152085074	152085074	C	A	Exonic	Stop-gain	*TCHH*	TCHH:NM_007113:exon3:c.G619T:p.E207X						3.317206,17.15
1	152083325	152083325	A	C	Exonic	Nonsynonymous SNV	*TCHH*	TCHH:NM_007113:exon3:c.T2368G:p.L790V	8.166e-06					
1	152059278	152059278	G	A	Exonic	Stop-gain	*TCHHL1*	TCHHL1:NM_001008536:exon3:c.C880T:p.Q294X	1.513e-03	0.0160	0.00539137	0.0204	rs61749316	3.656460,18.59

TABLE E2. Variants identified in non-EDC genes

No. of cases	Chromosome	Start	End	Reference allele	Alternative allele	Function	Exonic function	Gene	Amino acid change	ExAC_ALL	ExAC_AFR	1000g2014 oct_all	1000g2014 oct_afr	dbSNP accession no.	caddgt10 (raw,scaled)
1	2	215868969	215868969	C	T	Exonic	Nonsynonymous SNV	*ABCA12*	ABCA12:NM_015657:exon12: c.G1693A: p.D565N,ABCA12:NM_ 173076:exon20: c.G2647A:p.D883N	8.13E-006	0			rs200973428	4.525296,24.4
1	2	215866416	215866416	T	C	Exonic	Nonsynonymous SNV	*ABCA12*	ABCA12:NM_015657:exon13: c.A1775G:p.Q592R,ABCA12:NM_ 173076:exon21: c.A2729G:p.Q910R						2.725396,15.07
1	2	215835070	215835070	C	T	Exonic	Nonsynonymous SNV	*ABCA12*	ABCA12:NM_015657:exon29: c.G4663A:p.V1555I,ABCA12:NM_ 173076:exon37: c.G5617A:p.V1873I	2.29E-003	0.0245	0.00838658	0.031	rs114258385	
1	2	215890495	215890495	T	C	Exonic	Nonsynonymous SNV	*ABCA12*	ABCA12:NM_015657:exon3: c.A235G:p.R79G,ABCA12: NM_173076:exon11: c.A1189G:p.R397G						2.602984,14.66
2	2	215815751	215815751	T	G	Exonic	Nonsynonymous SNV	*ABCA12*	ABCA12:NM_015657:exon37: c.A5750C:p.E1917A,ABCA12:NM_ 173076:exon45: c.A6704C:p.E2235A	6.10E-004	9.46E-005			rs138504099	2.754834,15.17
2	19	6306857	6306857	C	T	Exonic	Nonsynonymous SNV	*ACER1*	ACER1:NM_133492:exon6: c.G663A:p.M221I	4.99E-003	0.0013	0.00259585	0.0008	rs76925618	
1	19	8808240	8808240	C	G	Exonic	Nonsynonymous SNV	*ACTL9*	ACTL9:NM_178525:exon1: c.G812C:p.R271P	0.02	0.0035	0.00998403	0.0008	rs73507819	1.841073,12.11
1	20	3654244	3654244	C	A	Exonic	Stop-gain	*ADAM33*	ADAM33: NM_001282447:exon10: c.G967T:p.E323X,ADAM33: NM_025220:exon10: c.G967T:p.E323X, ADAM33:NM_153202:exon10: c.G967T:p.E323X						8.928931,41
3	20	3655681	3655681	T	C	Exonic	Nonsynonymous SNV	*ADAM33*	ADAM33:NM_001282447:exon4: c.A326G:p.N109S,ADAM33:NM_ 025220:exon4:c.A326G: p.N109S,ADAM33:NM_153202: exon4: c.A326G:p.N109S	2.86E-003	0.0308	0.00958466	0.0348	rs41467948	1.512415,11.01
1	20	3655296	3655296	G	A	Exonic	Nonsynonymous SNV	*ADAM33*	ADAM33:NM_001282447:exon6: c.C455T:p.P152L,ADAM33:NM_ 025220:exon6:c.C455T:p.P152L, ADAM33:NM_153202:exon6:c.C455T: p.P152L						3.081046,16.29
1	8	38874823	38874823	G	C	Exonic	Nonsynonymous SNV	*ADAM9*	ADAM9:NM_003816:exon6: c.G496C:p.D166H					rs373355126	4.200465,21.8
1	8	38880817	38880817	G	A	Exonic	Nonsynonymous SNV	*ADAM9*	ADAM9:NM_003816:exon9: c.G887A:p.R296Q	1.63E-003	9.45E-005	0.00299521		rs140082569	2.627800,14.75
1	10	5138663	5138663	T	C	Exonic	Nonsynonymous SNV	*AKR1C3*	AKR1C3:NM_001253908:exon2: c.T146C:p.I49T,AKR1C3:NM_ 001253909:exon2:c.T146C: p.I49T,AKR1C3:NM_003739:exon2: c.T146C:p.I49T	7.32E-005	0	0.000199681		rs145911457	2.776111,15.24
1	17	6909217	6909217	G	A	Exonic	Nonsynonymous SNV	*ALOX12*	ALOX12:NM_000697:exon10: c.G1289A:p.R430H	1.90E-003	0.02	0.0061901	0.0227	rs11571342	
1	17	6901889	6901889	A	C	Exonic	Nonsynonymous SNV	*ALOX12*	ALOX12:NM_000697:exon3: c.A399C:p.K133N	1.05E-003	0.0003	0.000399361	0.0015	rs148602792	3.548690,18.10
1	17	6901839	6901839	G	C	Exonic	Nonsynonymous SNV	*ALOX12*	ALOX12:NM_000697:exon3: c.G349C:p.G117R	4.31E-004	0.0044	0.00179712	0.0068	rs145526271	
4	17	7984479	7984479	G	A	Exonic	Nonsynonymous SNV	*ALOX12B*	ALOX12B:NM_001139:exon3: c.C379T:p.P127S	0.017	0.0043	0.0107827	0.0038	rs72842957	2.928827,15.76
1	17	7945809	7945809	C	T	Exonic	Nonsynonymous SNV	*ALOX15B*	ALOX15B:NM_001039130:exon4: c.C572T:p.A191V,ALOX15B:NM_ 001039131:exon4:c.C572T:p.A191V, ALOX15B:NM_001141:exon4: c.C572T:p.A191V	3.25E-005	0	0.000199681			2.073766,12.89

1	17	8021425	8021425	G	C	Exonic	Nonsynonymous SNV	ALOXE3	ALOXE3:NM_001165960:exon2: c.C280G:p.P94A	4.30E-004	0.0076	0.00199681	0.0076	rs113345247	2.564922,14.54
1	17	8021407	8021407	G	C	Exonic	Nonsynonymous SNV	*ALOXE3*	ALOXE3:NM_001165960:exon2: c.C298G:p.R100G	0.017	0.0084	0.0105831	0.0015	rs112227180	1.662753,11.52
1	5	112043544	112043544	G	A	Exonic	Nonsynonymous SNV	*APC*	APC:NM_001127511:exon1: c.G130A:p.A44T	1.08E-004	0.0015	0.000199681	0.0008	rs367773779	2.392493,13.96
1	5	112176725	112176725	A	G	Exonic	Nonsynonymous SNV	*APC*	APC:NM_001127511:exon14: c.A5380G:p.K1794E,APC:NM_ 000038:exon16:c.A5434G: p.K1812E,APC:NM_001127510: exon17:c.A5434G:p.K1812E						2.719795,15.06
1	5	112177811	112177811	A	G	Exonic	Nonsynonymous SNV	*APC*	APC:NM_001127511:exon14: c.A6466G:p.S2156G,APC: NM_000038:exon16:c.A6520G: p.S2174G,APC:NM_001127510: exon17:c.A6520G:p.S2174G	8.14E-006	0.0001				3.011821,16.05
1	5	112176410	112176410	T	C	Exonic	Nonsynonymous SNV	*APC*	APC:NM_001127511:exon14: c.T5065C:p.S1689P,APC: NM_000038:exon16:c.T5119C: p.S1707P,APC:NM_001127510: exon17:c.T5119C:p.S1707P						
1	3	187451448	187451448	T	G	Exonic	Nonsynonymous SNV	*BCL6*	BCL6:NM_001134738:exon2: c.A34C:p.T12P,BCL6:NM_ 001130845:exon3:c.A34C: p.T12P,BCL6:NM_001706:exon3: c.A34C:p.T12P	4.88E-004	0.0011				4.951333,28.8
2	3	187447701	187447701	C	A	Exonic	Nonsynonymous SNV	*BCL6*	BCL6:NM_001134738:exon4: c.G492T:p.E164D,BCL6:NM_ 001130845:exon5:c.G492T: p.E164D,BCL6:NM_001706:exon5: c.G492T:p.E164D	0.021	0.0065	0.0107827	0.0023	rs61752081	1.732055,11.75
1	11	76256857	76256857	T	C	Exonic	Nonsynonymous SNV	*C11orf30*	C11orf30:NM_020193:exon20: c.T3290C:p.I1097T	2.44E-004	0				2.820587,15.39
2	7	2946283	2946283	C	T	Exonic	Nonsynonymous SNV	*CARD11*	CARD11:NM_032415:exon25: c.G3454A:p.D1152N	7.56E-004	0.008	0.00159744	0.0061	rs147422861	5.108491,32
1	3	112357730	112357730	C	A	Exonic	Nonsynonymous SNV	*CCDC80*	CCDC80:NM_199511:exon2: c.G1023T:p.L341F,CCDC80: NM_199512:exon2: c.G1023T:p.L341F	0.012	0.0163	0.0071885	0.0076	rs115738438	
1	3	112357653	112357653	C	T	Exonic	Nonsynonymous SNV	*CCDC80*	CCDC80:NM_199511:exon2: c.G1100A: p.R367Q,CCDC80: NM_199512:exon2: c.G1100A:p.R367Q	5.94E-004	0.0008	0.00139776	0.0045	rs145244203	2.681670,14.93
1	3	46401290	46401290	G	A	Exonic	Nonsynonymous SNV	*CCR2*	CCR2:NM_001123041:exon3: c.G1064A:p.G355E	1.40E-003	0.0168	0.00439297	0.0166	rs3918387	
1	16	68849662	68849662	C	T	Exonic	Nonsynonymous SNV	*CDH1*	CDH1:NM_004360:exon10: c.C1565T:p.T522I						1.965899,12.53
1	16	68855966	68855966	G	A	Exonic	Nonsynonymous SNV	*CDH1*	CDH1:NM_004360:exon12: c.G1774A:p.A592T	3.20E-003	0.0008	0.00119808	0.0008	rs35187787	2.781583,15.26
1	16	68845719	68845719	A	G	Exonic	Nonsynonymous SNV	*CDH1*	CDH1:NM_004360:exon7: c.A965G:p.N322S						
1	16	68718502	68718502	C	G	Exonic	Nonsynonymous SNV	*CDH3*	CDH3:NM_001793:exon10: c.C1199G:p.A400G					rs112133581	2.030100,12.75
1	6	31084191	31084191	T	C	Exonic	Nonsynonymous SNV	*CDSN*	CDSN:NM_001264:exon2: c.A1201G:p.S401G	0.017	0.0038	0.0119808	0.0008	rs33941312	
1	6	31084833	31084833	G	T	Exonic	Nonsynonymous SNV	*CDSN*	CDSN:NM_001264:exon2: c.C559A:p.L187I						
1	3	190039932	190039932	T	G	Exonic	Nonsynonymous SNV	*CLDN1*	CLDN1:NM_021101:exon1: c.A64C:p.I22L						5.463109,35
1	21	31538610	31538610	C	T	Exonic	Nonsynonymous SNV	*CLDN17*	CLDN17:NM_012131:exon1: c.G326A:p.G109D	8.13E-006	0			rs370125987	
4	6	155596864	155596864	C	G	Exonic	Nonsynonymous SNV	*CLDN20*	CLDN20:NM_001001346:exon2: c.C11G:p.A4G	2.55E-003	0.0284	0.0119808	0.0431	rs112008767	
4	3	48621180	48621180	C	T	Exonic	Nonsynonymous SNV	*COL7A1*	COL7A1:NM_000094:exon39: c.G4312A:p.V1438I	4.31E-004	0.0021	0.00159744	0.0061	rs148625586	

(Continued)

TABLE E2. (*Continued*)

No. of cases	Chromosome	Start	End	Reference allele	Alternative allele	Function	Exonic function	Gene	Amino acid change	ExAC_ALL	ExAC_AFR	1000g2014 oct_all	1000g2014 oct_afr	dbSNP accession no.	caddgt10 (raw,scaled)
1	3	48610668	48610668	C	G	Exonic	Nonsynonymous SNV	*COL7A1*	COL7A1:NM_000094:exon84: c.G6653C:p.G2218A						2.825948,15.41
1	3	41267044	41267044	G	T	Exonic	Nonsynonymous SNV	*CTNNB1*	CTNNB1:NM_001098209:exon5: c.G715T:p.A239S,CTNNB1: NM_001098210:exon5: c.G715T:p.A239S,CTNNB1: NM_001904:exon5:c.G715T:p.A239S						4.721857,26.3
1	11	57563074	57563074	C	T	Exonic	Nonsynonymous SNV	*CTNND1*	CTNND1:NM_001085462:exon4:c. C293T:p.T98I,CTNND1: NM_001206883: exon4:c.C131T:p.T44I,CTNND1: NM_001206884:exon4:c. C131T:p.T44I,CTNND1: NM_001206886:exon4:c. C131T:p.T44I,CTNND1:NM_ 001206887:exon4:c.C131T:p. T44I,CTNND1:NM_001206888 :exon4:c.C131T:p.T44I,CTNND1: NM_001085458:exon5:c.C293T:p. T98I,CTNND1:NM_ 001085459:exon5:c.C293T: p.T98I,CTNND1:NM_001085460: exon5:c.C293T:p.T98I,CTNND1: NM_001085461:exon5:c.C293T: p.T98I,CTNND1:NM_001206885: exon5:c.C293T:p.T98I,CTNND1: NM_001206889:exon5:c. C131T:p.T44I,CTNND1:NM_ 001206891:exon5:c.C131T:p. T44I,CTNND1:NM_001331:exon5: c.C293T:p.T98I	8.17E-006	0.0001			rs371716100	4.344590,22.9
1	11	57571227	57571227	C	T	Exonic	Nonsynonymous SNV	*CTNND1*	CTNND1:NM_001085469: exon5:c.C1252T:p.R418C,CTNND1: NM_001085463:exon6: c.C1252T:p.R418C,CTNND1: NM_001085464:exon6: c.C1252T:p.R418C,CTNND1: NM_001085465:exon6: c.C1252T:p.R418C,CTNND1: NM_001085466:exon6: c.C1252T:p.R418C,CTNND1: NM_001085467:exon6: c.C1252T:p.R418C,CTNND1: NM_001085468:exon6: c.C1252T:p.R418C,CTNND1: NM_001206890:exon6: c.C1252T:p.R418C,CTNND1: NM_001085462:exon7: c.C1555T:p.R519C,CTNND1: NM_001206883:exon7: c.C1393T:p.R465C,CTNND1: NM_001206884:exon7: c.C1393T:p.R465C,CTNND1: NM_001206886:exon7: c.C1393T:p.R465C,CTNND1: NM_001206887:exon7: c.C1393T:p.R465C,CTNND1: NM_001206888:exon7: c.C1393T:p.R465C,CTNND1: NM_001085458:exon8: c.C1555T:p.R519C,CTNND1: NM_001085459:exon8:	3.27E-005	0	0.000199681		rs181249834	4.213562,21.9

									c.C1555T:p.R519C,CTNND1: NM_001085460:exon8: c.C1555T:p.R519C,CTNND1: NM_001085461:exon8: c.C1555T:p.R519C,CTNND1: NM_001206885:exon8: c.C1555T:p.R519C,CTNND1: NM_001206889:exon8: c.C1393T:p.R465C,CTNND1: NM_001206891:exon8: c.C1393T:p.R465C,CTNND1: NM_001331:exon8: c.C1555T:p.R519C						
1	12	58159173	58159173	C	G	Exonic	Nonsynonymous SNV	*CYP27B1*	CYP27B1:NM_000785:exon3: c.G496C:p.V166L	0.01	0.0005	0.0145767		rs8176344	
1	3	196771513	196771513	G	A	Exonic	Nonsynonymous SNV	*DLG1*	DLG1:NM_001204388:exon21: c.C2348T:p.P783L,DLG1: NM_001204387:exon22: c.C2384T:p.P795L,DLG1: NM_001204386:exon25: c.C2660T:p.P887L,DLG1: NM_001098424:exon26: c.C2696T:p.P899L,DLG1: NM_001290983:exon26: c.C2696T:p.P899L,DLG1: NM_004087:exon26: c.C2762T:p.P921L	0.043	0.0077	0.0251597	0.003	rs34492126	4.022579,20.6
2	9	131708504	131708504	T	C	Exonic	Nonsynonymous SNV	*DOLK*	DOLK:NM_014908:exon1: c.A1079G:p.Y360C	1.49E-003	0.0004	0.000798722		rs138453255	3.397855,17.47
1	18	28737407	28737407	G	A	Exonic	Nonsynonymous SNV	*DSC1*	DSC1:NM_004948:exon3: c.C278T:p.S93F,DSC1: NM_024421:exon3: c.C278T:p.S93F	0.039	0.0106	0.0207668	0.0008	rs35338395	1.394435,10.60
1	18	28723711	28723711	C	—	Exonic	Frameshift deletion	*DSC1*	DSC1:NM_004948:exon8: c.983delG:p.G328fs,DSC1: NM_024421:exon8: c.983delG:p.G328fs						
2	18	28649070	28649070	C	G	Exonic	Nonsynonymous SNV	*DSC2*	DSC2:NM_004949:exon15: c.G2298C:p.Q766H,DSC2: NM_024422:exon15: c.G2298C:p.Q766H	4.07E-005	0.0003			rs139558481	
1	18	28666574	28666574	C	T	Exonic	Nonsynonymous SNV	*DSC2*	DSC2:NM_004949:exon7: c.G907A:p.V303M,DSC2: NM_024422:exon7: c.G907A:p.V303M	1.19E-003	0	0.00299521		rs145560678	3.088813,16.32
1	18	28602415	28602415	G	T	Exonic	Nonsynonymous SNV	*DSC3*	DSC3:NM_001941:exon7: c.C829A:p.H277N,DSC3: NM_024423:exon7: c.C829A:p.H277N						3.275628,17.00
2	18	28602337	28602337	C	T	Exonic	Nonsynonymous SNV	*DSC3*	DSC3:NM_001941:exon7: c.G907A:p.V303I,DSC3: NM_024423:exon7: c.G907A:p.V303I	1.54E-003	0.0167	0.00579073	0.0204	rs115383401	1.825351,12.06
1	18	28935224	28935224	A	T	Exonic	Nonsynonymous SNV	*DSG1*	DSG1:NM_001942:exon15: c.A3065T:p.H1022L						1.782376,11.92
1	18	28934485	28934485	C	T	Exonic	Nonsynonymous SNV	*DSG1*	DSG1:NM_001942:exon15: c.C2326T:p.P776S	3.25E-005	0.0004	0.000399361	0.0015	rs112401974	
1	18	28935262	28935262	G	A	Exonic	Nonsynonymous SNV	*DSG1*	DSG1:NM_001942:exon15: c.G3103A:p.A1035T						1.966678,12.53
2	18	28916495	28916495	C	G	Exonic	Nonsynonymous SNV	*DSG1*	DSG1:NM_001942:exon9: c.C1184G:p.T395S	2.56E-003	0.0275	0.0101837	0.0371	rs16961655	
1	18	29104739	29104739	T	C	Exonic	Nonsynonymous SNV	*DSG2*	DSG2:NM_001943:exon8: c.T902C:p.I301T						
2	18	29046606	29046606	G	A	Exonic	Nonsynonymous SNV	*DSG3*	DSG3:NM_001944:exon11: c.G1525A:p.V509M	0.027	0.0343	0.0489217	0.0469	rs16961975	3.347887,17.27
1	18	29055892	29055892	T	A	Exonic	Nonsynonymous SNV	*DSG3*	DSG3:NM_001944:exon16: c.T2669A:p.V890D						2.364816,13.87
1	18	28966732	28966732	G	A	Exonic		*DSG4*	DSG4:NM_001134453:exon3:	8.95E-005	0.0003	0.000199681	0.0008	rs200219673	3.493027,17.86

(Continued)

TABLE E2. (*Continued*)

No. of cases	Chromosome	Start	End	Reference allele	Alternative allele	Function	Exonic function	Gene	Amino acid change	ExAC_ALL	ExAC_AFR	1000g2014 oct_all	1000g2014 oct_afr	dbSNP accession no.	caddgt10 (raw,scaled)
							Nonsynonymous SNV		c.G166A:p.A56T,DSG4: NM_177986:exon3: c.G166A:p.A56T						
5	18	28968349	28968349	C	T	Exonic	Nonsynonymous SNV	*DSG4*	DSG4:NM_001134453:exon4: c.C236T:p.S79L,DSG4: NM_177986:exon4: c.C236T:p.S79L	4.17E-003	0.0046	0.00439297	0.0061	rs36040686	
2	18	28968862	28968862	G	A	Exonic	Nonsynonymous SNV	*DSG4*	DSG4:NM_001134453:exon5: c.G398A:p.R133Q,DSG4: NM_177986:exon5: c.G398A:p.R133Q	8.95E-005	9.56E-005			rs143110911	3.311574,17.13
1	18	28971048	28971048	G	A	Exonic	Nonsynonymous SNV	*DSG4*	DSG4:NM_001134453:exon7: c.G692A:p.S231N,DSG4: NM_177986:exon7: c.G692A:p.S231N						4.268358,22.3
1	18	28972253	28972253	G	A	Exonic	Nonsynonymous SNV	*DSG4*	DSG4:NM_001134453:exon8: c.G955A:p.D319N,DSG4: NM_177986:exon8: c.G955A:p.D319N	6.02E-004	9.49E-005	0.000599042		rs140750904	3.315418,17.15
5	18	28979427	28979427	G	A	Exonic	Nonsynonymous SNV	*DSG4*	DSG4:NM_001134453:exon9: c.G1198A:p.G400R,DSG4: NM_177986:exon9: c.G1198A:p.G400R	4.30E-003	0.0045	0.00439297	0.0061	rs35378785	1.657382,11.50
3	6	7576619	7576619	G	A	Exonic	Nonsynonymous SNV	*DSP*	DSP:NM_001008844:exon19: c.G2723A:p.R908H,DSP: NM_004415:exon19: c.G2723A:p.R908H	1.12E-003	0.0002			rs142494121	5.081731,31
1	6	7577213	7577213	G	A	Exonic	Nonsynonymous SNV	*DSP*	DSP:NM_001008844:exon20: c.G2815A:p.G939S,DSP: NM_004415:exon20: c.G2815A:p.G939S	3.68E-003	0.0413	0.0105831	0.0386	rs80325569	2.918304,15.72
1	6	7585240	7585240	T	G	Exonic	Nonsynonymous SNV	*DSP*	DSP:NM_001008844:exon24: c.T5948G:p.F1983C,DSP: NM_004415:exon24: c.T7745G:p.F2582C	2.44E-005	0				1.932983,12.42
2	1	150480710	150480710	T	A	Exonic	Nonsynonymous SNV	*ECM1*	ECM1:NM_001202858:exon1: c.T25A:p.L9M,ECM1: NM_004425:exon1: c.T25A:p.L9M,ECM1: NM_022664:exon1: c.T25A:p.L9M	8.13E-006	9.45E-005				2.852879,15.50
1	1	201981232	201981232	A	G	Exonic	Nonsynonymous SNV	*ELF3*	ELF3:NM_001114309:exon3: c.A311G:p.N104S,ELF3: NM_004433:exon3: c.A311G:p.N104S	1.66E-003	0.0172	0.00698882	0.025	rs58166377	
1	1	201981298	201981298	G	A	Exonic	Nonsynonymous SNV	*ELF3*	ELF3:NM_001114309:exon3: c.G377A:p.R126Q,ELF3: NM_004433:exon3: c.G377A:p.R126Q	1.66E-003	0.0177	0.0071885	0.025	rs79918642	
1	1	201981848	201981848	G	A	Exonic	Nonsynonymous SNV	*ELF3*	ELF3:NM_001114309:exon5: c.G559A:p.G187R,ELF3: NM_004433:exon5: c.G559A:p.G187R	3.50E-004	0			rs151290080	
1	1	16456763	16456763	C	T	Exonic	Nonsynonymous SNV	*EPHA2*	EPHA2:NM_004431:exon15: c.G2627A:p.R876H	0.017	0.0051	0.00778754	0.0015	rs35903225	4.986612,29.2
1	1	16464480	16464480	G	A	Exonic	Nonsynonymous SNV	*EPHA2*	EPHA2:NM_004431:exon5: c.C1180T:p.R394C	2.44E-005	9.54E-005				2.812296,15.37
1	2	128050307	128050307	T	C	Exonic	Nonsynonymous SNV	*ERCC3*	ERCC3:NM_000122:exon3: c.A350G:p.K117R	4.07E-005	9.45E-005	0.000199681	0.0008	rs1805161	1.447521,10.78
1	2	128047306	128047306	C	T	Exonic		*ERCC3*							3.345804,17.27

							Nonsynonymous SNV		ERCC3:NM_000122:exon5: c.G616A:p.A206T						
6	1	8074334	8074334	C	T	Exonic	Nonsynonymous SNV	*ERRFI1*	ERRFI1:NM_018948:exon4: c.G325A:p.D109N	0.011	0.0024	0.00559105	0.0023	rs34781518	2.599372,14.65
1	17	74010607	74010607	C	G	Exonic	Nonsynonymous SNV	*EVPL*	EVPL:NM_001988:exon18: c.G2273C:p.C758S	1.77E-003	0.0028	0.000798722	0.0015	rs142251448	
1	17	74004853	74004853	G	A	Exonic	Nonsynonymous SNV	*EVPL*	EVPL:NM_001988:exon22: c.C4433T:p.T1478M	8.13E-006	0				2.061342,12.85
1	17	74003539	74003539	G	A	Exonic	Nonsynonymous SNV	*EVPL*	EVPL:NM_001988:exon22: c.C5747T:p.S1916L	2.44E-005	0				4.734576,26.4
1	17	74005802	74005802	C	T	Exonic	Nonsynonymous SNV	*EVPL*	EVPL:NM_001988:exon22: c.G3484A:p.E1162K	4.34E-003	0.0013	0.00339457	0.0015	rs146508997	2.811855,15.36
5	17	74005700	74005700	C	T	Exonic	Nonsynonymous SNV	*EVPL*	EVPL:NM_001988:exon22: c.G3586A:p.V1196I	2.07E-003	0.0009	0.00259585	0.0008	rs144978675	
1	17	74004671	74004671	C	G	Exonic	Nonsynonymous SNV	*EVPL*	EVPL:NM_001988:exon22: c.G4615C:p.V1539L	1.06E-003	0.0118	0.00499201	0.0182	rs147437042	
1	17	74019667	74019667	C	A	Exonic	Nonsynonymous SNV	*EVPL*	EVPL:NM_001988:exon3: c.G267T:p.E89D						1.431180,10.73
1	11	108381516	108381516	T	A	Exonic	Nonsynonymous SNV	*EXPH5*	EXPH5:NM_015065:exon6: c.A4718T:p.N1573I	2.16E-003	0.0221	0.00758786	0.028	rs34979772	2.843440,15.47
1	11	108381250	108381250	T	C	Exonic	Nonsynonymous SNV	*EXPH5*	EXPH5:NM_015065:exon6: c.A4984G:p.N1662D	2.16E-003	0.0221	0.00758786	0.028	rs35276439	
1	11	108383883	108383883	G	A	Exonic	Nonsynonymous SNV	*EXPH5*	EXPH5:NM_015065:exon6: c.C2351T:p.P784L	6.83E-004	0.0076	0.00159744	0.0061	rs115994428	1.281182,10.19
1	11	108381178	108381178	G	T	Exonic	Nonsynonymous SNV	*EXPH5*	EXPH5:NM_015065:exon6: c.C5056A:p.H1686N	2.16E-003	0.0221	0.00798722	0.0295	rs34026967	
1	11	108384405	108384405	A	G	Exonic	Nonsynonymous SNV	*EXPH5*	EXPH5:NM_015065:exon6: c.T1829C:p.I610T	4.96E-004	0.0048	0.00279553	0.0098	rs115982109	2.834022,15.44
1	11	108382794	108382794	A	G	Exonic	Nonsynonymous SNV	*EXPH5*	EXPH5:NM_015065:exon6: c.T3440C:p.M1147T	2.16E-003	0.0223	0.00758786	0.028	rs62000364	
1	1	160970093	160970093	A	G	Exonic	Nonsynonymous SNV	*F11R*	F11R:NM_016946:exon5: c.T434C:p.I145T	1.14E-004	0.0005			rs138803658	
2	1	160968873	160968873	C	T	Exonic	Nonsynonymous SNV	*F11R*	F11R:NM_016946:exon9: c.G824A:p.S275N	7.73E-004	0.0084	0.00219649	0.0076	rs145312674	
1	8	38287385	38287385	C	T	Exonic	Nonsynonymous SNV	*FGFR1*	FGFR1:NM_001174063:exon3: c.G173A:p.R58Q,FGFR1: NM_001174065:exon3: c.G173A:p.R58Q,FGFR1: NM_015850:exon3: c.G173A:p.R58Q,FGFR1: NM_023110:exon3: c.G173A:p.R58Q,FGFR1: NM_001174064:exon4: c.G149A:p.R50Q,FGFR1: NM_001174067:exon4: c.G272A:p.R91Q	1.63E-005	0	0.000199681		rs200116660	3.466207,17.75
1	8	38271301	38271301	G	A	Exonic	Nonsynonymous SNV	*FGFR1*	FGFR1:NM_001174066:exon17: c.C2047T:p.P683S,FGFR1: NM_023105:exon17: c.C2047T:p.P683S,FGFR1: NM_023106:exon17: c.C2041T:p.P681S,FGFR1: NM_001174063:exon18: c.C2308T:p.P770S,FGFR1: NM_001174065:exon18: c.C2308T:p.P770S,FGFR1: NM_015850:exon18: c.C2308T:p.P770S,FGFR1: NM_023110:exon18: c.C2314T:p.P772S,FGFR1: NM_001174064:exon19: c.C2284T:p.P762S,FGFR1: NM_001174067:exon19: c.C2407T:p.P803S	3.83E-003	0.0447	0.0091853	0.0333	rs56234888	3.246198,16.89
1	10	49440196	49440196	A	T	Exonic	Nonsynonymous SNV	*FRMPD2*	FRMPD2:NM_001018071:exon10: c.T1130A:p.L377H						2.861308,15.53

(Continued)

TABLE E2. (*Continued*)

No. of cases	Chromosome	Start	End	Reference allele	Alternative allele	Function	Exonic function	Gene	Amino acid change	ExAC_ALL	ExAC_AFR	1000g2014 oct_all	1000g2014 oct_afr	dbSNP accession no.	caddgt10 (raw,scaled)
1	10	49431225	49431225	C	A	Exonic	Nonsynonymous SNV	*FRMPD2*	FRMPD2:NM_001018071:exon11: c.G1257T:p.M419I	1.14E-004	0			rs148906229	
1	10	49446125	49446125	C	T	Exonic	Nonsynonymous SNV	*FRMPD2*	FRMPD2:NM_001018071:exon8: c.G830A:p.R277Q	1.38E-003	0.0154	0.00579073	0.0212	rs114531795	
1	3	33110383	33110383	G	A	Exonic	Nonsynonymous SNV	*GLB1*	GLB1:NM_000404:exon3: c.C325T:p.R109W,GLB1: NM_001079811:exon3: c.C235T:p.R79W	0.018	0.0037	0.0091853	0.0015	rs35289681	1.592336,11.28
1	3	33059981	33059981	G	A	Exonic	Nonsynonymous SNV	*GLB1*	GLB1:NM_001135602:exon10: c.C913T:p.L305F,GLB1: NM_000404:exon13: c.C1306T:p.L436F,GLB1: NM_001079811:exon13: c.C1216T:p.L406F	0.012	0.0026	0.00479233	0.0008	rs34421970	
1	3	33055705	33055705	C	T	Exonic	Nonsynonymous SNV	*GLB1*	GLB1:NM_001135602:exon12: c.G1184A:p.G395D,GLB1: NM_000404:exon15: c.G1577A:p.G526D,GLB1: NM_001079811:exon15: c.G1487A:p.G496D	1.39E-003	0.014	0.00559105	0.0204	rs147332381	
1	6	158613020	158613020	T	G	Exonic	Nonsynonymous SNV	*GTF2H5*	GTF2H5:NM_207118:exon3: c.T47G:p.M16R	8.13E-006	0				4.501871,24.2
1	9	21077371	21077371	T	C	Exonic	Nonsynonymous SNV	*IFNB1*	IFNB1:NM_002176:exon1: c.A498G:p.I166M	1.70E-003	0.0168	0.00698882	0.025	rs141894933	1.585045,11.26
1	19	39787103	39787103	A	—	Exonic	Frameshift deletion	*IFNL1*	IFNL1:NM_172140:exon1: c.42delA:p.L14fs	3.25E-005	0.0003	0.000599042	0.0023		
1	19	39787143	39787143	A	G	Exonic	Nonsynonymous SNV	*IFNL1*	IFNL1:NM_172140:exon1: c.A82G:p.T28A	4.25E-003	0.0421	0.0129792	0.0454	rs114823100	
1	2	102791086	102791086	C	T	Exonic	Nonsynonymous SNV	*IL1R1*	IL1R1:NM_000877:exon10: c.C1031T:p.T344M,IL1R1: NM_001288706:exon10: c.C1031T:p.T344M	0.025	0.01	0.0455272	0.0083	rs28362304	
1	2	102791994	102791994	G	A	Exonic	Nonsynonymous SNV	*IL1R1*	IL1R1:NM_000877:exon11: c.G1192A:p.G398R	1.78E-003	9.45E-005	0.000798722		rs34835752	2.186750,13.27
1	2	102782690	102782690	T	C	Exonic	Nonsynonymous SNV	*IL1R1*	IL1R1:NM_000877:exon6: c.T604C:p.Y202H,IL1R1: NM_001288706:exon6: c.T604C:p.Y202H	1.78E-003	9.45E-005	0.000798722		rs34889382	2.334455,13.76
1	2	102957136	102957136	C	T	Exonic	Nonsynonymous SNV	*IL1RL1*	IL1RL1:NM_001282408:exon4: c.C107T:p.A36V,IL1RL1: NM_003856:exon5: c.C458T:p.A153V,IL1RL1: NM_016232:exon5: c.C458T:p.A153V	2.04E-003	0.0222	0.00399361	0.0136	rs114797672	1.390800,10.58
1	2	102955408	102955408	C	T	Exonic	Nonsynonymous SNV	*IL1RL1*	IL1RL1:NM_003856:exon3: c.C173T:p.P58L,IL1RL1: NM_016232:exon3: c.C173T:p.P58L	3.01E-004	0			rs140931129	3.189243,16.68
1	2	102968075	102968075	T	G	Exonic	Nonsynonymous SNV	*IL1RL1*	IL1RL1:NM_016232:exon11: c.T1365G:p.N455K						
1	16	27373980	27373980	C	T	Exonic	Nonsynonymous SNV	*IL4R*	IL4R:NM_001257406:exon10: c.C1307T:p.S436L,IL4R: NM_001257997:exon10: c.C827T:p.S276L,IL4R: NM_000418:exon11: c.C1307T:p.S436L,IL4R: NM_001257407:exon11: c.C1262T:p.S421L	0.036	0.0261	0.0247604	0.0257	rs1805013	
1	16	27374696	27374696	C	T	Exonic	Nonsynonymous SNV	*IL4R*	IL4R:NM_001257406:exon10: c.C2023T:p.P675S,IL4R: NM_001257997:exon10: c.C1543T:p.P515S,IL4R:	0.011	0.0034	0.00519169	0.0015	rs3024678	1.819561,12.04

									NM_000418:exon11: c.C2023T:p.P675S,IL4R: NM_001257407:exon11: c.C1978T:p.P660S						
1	5	131877775	131877775	G	C	Exonic	Nonsynonymous SNV	*IL5*	IL5:NM_000879:exon3: c.C238G:p.Q80E						
1	1	62550280	62550280	G	C	Exonic	Nonsynonymous SNV	*INADL*	INADL:NM_176877:exon33: c.G4337C:p.G1446A	1.55E-004	0	0.000199681			4.313408,22.6
1	1	62232066	62232066	C	T	Exonic	Nonsynonymous SNV	*INADL*	INADL:NM_176877:exon4: c.C305T:p.S102L	4.88E-005	9.45E-005	0.000199681	0.0008	rs190078763	
1	1	62234977	62234977	A	T	Exonic	Nonsynonymous SNV	*INADL*	INADL:NM_176877:exon5: c.A407T:p.D136V						2.793972,15.30
1	1	62253546	62253546	G	A	Exonic	Nonsynonymous SNV	*INADL*	INADL:NM_176877:exon8: c.G970A:p.V324I	6.75E-004	0.0074	0.000798722	0.003	rs139601247	
1	12	66641863	66641863	C	T	Exonic	Nonsynonymous SNV	*IRAK3*	IRAK3:NM_001142523:exon11: c.C1520T:p.P507L,IRAK3: NM_007199:exon12: c.C1703T:p.P568L	1.79E-004	0.0015	0.000599042	0.0015	rs138274217	1.534164,11.08
1	17	39919560	39919560	C	T	Exonic	Nonsynonymous SNV	*JUP*	JUP:NM_002230:exon8: c.G1172A:p.S391N,JUP: NM_021991:exon8: c.G1172A:p.S391N	2.36E-004	9.54E-005	0.000199681	0.0008	rs199826380	
1	1	15429886	15429886	C	T	Exonic	Nonsynonymous SNV	*KAZN*	KAZN:NM_201628:exon12: c.C1811T:p.T604M	2.47E-004	0.0044	0.00139776	0.0045	rs141085366	2.253204,13.49
1	19	51462454	51462454	G	A	Exonic	Nonsynonymous SNV	*KLK6*	KLK6:NM_001012965:exon5: c.C380T:p.T127M,KLK6: NM_001012964:exon6: c.C701T:p.T234M,KLK6: NM_002774:exon7: c.C701T:p.T234M	5.99E-003	0.0327	0.0107827	0.0363	rs77760094	
1	1	152733797	152733797	—	T	Exonic	Frameshift insertion	*KPRP*	KPRP:NM_001025231:exon2: c.1734dupT:p.Y578fs	2.25E-003	0.0241	0.00998403	0.0325	rs143740958	
1	1	152733472	152733472	C	T	Exonic	Nonsynonymous SNV	*KPRP*	KPRP:NM_001025231:exon2: c.C1408T:p.P470S	9.76E-004	0.0002	0.00119808	0.0008	rs141557248	3.036207,16.13
1	1	152733677	152733677	G	T	Exonic	Nonsynonymous SNV	*KPRP*	KPRP:NM_001025231:exon2: c.G1613T:p.G538V	3.53E-003	0.0386	0.0123802	0.0469	rs114002153	2.730801,15.09
4	1	152732786	152732786	G	A	Exonic	Nonsynonymous SNV	*KPRP*	KPRP:NM_001025231:exon2: c.G722A:p.G241E	1.29E-003	0.0135	0.00359425	0.0136	rs143680696	1.256895,10.10
1	12	53073829	53073829	C	T	Exonic	Nonsynonymous SNV	*KRT1*	KRT1:NM_006121:exon1: c.G304A:p.G102S						
1	17	38978680	38978680	C	T	Exonic	Nonsynonymous SNV	*KRT10*	KRT10:NM_000421:exon1: c.G158A:p.S53N	2.44E-004	9.57E-005			rs146835683	1.795279,11.96
1	17	38978794	38978794	C	T	Exonic	Nonsynonymous SNV	*KRT10*	KRT10:NM_000421:exon1: c.G44A:p.R15H	8.30E-004	0.0096	0.00179712	0.0068	rs28411890	3.315554,17.15
1	17	38976653	38976653	A	G	Exonic	Nonsynonymous SNV	*KRT10*	KRT10:NM_000421:exon4: c.T890C:p.V297A						
3	17	38975308	38975319	GCCGCC GTGGCC	—	Exonic	Nonframeshift deletion	*KRT10*	KRT10:NM_000421:exon7: c.1468_1479del:p.490_493del						
2	17	38975250	38975250	—	GCC	Exonic	Nonframeshift insertion	*KRT10*	KRT10:NM_000421:exon7: c.1536_1537insGGC: p.Y513delinsGY						
3	17	38975151	38975151	T	C	Exonic	Nonsynonymous SNV	*KRT10*	KRT10:NM_000421:exon7: c.A1636G:p.S546G						1.565756,11.19
3	17	38975149	38975149	G	T	Exonic	Nonsynonymous SNV	*KRT10*	KRT10:NM_000421:exon7: c.C1638A:p.S546R	0.014	0.0482				
1	17	38975190	38975190	C	T	Exonic	Nonsynonymous SNV	*KRT10*	KRT10:NM_000421:exon7: c.G1597A:p.G533S	4.21E-004	0.0075	0.00519169	0.0189	rs184159044	2.159274,13.18
1	17	38975130	38975130	A	T	Exonic	Nonsynonymous SNV	*KRT10*	KRT10:NM_000421:exon7: c.T1657A:p.S553T						1.532464,11.08
1	12	53039173	53039173	G	C	Exonic	Nonsynonymous SNV	*KRT2*	KRT2:NM_000423:exon9: c.C1550G:p.A517G	3.47E-003	0.037	0.00998403	0.0371	rs35043606	
1	12	53039024	53039024	C	A	Exonic	Nonsynonymous SNV	*KRT2*	KRT2:NM_000423:exon9: c.G1699T:p.G567C	8.13E-006					1.576390,11.23
1	17	39643844	39643844	G	T	Exonic	Nonsynonymous SNV	*KRT36*	KRT36:NM_003771:exon4: c.C845A:p.A282D	1.90E-003	0.0207	0.00638978	0.0242	rs57989439	
3	17	39643658	39643658	T	A	Exonic	Nonsynonymous	*KRT36*	KRT36:NM_003771:exon5:	2.21E-003	0.0005	0.00239617	0.0008	rs139865124	4.809728,27.2

(Continued)

TABLE E2. (*Continued*)

No. of cases	Chromosome	Start	End	Reference allele	Alternative allele	Function	Exonic function	Gene	Amino acid change	ExAC_ALL	ExAC_AFR	1000g2014 oct_all	1000g2014 oct_afr	dbSNP accession no.	caddgt10 (raw,scaled)
							SNV		c.A932T:p.E311V						
3	17	39643659	39643659	C	A	Exonic	Stop-gain	*KRT36*	KRT36: NM_003771:exon5: c.G931T:p.E311X	2.21E-003	0.0005	0.00239617	0.0008	rs145372311	5.964947,36
1	12	52775176	52775176	C	T	Exonic	Nonsynonymous SNV	*KRT84*	KRT84:NM_033045:exon5: c.G1046A:p.R349Q			0.000399361	0.0015	rs113837792	5.141118,32
1	13	21562239	21562239	G	C	Exonic	Nonsynonymous SNV	*LATS2*	LATS2:NM_014572:exon4: c.C1680G:p.S560R						
4	13	21563311	21563311	G	A	Exonic	Nonsynonymous SNV	*LATS2*	LATS2:NM_014572:exon4: c.C608T:p.A203V	0.02	0.0033	0.0205671		rs77919685	
3	10	90524335	90524335	C	T	Exonic	Nonsynonymous SNV	*LIPN*	LIPN:NM_001102469:exon3: c.C395T:p.S132L			0.00878594	0.0008	rs41284088	2.890592,15.63
2	19	501762	501762	A	C	Exonic	Nonsynonymous SNV	*MADCAM1*	MADCAM1:NM_130760:exon4: c.A761C:p.Q254P					rs200007467	
6	19	501738	501738	C	A	Exonic	Nonsynonymous SNV	*MADCAM1*	MADCAM1: NM_130760:exon4: c.C737A:p.P246Q					rs1063736	
1	19	504745	504745	C	T	Exonic	Nonsynonymous SNV	*MADCAM1*	MADCAM1:NM_130762:exon4: c.C668T:p.A223V,MADCAM1: NM_130760:exon5: c.C929T:p.S310L	4.07E-005	0			rs199507986	
1	10	28438966	28438966	T	C	Exonic	Nonsynonymous SNV	*MPP7*	MPP7:NM_173496:exon6: c.A179G:p.Y60C	6.51E-005	0				3.460839,17.73
3	8	98657041	98657041	C	G	Exonic	Nonsynonymous SNV	*MTDH*	MTDH:NM_178812:exon1: c.C307G:p.L103V	4.88E-003	0.0208	0.00738818	0.0166	rs188271601	
1	8	98731403	98731403	G	A	Exonic	Nonsynonymous SNV	*MTDH*	MTDH:NM_178812:exon10: c.G1507A:p.V503I	8.95E-005	9.57E-005			rs368307370	
1	17	1374586	1374586	C	T	Exonic	Nonsynonymous SNV	*MYO1C*	MYO1C:NM_001080779:exon20: c.G2066A:p.R689Q,MYO1C: NM_001080950:exon20: c.G2009A:p.R670Q,MYO1C: NM_033375:exon20: c.G1961A:p.R654Q	1.63E-005	0				
1	20	46262806	46262806	C	T	Exonic	Nonsynonymous SNV	*NCOA3*	NCOA3:NM_001174087:exon10: c.C979T:p.H327Y,NCOA3: NM_001174088:exon10: c.C1009T:p.H337Y,NCOA3: NM_006534:exon10: c.C979T:p.H327Y,NCOA3: NM_181659:exon10: c.C979T:p.H327Y	2.44E-005	0				4.706267,26.1
1	20	46265498	46265498	A	G	Exonic	Nonsynonymous SNV	*NCOA3*	NCOA3:NM_001174087:exon12: c.A2368G:p.S790G,NCOA3: NM_001174088:exon12: c.A2398G:p.S800G,NCOA3: NM_006534:exon12: c.A2368G:p.S790G,NCOA3: NM_181659:exon12: c.A2368G:p.S790G	8.13E-006	0				
1	20	46264760	46264760	C	T	Exonic	Nonsynonymous SNV	*NCOA3*	NCOA3:NM_001174087:exon12: c.C1630T:p.P544S,NCOA3: NM_001174088:exon12: c.C1660T:p.P554S,NCOA3: NM_006534:exon12: c.C1630T:p.P544S,NCOA3: NM_181659:exon12: c.C1630T:p.P544S	1.63E-005	0.0002			rs113650666	3.390654,17.44
2	20	46267763	46267763	T	A	Exonic	Nonsynonymous SNV	*NCOA3*	NCOA3:NM_001174087:exon14: c.T2524A:p.S842T,NCOA3: NM_001174088:exon14: c.T2554A:p.S852T,NCOA3:	4.07E-005	0.0003			rs376607758	2.405769,14.00

									NM_006534:exon14: c.T2524A:p.S842T,NCOA3: NM_181659:exon14: c.T2524A:p.S842T							
1	20	46279865	46279865	—	GC	Exonic	Frameshift insertion	*NCOA3*	NCOA3:NM_001174087:exon20: c.3788_3789insGC: p.Q1263fs,NCOA3: NM_001174088:exon20: c.3764_3765insGC: p.Q1255fs,NCOA3: NM_006534:exon20: c.3779_3780insGC: p.Q1260fs,NCOA3: NM_181659:exon20: c.3791_3792insGC:p.Q1264fs	2.69E-003	0.0294			rs11472494	
1	20	46279866	46279866	—	G	Exonic	Frameshift insertion	*NCOA3*	NCOA3:NM_001174087:exon20: c.3789_3790insG: p.Q1263fs,NCOA3: NM_001174088:exon20: c.3765_3766insG: p.Q1255fs,NCOA3: NM_006534:exon20: c.3780_3781insG: p.Q1260fs,NCOA3: NM_181659:exon20: c.3792_3793insG:p.Q1264fs	1.81E-003				rs376225312	
4	17	5463280	5463280	T	C	Exonic	Nonsynonymous SNV	*NLRP1*	NLRP1:NM_001033053:exon4: c.A736G:p.T246A,NLRP1: NM_014922:exon4: c.A736G:p.T246A,NLRP1: NM_033004:exon4: c.A736G:p.T246A,NLRP1: NM_033006:exon4: c.A736G:p.T246A,NLRP1: NM_033007:exon4: c.A736G:p.T246A	5.53E-004	0.0015	0.00139776	0.0015	rs61754792	
2	17	5462548	5462548	A	C	Exonic	Nonsynonymous SNV	*NLRP1*	NLRP1:NM_001033053:exon4: c.T1468G:p.F490V,NLRP1: NM_014922:exon4: c.T1468G:p.F490V,NLRP1: NM_033004:exon4: c.T1468G:p.F490V,NLRP1: NM_033006:exon4: c.T1468G:p.F490V,NLRP1: NM_033007:exon4: c.T1468G:p.F490V						3.715342,18.87
4	17	5463194	5463194	A	C	Exonic	Nonsynonymous SNV	*NLRP1*	NLRP1:NM_001033053:exon4: c.T822G:p.F274L,NLRP1: NM_014922:exon4: c.T822G:p.F274L,NLRP1: NM_033004:exon4: c.T822G:p.F274L,NLRP1: NM_033006:exon4: c.T822G:p.F274L,NLRP1: NM_033007:exon4: c.T822G:p.F274L	5.45E-004	0.0015	0.00139776	0.0015	rs148499417	
1	17	5436233	5436233	G	A	Exonic	Nonsynonymous SNV	*NLRP1*	NLRP1:NM_033006:exon10: c.C3115T:p.H1039Y,NLRP1: NM_033007:exon10: c.C3115T:p.H1039Y,NLRP1: NM_001033053:exon11: c.C3217T:p.H1073Y,NLRP1: NM_014922:exon11: c.C3205T:p.H1069Y,NLRP1: NM_033004:exon11: c.C3205T:p.H1069Y	1.77E-003	0.0182	0.00479233	0.0182	rs9907167	1.269114,10.14

(Continued)

TABLE E2. (*Continued*)

No. of cases	Chromosome	Start	End	Reference allele	Alternative allele	Function	Exonic function	Gene	Amino acid change	ExAC_ALL	ExAC_AFR	1000g2014 oct_all	1000g2014 oct_afr	dbSNP accession no.	caddgt10 (raw,scaled)
2	17	5436224	5436224	G	C	Exonic	Nonsynonymous SNV	*NLRP1*	NLRP1:NM_033006:exon10: c.C3124G:p.P1042A,NLRP1: NM_033007:exon10: c.C3124G:p.P1042A,NLRP1: NM_001033053:exon11: c.C3226G:p.P1076A,NLRP1: NM_014922:exon11: c.C3214G:p.P1072A,NLRP1: NM_033004:exon11: c.C3214G:p.P1072A	2.44E-005	0.0002			rs149973177	
1	11	7982432	7982432	G	A	Exonic	Nonsynonymous SNV	*NLRP10*	NLRP10:NM_176821:exon2: c.C727T:p.R243W	0.013	0.0398	0.0325479	0.0446	rs59039403	2.715929,15.04
1	7	30496435	30496435	G	A	Exonic	Nonsynonymous SNV	*NOD1*	NOD1:NM_006092:exon4: c.C103T:p.R35C	8.13E-006	9.45E-005				3.128304,16.46
2	7	30491081	30491081	G	A	Exonic	Nonsynonymous SNV	*NOD1*	NOD1:NM_006092:exon6: c.C1952T:p.T651M	4.55E-004	0.0044	0.000798722	0.003	rs151170709	3.395795,17.46
1	7	30491919	30491919	C	T	Exonic	Nonsynonymous SNV	*NOD1*	NOD1:NM_006092:exon6: c.G1114A:p.D372N	4.08E-003	0.0362	0.0125799	0.0424	rs5743342	
1	7	30492143	30492143	C	T	Exonic	Nonsynonymous SNV	*NOD1*	NOD1:NM_006092:exon6: c.G890A:p.R297H	8.13E-006	0			rs369566061	1.885232,12.26
1	16	50733699	50733699	C	T	Exonic	Nonsynonymous SNV	*NOD2*	NOD2:NM_001293557:exon1: c.C293T:p.P98L,NOD2: NM_022162:exon2: c.C374T:p.P125L	2.36E-004	0.002	0.000399361	0.0015	rs149390911	1.417378,10.68
1	16	50744892	50744892	A	C	Exonic	Nonsynonymous SNV	*NOD2*	NOD2:NM_001293557:exon3: c.A989C:p.D330A,NOD2: NM_022162:exon4: c.A1070C:p.D357A	2.03E-004	0				1.848004,12.14
1	16	50744939	50744939	C	T	Exonic	Nonsynonymous SNV	*NOD2*	NOD2:NM_001293557:exon3: c.C1036T:p.R346C,NOD2: NM_022162:exon4: c.C1117T:p.R373C	1.79E-004	0			rs145293873	
1	16	50745137	50745137	C	T	Exonic	Nonsynonymous SNV	*NOD2*	NOD2:NM_001293557:exon3: c.C1234T:p.R412C,NOD2: NM_022162:exon4: c.C1315T:p.R439C	6.51E-005	9.66E-005			rs375201229	
1	16	50745657	50745657	C	T	Exonic	Nonsynonymous SNV	*NOD2*	NOD2:NM_001293557:exon3: c.C1754T:p.A585V,NOD2: NM_022162:exon4: c.C1835T:p.A612V	1.63E-005	0				2.401670,13.99
1	16	50744493	50744493	C	T	Exonic	Nonsynonymous SNV	*NOD2*	NOD2:NM_001293557:exon3: c.C590T:p.A197V,NOD2: NM_022162:exon4: c.C671T:p.A224V	1.63E-005	0.0002	0.000199681	0.0008	rs375336137	
1	16	50745596	50745596	G	A	Exonic	Nonsynonymous SNV	*NOD2*	NOD2:NM_001293557:exon3: c.G1693A:p.V565M,NOD2: NM_022162:exon4: c.G1774A:p.V592M	1.38E-004	0.0009	0.00119808	0.0015	rs148683734	
1	16	50745960	50745960	G	A	Exonic	Nonsynonymous SNV	*NOD2*	NOD2:NM_001293557:exon3: c.G2057A:p.R686H,NOD2: NM_022162:exon4: c.G2138A:p.R713H	3.42E-004	0				1.595037,11.29
2	16	50750581	50750581	C	T	Exonic	Nonsynonymous SNV	*NOD2*	NOD2:NM_001293557:exon4: c.C2465T:p.A822V,NOD2: NM_022162:exon5: c.C2546T:p.A849V	9.76E-005	9.52E-005	0.000199681	0.0008		4.943674,28.7
6	16	50756540	50756540	G	C	Exonic	Nonsynonymous SNV	*NOD2*	NOD2:NM_001293557:exon7: c.G2641C:p.G881R,NOD2: NM_022162:exon8: c.G2722C:p.G908R	9.93E-003	0.0013	0.00459265			4.373037,23.1
3	16	50756570	50756570	G	T	Exonic	Nonsynonymous SNV	*NOD2*	NOD2:NM_001293557:exon7: c.G2671T:p.A891S,NOD2:						4.806219,27.2

									NM_022162:exon8: c.G2752T:p.A918S						
1	9	139400219	139400219	G	A	Exonic	Nonsynonymous SNV	*NOTCH1*	NOTCH1:NM_017617:exon25: c.C4129T:p.P1377S	0.016	0.0062	0.00638978	0.0023	rs61751542	
1	9	139396940	139396940	C	T	Exonic	Nonsynonymous SNV	*NOTCH1*	NOTCH1:NM_017617:exon28: c.G5168A:p.S1723N						5.322257,34
1	9	139391200	139391200	C	T	Exonic	Nonsynonymous SNV	*NOTCH1*	NOTCH1:NM_017617:exon34: c.G6991A:p.A2331T	1.57E-003	0.018	0.00758786	0.025	rs111309246	
1	7	34888194	34888194	T	C	Exonic	Nonsynonymous SNV	*NPSR1*	NPSR1:NM_207172:exon8: c.T944C:p.I315T,NPSR1: NM_207173:exon8: c.T944C:p.I315T	1.26E-003	0.0128	0.0071885	0.025	rs10270766	3.372349,17.37
1	10	34671738	34671738	A	G	Exonic	Nonsynonymous SNV	*PARD3*	PARD3:NM_001184790:exon8: c.T997C:p.Y333H,PARD3: NM_001184791:exon8: c.T997C:p.Y333H,PARD3: NM_001184785:exon9: c.T1129C:p.Y377H,PARD3: NM_001184786:exon9: c.T1129C:p.Y377H,PARD3: NM_001184787:exon9: c.T1129C:p.Y377H,PARD3: NM_001184788:exon9: c.T1129C:p.Y377H,PARD3: NM_001184789:exon9: c.T1129C:p.Y377H,PARD3: NM_001184792:exon9: c.T1129C:p.Y377H,PARD3: NM_001184793:exon9: c.T1129C:p.Y377H,PARD3: NM_001184794:exon9: c.T1129C:p.Y377H,PARD3: NM_019619:exon9: c.T1129C:p.Y377H	4.07E-005	0			rs199689029	
1	16	67696294	67696294	G	A	Exonic	Nonsynonymous SNV	*PARD6A*	PARD6A:NM_001037281:exon3: c.G782A:p.R261H,PARD6A: NM_016948:exon3: c.G785A:p.R262H	3.25E-005	0				2.835809,15.45
6	16	67696365	67696365	G	A	Exonic	Nonsynonymous SNV	*PARD6A*	PARD6A:NM_001037281:exon3: c.G853A:p.V285I,PARD6A: NM_016948:exon3: c.G856A:p.V286I	0.032	0.0109	0.0153754	0.0053	rs35356834	1.440208,10.76
2	6	138428353	138428353	C	A	Exonic	Nonsynonymous SNV	*PERP*	PERP:NM_022121:exon1: c.G125T:p.G42V	2.24E-003	0.0259	0.00878594	0.031	rs78795891	
1	6	137187772	137187772	G	C	Exonic	Nonsynonymous SNV	*PEX7*	PEX7:NM_000288:exon6: c.G534C:p.Q178H	1.63E-005	0				1.364225,10.49
2	12	33049590	33049590	C	T	Exonic	Nonsynonymous SNV	*PKP2*	PKP2:NM_001005242:exon1: c.G76A:p.D26N,PKP2: NM_004572:exon1: c.G76A:p.D26N	5.93E-003	0.0031	0.00299521	0.0008	rs143004808	5.290752,33
1	12	32949167	32949167	T	C	Exonic	Nonsynonymous SNV	*PKP2*	PKP2:NM_001005242:exon11: c.A2233G:p.I745V,PKP2: NM_004572:exon12: c.A2365G:p.I789V	3.50E-004	0				
1	12	33031023	33031023	G	A	Exonic	Nonsynonymous SNV	*PKP2*	PKP2:NM_001005242:exon3: c.C791T:p.A264V,PKP2: NM_004572:exon3: c.C791T:p.A264V	3.05E-003	0.0334	0.0115815	0.0408	rs62001016	
1	11	397221	397221	C	A	Exonic	Nonsynonymous SNV	*PKP3*	PKP3:NM_007183:exon3: c.C720A:p.S240R	2.53E-005	0.0005	0.000199681	0.0008		1.622560,11.38
1	11	397331	397331	G	C	Exonic	Nonsynonymous SNV	*PKP3*	PKP3:NM_007183:exon3: c.G830C:p.R277P	0.037	0.0234			rs200371913	2.060597,12.85
4	11	397390	397390	G	T	Exonic	Nonsynonymous SNV	*PKP3*	PKP3:NM_007183: exon3: c.G889T:p.V297L	2.81E-003	0.0402	0.0107827	0.0393	rs77752215	
1	14	39650438	39650438	G	C	Exonic	Nonsynonymous SNV	*PNN*	PNN:NM_002687:exon9: c.G1525C:p.V509L	7.40E-004	0.0069	0.00259585	0.0098	rs34377372	
1	6	36263171	36263171	G	A	Exonic	Nonsynonymous	*PNPLA1*	PNPLA1:NM_001145716: exon5:	2.58E-003	0.0022	0.00399361	0.0053	rs45524833	

(Continued)

TABLE E2. (*Continued*)

No. of cases	Chromosome	Start	End	Reference allele	Alternative allele	Function	Exonic function	Gene	Amino acid change	ExAC_ALL	ExAC_AFR	1000g2014 oct_all	1000g2014 oct_afr	dbSNP accession no.	caddgt10 (raw,scaled)
							SNV		c.G487A:p.E163K, PNPLA1:NM_001145717: exon5:c.G745A: p.E249K,PNPLA1: NM_173676:exon5: c.G460A:p.E154K						
1	11	824777	824777	C	G	Exonic	Nonsynonymous SNV	*PNPLA2*	PNPLA2:NM_020376: exon10:c.C1430G:p.P477R	1.42E-003		0.0115815	0.0401	rs142588621	
1	13	29252223	29252223	A	G	Exonic	Nonsynonymous SNV	*POMP*	POMP:NM_015932:exon6: c.A410G:p.K137R						3.572232,18.20
1	12	42840018	42840018	C	G	Exonic	Nonsynonymous SNV	*PPHLN1*	PPHLN1:NM_001143787: exon11:c.C1204G: p.R402G,PPHLN1: NM_016488:exon12: c.C1276G:p.R426G						
3	16	4940288	4940288	C	T	Exonic	Nonsynonymous SNV	*PPL*	PPL:NM_002705:exon18: c.G2210A:p.R737H	4.47E-004	0.0041	0.000399361	0.0015	rs140546373	1.551205,11.14
1	16	4934795	4934795	C	A	Exonic	Nonsynonymous SNV	*PPL*	PPL:NM_002705:exon22: c.G3861T:p.Q1287H	8.13E-006					2.634450,14.77
1	1	1986954	1986954	G	A	Exonic	Nonsynonymous SNV	*PRKCZ*	PRKCZ:NM_002744:exon2: c.G146A:p.R49H	2.37E-003	0.0255	0.0081869	0.0303	rs35271800	
2	17	38487598	38487598	C	G	Exonic	Nonsynonymous SNV	*RARA*	RARA:NM_000964:exon2: c.C128G:p.T43S,RARA: NM_001145301:exon2: c.C128G:p.T43S,RARA: NM_001145302:exon2: c.C128G:p.T43S	1.97E-003	0.0215	0.00838658	0.031	rs116538651	1.758286,11.84
1	2	79386525	79386525	G	A	Exonic	Nonsynonymous SNV	*REG3A*	REG3A:NM_138938:exon1: c.C7T:p.P3S,REG3A: NM_002580:exon2:c.C7T: p.P3S,REG3A:NM_138937: exon2:c.C7T:p.P3S						
1	2	79386463	79386463	C	A	Exonic	Nonsynonymous SNV	*REG3A*	REG3A:NM_138938:exon1: c.G69T:p.Q23H,REG3A: NM_002580:exon2:c.G69T: p.Q23H,REG3A:NM_138937: exon2:c.G69T:p.Q23H						
1	2	7018047	7018047	T	A	Exonic	Nonsynonymous SNV	*RSAD2*	RSAD2:NM_080657: exon1:c.T116A:p.F39Y						
1	2	7023598	7023598	G	A	Exonic	Nonsynonymous SNV	*RSAD2*	RSAD2:NM_080657:exon2: c.G443A:p.R148Q	4.72E-004	0.0047	0.00199681	0.0076	rs149793142	
1	13	78191780	78191783	ACAA	—	Exonic	Frameshift deletion	*SCEL*	SCEL:NM_001160706:exon23: c.1372_1375del:p.T458fs,SCEL: NM_003843:exon24: c.1438_1441del:p.T480fs,SCEL: NM_144777:exon25: c.1498_1501del:p.T500fs	2.44E-005	0.0001				
1	13	78214890	78214890	C	T	Exonic	Stop-gain	*SCEL*	SCEL:NM_ 001160706:exon29: c.C1792T:p.Q598X,SCEL: NM_003843:exon30: c.C1858T:p.Q620X,SCEL: NM_144777:exon31: c.C1918T:p.Q640X						6.715788,38
1	1	27190440	27190440	C	T	Exonic	Nonsynonymous SNV	*SFN*	SFN:NM_006142: exon1:c.C737T:p.P246L	1.95E-004	0	0.000399361		rs191803556	2.275955,13.57
1	8	145158607	145158607	G	A	Exonic	Nonsynonymous SNV	*SHARPIN*	SHARPIN:NM_030974: exon1:c.C50T:p.S17F	0.042	0.0278	0.0315495	0.0053	rs34173062	2.759686,15.19
1	19	11097199	11097199	—	GGCCCT	Exonic	Nonframeshift insertion	*SMARCA4*	SMARCA4:NM_001128845:exon3: c.690_691insGGCCCT: p.P230delinsPGP,SMARCA4:						

									NM_001128846:exon3: c.690_691insGGCCCT: p.P230delinsPGP,SMARCA4: NM_001128847:exon3: c.690_691insGGCCCT: p.P230delinsPGP,SMARCA4: NM_001128848:exon3: c.690_691insGGCCCT: p.P230delinsPGP,SMARCA4: NM_001128849:exon4: c.690_691insGGCCCT: p.P230delinsPGP,SMARCA4: NM_003072:exon4: c.690_691insGGCCCT: p.P230delinsPGP,SMARCA4: NM_001128844:exon5: c.690_691insGGCCCT: p.P230delinsPGP						
2	22	21213511	21213511	C	T	Exonic	Nonsynonymous SNV	*SNAP29*	SNAP29:NM_004782: exon1:c.C113T:p.P38L	4.76E-004	0.0073	0.00139776	0.0053	rs200628919	2.683693,14.93
1	22	21213591	21213591	G	A	Exonic	Nonsynonymous SNV	*SNAP29*	SNAP29:NM_004782: exon1:c.G193A:p.A65T						1.522956,11.04
1	22	21213616	21213616	T	C	Exonic	Nonsynonymous SNV	*SNAP29*	SNAP29:NM_004782: exon1:c.T218C:p.V73A					rs369033557	3.090122,16.32
8	5	147480027	147480027	G	A	Exonic	Nonsynonymous SNV	*SPINK5*	SPINK5:NM_001127698: exon13:c.G1103A:p.S368N	0.506	0.2417	0.43151	0.1982	rs2303063	
8	5	147480955	147480955	A	G	Exonic	Nonsynonymous SNV	*SPINK5*	SPINK5:NM_001127698: exon14:c.A1258G:p.K420E	0.507	0.2433	0.433107	0.1989	rs2303067	
1	5	147481363	147481363	G	A	Exonic	Nonsynonymous SNV	*SPINK5*	SPINK5:NM_001127698: exon15:c.G1322A:p.R441H,SPINK5: NM_001127699:exon15:c.G1322A: p.R441H,SPINK5:NM_006846: exon15:c.G1322A:p.R441H	2.21E-003	0.0243	0.0061901	0.0219	rs34393923	2.285085,13.60
1	5	147496004	147496006	GTG	—	Exonic	Nonframeshift deletion	*SPINK5*	SPINK5:NM_001127698: exon22:c.2087_2089del: p.696_697del,SPINK5: NM_001127699:exon22: c.2087_2089del: p.696_697del,SPINK5: NM_006846:exon22: c.2087_2089del: p.696_697del	2.13E-003	0.0238	0.0061901	0.0219	rs111662216	
1	5	147449998	147449998	C	T	Exonic	Nonsynonymous SNV	*SPINK5*	SPINK5:NM_001127698:exon3: c.C194T:p.T65M,SPINK5: NM_001127699:exon3: c.C194T:p.T65M,SPINK5: NM_006846:exon3: c.C194T:p.T65M	2.45E-005	0	0.000199681			1.795929,11.96
1	5	147469114	147469114	G	A	Exonic	Nonsynonymous SNV	*SPINK5*	SPINK5:NM_001127698: exon7:c.G532A:p.E178K,SPINK5: NM_001127699:exon7: c.G532A:p.E178K,SPINK5: NM_006846:exon7: c.G532A:p.E178K	1.63E-005	0.0001				4.398269,23.3
1	5	147506583	147506583	A	G	Exonic	Nonsynonymous SNV	*SPINK5*	SPINK5:NM_006846:exon30: c.A2905G:p.K969E,SPINK5: NM_001127698:exon31: c.A2995G:p.K999E	2.85E-003	0.0256	0.00638978	0.0219	rs3188691	
1	11	130079420	130079420	A	T	Exonic	Nonsynonymous SNV	*ST14*	ST14:NM_021978:exon18: c.A2353T:p.T785S						4.693141,26.0
1	11	130059647	130059647	A	G	Exonic	Nonsynonymous SNV	*ST14*	ST14:NM_021978: exon5:c.A454G:p.I152V	3.06E-003	0.033	0.00938498	0.0333	rs79445381	2.326450,13.74
1	2	37129796	37129796	T	C	Exonic	Nonsynonymous SNV	*STRN*	STRN:NM_003162: exon5:c.A590G:p.E197G	5.69E-005	0.0006			rs141990672	1.621396,11.38
1	14	24731015	24731015	C	T	Exonic	Nonsynonymous SNV	*TGM1*	TGM1:NM_000359:exon3: c.G394A:p.D132N	8.13E-004	0.0089	0.00299521	0.0098	rs2229462	3.604686,18.35

(Continued)

TABLE E2. (*Continued*)

No. of cases	Chromosome	Start	End	Reference allele	Alternative allele	Function	Exonic function	Gene	Amino acid change	ExAC_ALL	ExAC_AFR	1000g2014 oct_all	1000g2014 oct_afr	dbSNP accession no.	caddgt10 (raw,scaled)
1	20	2321094	2321094	G	A	Exonic	Nonsynonymous SNV	*TGM3*	TGM3:NM_003245:exon13: c.G1949A:p.G650E	2.72E-003	0.0302	0.00998403	0.0363	rs114998364	
1	15	43525791	43525791	A	G	Exonic	Nonsynonymous SNV	*TGM5*	TGM5:NM_004245:exon11: c.T1724C:p.V575A,TGM5: NM_201631:exon12: c.T1970C:p.V657A	2.85E-003	0.0319	0.00758786	0.0287	rs80058195	3.279297,17.01
1	15	43545103	43545103	T	C	Exonic	Nonsynonymous SNV	*TGM5*	TGM5:NM_004245:exon5: c.A470G:p.N157S,TGM5: NM_201631:exon6: c.A716G:p.N239S	8.13E-006	0	0.000199681		rs140779290	2.650914,14.82
1	15	43552428	43552428	G	C	Exonic	Nonsynonymous SNV	*TGM5*	TGM5:NM_201631: exon3:c.C258G:p.S86R	2.44E-004	0	0.000199681		rs138507857	
1	5	109904168	109904168	T	A	Exonic	Nonsynonymous SNV	*TMEM232*	TMEM232:NM_001039763: exon11:c.A1435T:p.N479Y						2.891062,15.63
1	5	109864464	109864466	CTT	—	Exonic	Nonframeshift deletion	*TMEM232*	TMEM232:NM_001039763: exon12:c.1526_1528del: p.509_510del						
1	5	109864403	109864403	G	A	Exonic	Nonsynonymous SNV	*TMEM232*	TMEM232:NM_001039763: exon12:c.C1589T:p.P530L					rs112074804	1.389955,10.58
2	5	109756361	109756361	C	G	Exonic	Nonsynonymous SNV	*TMEM232*	TMEM232:NM_001039763: exon14:c.G1894C:p.E632Q			0.000399361	0.0015	rs182807123	2.477858,14.24
1	5	109756292	109756292	C	A	Exonic	Stop-gain	*TMEM232*	TMEM232: NM_00103976 3: exon14:c.G1963T:p.E655X			0.000399361	0.0015	rs192501577	3.899788,19.83
1	5	109963559	109963559	C	T	Exonic	Nonsynonymous SNV	*TMEM232*	TMEM232:NM_001039763: exon6:c.G524A:p.R175Q						4.390159,23.2
1	5	109954164	109954164	C	T	Exonic	Nonsynonymous SNV	*TMEM232*	TMEM232:NM_001039763: exon8:c.G868A:p.V290I	0.016	0.0303	0.0165735	0.0219	rs61978570	
1	1	156255411	156255411	A	G	Exonic	Nonsynonymous SNV	*TMEM79*	TMEM79:NM_032323: exon2:c.A394G:p.I132V	8.13E-006	9.48E-005				3.387094,17.43
1	17	15554433	15554433	—	A	Exonic	Frameshift insertion	*TRIM16*	TRIM16:NM_006470: exon4:c.490dupT:p.S164fs						
1	17	3495391	3495391	T	C	Exonic	Nonsynonymous SNV	*TRPV1*	TRPV1:NM_080706:exon1: c.A254G:p.Q85R,TRPV1: NM_018727:exon2: c.A254G:p.Q85R,TRPV1: NM_080705:exon2: c.A254G:p.Q85R,TRPV1: NM_080704:exon3: c.A254G:p.Q85R	0.027	0.0055	0.0169728		rs55916885	
1	17	3493636	3493636	T	C	Exonic	Nonsynonymous SNV	*TRPV1*	TRPV1:NM_080706:exon4: c.A655G:p.T219A,TRPV1: NM_018727:exon5: c.A655G:p.T219A,TRPV1: NM_080705:exon5:c.A655G: p.T219A,TRPV1:NM_080704: exon6:c.A655G:p.T219A	2.14E-003	0.0245	0.00778754	0.0295	rs149386111	1.680094,11.58
1	17	3493183	3493183	T	G	Exonic	Nonsynonymous SNV	*TRPV1*	TRPV1:NM_080706:exon5: c.A962C:p.H321P,TRPV1: NM_018727:exon6:c.A962C: p.H321P,TRPV1:NM_080705: exon6:c.A962C:p.H321P,TRPV1: NM_080704:exon7: c.A962C:p.H321P	2.12E-004	0.0005			rs201937125	1.474907,10.88
1	11	18505477	18505477	T	G	Exonic	Nonsynonymous SNV	*TSG101*	TSG101:NM_006292:exon8: c.A783C:p.E261D	1.14E-004	0			rs140101726	2.612639,14.70
2	1	145440096	145440096	G	A	Exonic	Nonsynonymous SNV	*TXNIP*	TXNIP:NM_006472:exon4: c.G530A:p.R177Q	3.26E-003	0.015	0.00858626	0.0212	rs6674773	
1	7	120969820	120969820	A	T	Exonic	Nonsynonymous SNV	*WNT16*	WNT16:NM_016087:exon2: c.A265T:p.T89S,WNT16:	3.26E-004	0.0036	0.00119808	0.0045	rs115876139	

									NM_057168:exon2: c.A295T:p.T99S						
1	7	120971851	120971851	G	A	Exonic	Nonsynonymous SNV	*WNT16*	WNT16:NM_016087:exon3: c.G436A:p.G146S,WNT16: NM_057168:exon3: c.G466A:p.G156S	3.25E-005	0.0003			rs146631240	1.426754,10.71
2	10	64136072	64136072	G	C	Exonic	Nonsynonymous SNV	*ZNF365*	ZNF365:NM_014951:exon2: c.G120C:p.L40F,ZNF365: NM_199450:exon2: c.G120C:p.L40F,ZNF365: NM_199451:exon2: c.G120C:p.L40F	2.68E-003	0.0251	0.00878594	0.0303	rs79142251	3.613689,18.39
1	10	64415332	64415332	C	T	Exonic	Nonsynonymous SNV	*ZNF365*	ZNF365:NM_199452:exon4: c.C332T:p.S111L	3.38E-003	0.0374	0.00958466	0.0348	rs115145632	1.702837,11.65
1	10	64415302	64415302	G	A	Exonic	Nonsynonymous SNV	*ZNF365*	ZNF365:NM_199452:exon4: c.G302A:p.R101H	8.13E-005	0.0007	0.000399361	0.0015	rs111472605	2.543655,14.47
1	10	64425957	64425957	T	A	Exonic	Nonsynonymous SNV	*ZNF365*	ZNF365:NM_199452:exon6: c.T551A:p.V184E,ZNF365: NM_199451:exon7: c.T1289A:p.V430E						
1	10	64429997	64429997	A	G	Exonic	Nonsynonymous SNV	*ZNF365*	ZNF365:NM_199452:exon7: c.A587G:p.E196G,ZNF365: NM_199451:exon8: c.A1325G:p.E442G	1.20E-003	0.0117	0.00439297	0.0159	rs74156089	

ARTICLE IN PRESS

TABLE E3. Results from allelic discrimination assays

Chromosome	Start	End	Reference allele	Alternative allele	Gene	Amino acid change	Cases REF/REF	Cases REF/ALT	Cases ALT/ALT	MAF for cases	Control subjects REF/REF	Control subjects REF/ALT	Control subjects ALT/ALT	MAF for control subjects	Assay call rate (%)	*P* value	Odds ratio	95% CI
1	153507176	153507176	C	T	*S100A6*	NM_014624:exon3: c.G269A:p.G90D	128	25	0	0.081	157	22	1	0.067	96	.46	0.80	0.42-1.50
5	147469114	147469114	G	A	*SPINK5*	NM_001127698:exon7: c.G532A:p.E178K	145	6	0	0.02	191	1	0	0.002	98.8	.12	0.17	0.0037-1.43
5	147481363	147481363	G	A	*SPINK5*	NM_001127698:exon15: c.G1322A:p.R441H	152	1	0	0.003	177	6	0	0.016	96.8	.13	5.07	0.61-234.32
5	147480027	147480027	G	A	*SPINK5*	NM_001127698: c.G1103A:p.S368N	68	59	23	0.35	72	90	22	0.36	96.3	.74	1.06	0.76-1.48
5	147480955	147480955	A	G	*SPINK5*	NM_001127698: c.A1258G:p.K420E	66	59	23	0.35	68	91	20	0.36	94.2	.80	1.05	0.75-1.46
6	7585240	7585240	T	G	*DSP*	NM_001008844:exon24: c.T5948G:p.F1983C	148	4	1	0.02	179	6	0	0.016	97.4	.77	0.82	0.21-3.12
17	74003539	74003539	G	A	*EVPL*	NM_001988:exon22: c.C5747T:p.S1916L	150	5	0	0.016	186	2	0	0.005	98.8	.25	0.33	0.03-2.012