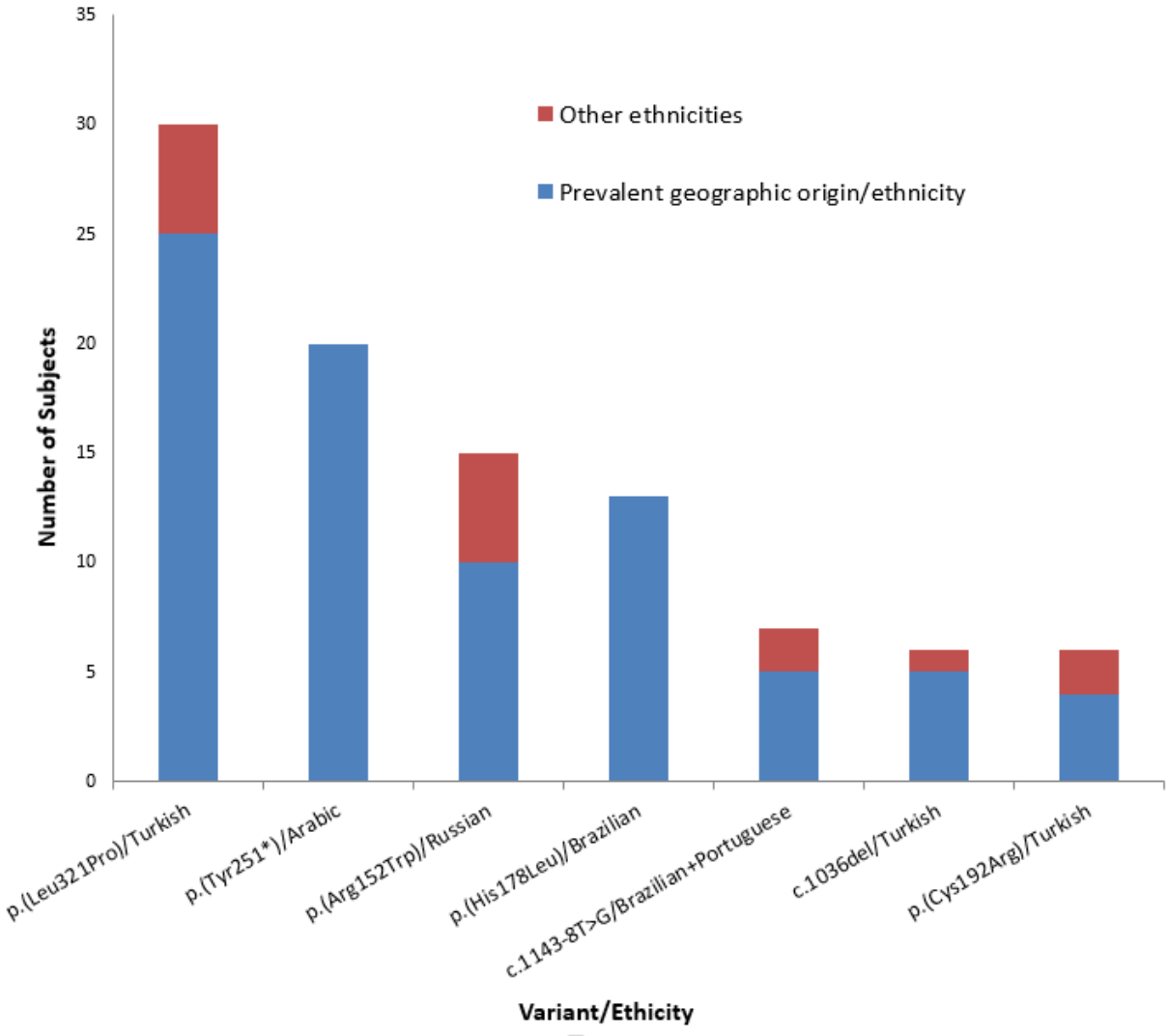
Supplemental Material S4. Variants and ethnicities of the most represented homozygote subjects



Supplemental Material S1. Search Strategies

Primary search strategy:
('maroteaux lamy syndrome'/exp OR 'mps vi' OR 'maroteaux lamy' OR 'maroteaux lamy disease' OR 'maroteaux lamy syndrome' OR 'arylsulfatase b deficiency syndrome' OR 'mucopolysaccharidosis 6' OR 'mucopolysaccharidosis type 6' OR 'mucopolysaccharidosis type vi' OR 'mucopolysaccharidosis vi' OR 'n acetylgalactosamine 4 sulfatase deficiency syndrome' OR 'n acetylgalactosamine 4 sulfatase'/exp OR 'arylsulfatase b' OR 'chondroitinase' OR 'chondroitinases' OR 'chondroitinsulfatase' OR 'chondroitinsulfatases' OR 'e.c. 3.1.6.12' OR 'n acetyl d galactosamine 4 sulfate 4 sulfohydrolase' OR 'n acetyl d galactosamine 4 sulfate sulfohydrolase' OR 'n acetyl d galactosamine 4 sulphate 4 sulfohydrolase' OR 'n acetyl d galactosamine 4 sulphate sulfohydrolase' OR 'n acetylgalactosamine 4 sulfatase' OR 'n acetylgalactosamine 4 sulfate sulfatase' OR 'n acetylgalactosamine 4 sulphate sulfatase' OR 'n-acetylgalactosamine-4-sulfatase') AND ('mutation'/exp OR 'gene alteration' OR 'genome mutation' OR 'mutation' OR 'gene mutation'/exp OR 'gene mutation' OR 'mutation, gene' OR 'genetic variability'/exp OR 'genetic variant' OR 'genotype variation' OR 'genotypic variation' OR 'arsb gene'/exp OR 'arsb gene' OR 'arsb gene mutation' OR 'indel mutation'/exp OR 'indel' OR 'indel mutation' OR 'indels' OR 'insertion and deletion' OR 'insertion deletion' OR 'insertions and deletions' OR 'insertions deletions' OR 'missense mutation'/exp OR 'missense mutation' OR 'mutation, missense' OR 'point mutation'/exp OR 'mutation, point' OR 'point mutation' OR 'frameshift mutation'/exp OR 'frameshift mutation' OR 'mutation, reading frame' OR 'reading frame mutation' OR 'reading frame shift' OR 'silent mutation'/exp OR 'silent mutation' OR 'nucleotide sequence'/exp OR 'base sequence' OR 'nucleic acid base sequence' OR 'nucleic acid sequence' OR 'nucleoside sequence' OR 'nucleotide base sequence' OR 'nucleotide sequence' OR 'oligonucleotide sequence' OR 'polynucleotide sequence' OR 'ribonucleotide sequence' OR 'sequence, base' OR 'genetic heterogeneity'/exp OR 'genetic heterogeneity' OR 'genetic heterogenicity' OR 'genotype heterogeneity' OR 'heterogeneity, genetic' OR 'heterogenicity, genetic' OR 'genotype'/exp OR 'genotype' OR 'genotyping' OR 'allele'/exp OR 'allele' OR 'alleles' OR 'allelic gene' OR 'allelomorph' OR 'gene, allelic' OR 'gene sequence'/exp OR 'gene sequence' OR 'gene sequencing' OR 'sequence, gene' OR 'sequencing, gene') AND 'human'/de AND ('article'/it OR 'article in press'/it OR 'review'/it)

Supplemental Material S2. Table reporting the genotypes of the patients analyzed.(.xls file)

Supplemental Material S3. *ARSB* sequence variants identified in patients with MPS VI

(§Variants classified per Richards S, Aziz N, Bale S, et al. (2015). Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med, 17(5), 405-424. ClinVar accessed 06/05/2017)

Exon/ Intron	Nucleotide change (HGVS; NM_000046.4)	Predicted amino acid change	Number of reports	Clinical significance §	Variant identifier (ClinVar ID and/or dbSNP number, if available)	Literature Reference	Notes
Exon 1	c.98C>T	p.(Ala33Val)	1	Benign	ClinVar Allele ID: 190201	Karageorgos (2007) Hum Mutat 28, 897	
Exon 1	c.108_120del	p.(Ser37Profs*15)	1	Likely pathogenic		Karageorgos (2007) Hum Mutat 28, 897	
Exon 1	c.113_121del	p.(Gly38_Gly40del)	2	Benign		Mathew (2015) Mol Genet Metab Rep 4, 53	
Exon 1	c.114del	p.(Ala39Profs*17)	1	Likely pathogenic		Karageorgos (2007) Hum Mutat 28, 897	
Exon 1	c.116_123del	p.(Ala39Glufs*85)	2	Pathogenic		Karageorgos (2007) Hum Mutat 28, 897	
Exon 1	c.149T>A	p.(Leu50Ter)	1	Likely pathogenic		Garcia (2010) J Ped Rehab Med 3, 63	
Exon 1	c.157G>A	p.(Asp53Asn)	6	Likely pathogenic		Uttarilli (2015) Indian J Med Res 142, 414 Mathew (2015) Mol Genet Metab Rep 4, 53 Kantaputra (2014) Am J Med Genet A 164A, 1443	
Exon 1	c.160G>A	p.(Asp54Asn)	5	Likely pathogenic		Karageorgos (2007) Hum Mutat 28, 897 Zanetti (2014) JIMD Rep 14, 1 Uttarilli (2015) Indian J Med Res 142, 414	
Exon 1	c.167G>A	p.(Gly56Asp)	2	Uncertain significance		Cobos (2015) JIMD Rep 15, 123	
Exon 1	c.171G>C	p.(Trp57Cys)	2	Uncertain significance		Karageorgos (2007) Hum Mutat 28, 897 Jurecka (2012) Mol Genet Metab 105, 237 Jurecka (2014) Ped Intl 56, 520	
Exon 1	c.175G>A	p.(Asp59Asn)	2	Uncertain significance		Petry (2005) J Inherit Metab Dis 28, 1027 Horovitz (2015) Mol Gen Metab Rep 5, 19	
Exon 1	c.176A>T	p.(Asp59Val)	2	Likely pathogenic		Debiec (2014) J Am Soc Nephrol25, 675	
Exon 1	c.194C>T	p.(Ser65Phe)	2	Uncertain significance		Villani (1999) Biochim Biophys Acta 1453, 185	
Exon 1	c.206C> T	p.(Thr69Met)	1	Uncertain significance		McGill (2010) Clin Genet 5, 492	
Exon1	c.207_213dup	p.(Leu72Alafs*57)	2	Likely pathogenic		Sandberg (2008) Mol Genet Metab 93, S34	
Exon 1	c.208_215del	p.(Pro70Glyfs*54)	2	Pathogenic		Kantaputra (2014) Am J Med Genet A 164A, 1443	

Exon 1	c.215T>A	p.(Leu72Gln)	1	Uncertain significance		Isbrandt (1996) Hum Mutat 7, 361	
Exon 1	c.215T>C	p.(Leu72Pro)	2	Uncertain significance	ClinVar Allele ID: 15922	Jurecka (2014) Ped Intl 56, 520	
Exon 1	c.215T>G	p.(Leu72Arg)	13	Likely pathogenic		Petry (2005) J Inherit Metab Dis 28, 1027 Karageorgos (2007) Hum Mutat 28, 897 Karageorgos (2007) Mol Genet Metab 90, 164 Zheng (2014) Chin J Pediatr 52, 403	
Exon 1	c.219del	p.(Asp73Glufs*41)	1	Likely pathogenic		Isbrandt (1996) Hum Mutat 7, 361	
Exon1	c.223_232del	p.(Leu75Alafs*36)	1	Likely pathogenic		Isbrandt (1996) Hum Mutat 7, 361	
Exon 1	c.236G>A	p.(Gly79Glu)	2	Uncertain significance		Kilic (2017) Am J Med GenetA 173A, 2954	
Exon 1	c.237_243del	p.(Val80Trpfs*32)	1	Likely pathogenic		Voskoboeva (1994) Hum Genet 93, 259 Voskoboeva (2000) Genetika 6, 837 Garrido (2007) Mol Genet Metab 92, 122 Jurecka (2013) Am J Med Genet A 161A, 1291	
Exon 1	c.238del	p.(Val80Cysfs*34)	6	Pathogenic	ClinVar Allele ID: 15920; rs750845916	Litjens (1992) Hum Mutat 1, 397 Garrido (2007) Mol Genet Metab 92, 122 Karageorgos (2007) Mol Genet Metab 90, 164 Karageorgos (2007) Hum Mutat 28, 897	
Exon 1	c.245del	p.(Leu82Argfs*32)	2	Likely pathogenic		Voskoboeva (2000) Genetika 6, 837 Karageorgos (2007) Hum Mutat 28, 897	
Exon 1	c.245T>G	p.(Leu82Arg)	3	Likely pathogenic	rs750845916	Garrido (2007) Mol Genet Metab 92, 122 Di Natale (2008) Biotechnol Appl Biochem 49, 219 Zanetti (2009) Eur J Hum Genet 17, 1160	
Exon 1	c.246G>A	p.(Leu82Leu)	1	Uncertain significance		Karageorgos (2007) Hum Mutat 28, 897	
Exon 1	c.247_248del	p.(Asp83Glnfs*43)	1	Likely pathogenic		Jurecka (2014) Ped Intl 56, 520	
Exon 1	c.247G>T	p.(Asp83Tyr)	1	Uncertain significance		Karageorgos (2007) Hum Mutat 28, 897	
Exon 1	c.253T>C	p.(Tyr85His)	4	Likely pathogenic		Furujo (2011) Mol Genet Metab 104, 597	
Exon 1	c.260C>G	p.(Thr87Arg)	2	Uncertain significance		Pollard (2013) J Inherit Metab Dis 36, 179	

Exon 1	c.262C>T	p.(Gln88Ter)	4	Pathogenic		Jurecka (2011) Cent Eur J Med 6, 163 Jurecka (2013) Am J Med GenetA 161A, 1291 Jurecka (2014) Ped Intl 56, 520 Chistiakov (2014) Clin Chim Acta 436C, 112	
Exon 1	c.263dup	p.(Pro89Alafs*38)	1	Likely pathogenic		Jurecka (2014) Ped Intl 56, 520 Jurecka (2014) Clin Rheumatol 33, 725	
Exon 1	c.264G>C	p.(Gln88His)	1	Uncertain significance		Petry (2005) J Inherit Metab Dis 28, 1027	
Exon 1	c.270_274del	p.(Cys91Alafs*34)	2	Pathogenic		Al-Sannaa (2018) J Community Genet 9, 65	
Exon 1	c.271T>C	p.(Cys91Arg)	2	Uncertain significance		Mathew (2015) Mol Genet Metab Rep 4, 53	
Exon 1	(c.272G>A)	p.(Cys91Tyr)	1	Uncertain significance		Jurecka (2014) Ped Intl 56, 520	c. annotation was predicted
Exon 1	c.275C>A	p.(Thr92Lys)	9	Uncertain significance		Karageorgos (2007) Hum Mutat 28, 897 Jurecka (2012) Mol Genet Metab 105, 237 Jurecka (2014) Ped Intl 56, 520 Cobos (2015) JIMD Rep 15, 123	
Exon 1	c.275C>T	p.(Thr92Met)	2	Uncertain significance		Litjens (1996) Am J Hum Genet 58, 1127 Pollard (2013) J Inherit Metab Dis 36, 179	
Exon 1	c.277C>T	p.(Pro93Ser)	1	Uncertain significance		Petry (2005) J Inherit Metab Dis 28, 1027	
Exon 1	c.278C>T	p.(Pro93Leu)	2	Uncertain significance	rs118203942	Okamura (2013) J Dermatol 40, 758	
Exon 1	c.284G>A	p.(Arg95Gln)	6	Likely pathogenic	ClinVar Allele ID: 15923	Litjens (1996) Am J Hum Genet 58, 1127 Karageorgos (2007) Mol Genet Metab 90, 164 Karageorgos (2007) Hum Mutat 28, 897 Garrido (2007) Mol Genet Metab 92, 122	
Exon 1	c.288C>G	p.(Ser96Arg)	1	Uncertain significance		Karageorgos (2007) Hum Mutat 28, 897	
Exon 1	c.289C>T	p.(Gln97Ter)	4	Likely pathogenic		Karageorgos (2004) Hum Mutat 23, 229 Karageorgos (2007) Hum Mutat 28, 897 Jurecka (2012) Mol Genet Metab 105, 237 Jurecka (2014) Ped Intl 56, 520	
Exon 1	c.293T>A	p.(Leu98Gln)	4	Likely pathogenic		Karageorgos (2007) Hum Mutat 28, 897	
Exon 1	c.293T>C	p.(Leu98Pro)	2	Uncertain significance		Voskoboeva (2000) Genetika 6, 837 Cobos (2015) JIMD Rep 15, 123	

Exon 1	c.293T>G	p. (Leu98Arg)	8	Likely pathogenic		Uttarilli (2015) Indian J Med Res 142, 414 Mathew (2015) Mol Genet Metab Rep 4, 53	
Exon 1	c.305G>A	p.(Arg102His)	2	Uncertain significance		Karageorgos (2007) Mol Genet Metab 90, 164 Karageorgos (2007) Hum Mutat 28, 897	
Exon 1	c.307_312+147del	---	2	Pathogenic			
Exon 1	c.312G>C	p.(Gln104His)	4	Uncertain significance	rs150087888	Karageorgos (2007) Hum Mutat 28, 897 Thümler (2012) J Inherit Metab Dis 35, 1071 Pollard (2013) J Inherit Metab Dis 36, 179	
Exons 2-3	c.313-7412_690+1601del	---	2	Likely pathogenic		Ittiwut (2017) Genet Test Mol Biomarkers 21, 58	Deletion of exon 2-3 with defined breakpoints
Exons 2-3	c.(312+1_313-1)_(690+1_691-1)del	---	2	Likely pathogenic		Zheng (2014) Chin J Pediatr 52, 403	Deletion of exon 2-3 without defined breakpoints
Exon 2	c.317G>A	p.(Arg106His)	1	Uncertain significance	rs768802200	Karageorgos (2007) Hum Mutat 28, 897	
Exon 2	c.323G>T	p.(Gly108Val)	1	Uncertain significance		Karageorgos (2007) Mol Genet Metab 90, 164	
Exon 2	c.328C>T	p.(Gln110*)	1	Likely pathogenic		Chistiakov (2014) Clin Chim Acta 436C, 112	
Exon 2	c.332A>C	p.(His111Pro)	5	Uncertain significance	rs775780931	Giraldo (2016) Meta Gene 7, 83	
Exon 2	Not given	p.(Ile114Ile)	1	Uncertain significance		Villani (1999) Biochim Biophys Acta 1453, 185	
Exon 2	c.347C>A	p.(Pro116His)	2	Uncertain significance	rs118203939	Villani (1999) Biochim Biophys Acta 1453, 185	
Exon 2	c.349T>C	p.(Cys117Arg)	6	Likely pathogenic	ClinVar Allele ID: 15917	Jin (1992) Am J Hum Genet 50, 795 Karageorgos (2007) Hum Mutat 28, 897	
Exon 2	c.356_358del	p.(Pro119_Ser120delinsArg)	1	Uncertain significance		Karageorgos (2004) Hum Mutat 23, 229 Karageorgos (2007) Hum Mutat 28, 897	
Exon 2	c.361T>C	p.(Cys121Arg)	1	Uncertain significance		Giraldo (2016) Meta Gene 7, 83	
Exon 2	Not given	p.(Leu124Leu)	1	Uncertain significance		Villani (1999) Biochim Biophys Acta 1453, 185	
Exon 2	c.375dup	p.(Glu126*)	1	Likely pathogenic		Jurecka (2012) Mol Genet Metab 105, 237 Jurecka (2014) Ped Intl 56, 520	
Exon 2	c.384_386del	p.(Leu129del)	3	Uncertain significance	ClinVar Allele ID: 106583	Fernández-Marmiesse (2014) Orphanet J Rare Dis 9, 59 Giraldo (2016) Meta Gene 7, 83	
Exon 2	c.389C>T	p.(Pro130Leu)	1	Uncertain significance		Karageorgos (2007) Mol Genet Metab 90, 164 Karageorgos (2007) Hum Mutat 28, 897	

Exon 2	c.395T>C	p.(Leu132Pro)	3	Likely pathogenic		Lin (2008) Clin Chim Acta 394, 89	
Exon 2	c.410G>T	p.(Gly137Val)	2	Pathogenic	ClinVar Allele ID: 15916	Wicker (1991) J Biol Chem 266, 21386	
Exon 2	c.413A>G	p.(Tyr138Cys)	1	Uncertain significance		Garrido (2007) Mol Genet Metab 92, 122	
Exon 2	c.418A>C	p.(Thr140Pro)	1	Uncertain significance		Karageorgos (2007) Hum Mutat 28, 897	
Exon 2	c.426G>C	p.(Met142Ile)	1	Uncertain significance	rs766914147	Simonaro (1995) Biochim Biophys Acta 1272, 129	
Exon 2	c.427del	p.(Val143Serfs*41)	12	Pathogenic	rs746206847	Karageorgos (2004) Hum Mutat 23, 229 Petry (2005) J Inherit Metab Dis 28, 1027 Garrido (2007) Mol Genet Metab 92, 122 Karageorgos (2007) Hum Mutat 28, 897 Jurecka (2013) Am J Med Genet A 161A, 1291 Fernández-Marmiesse (2014) Orphanet J Rare Dis 9, 59	
Exon 2	c.430G>A	p.(Gly144Arg)	8	Likely pathogenic		Isbrandt (1994) Am J Hum Genet 54, 454 Petry (2005) J Inherit Metab Dis 28, 1027 Karageorgos (2007) Hum Mutat 28, 897 Chistiakov (2014) Clin Chim Acta 436C, 112 Giraldo (2016) Meta Gene 7, 83	
Exon 2	c.436T>C	p.(Trp146Arg)	1	Uncertain significance		Simonaro (1995) Biochim Biophys Acta 1272, 129	
Exon 2	c.437G>T	p.(Trp146Leu)	1	Uncertain significance	rs757061042	Simonaro (1995) Biochim Biophys Acta 1272, 129	
Exon 2	c.437G>C	p.(Trp146Ser)	2	Uncertain significance		Simonaro (1995) Biochim Biophys Acta 1272, 129	
Exon 2	c.438G>A	p.(Trp146*)	4	Likely pathogenic		Voskoboeva (2000) Genetika 6, 837 Karageorgos (2007) Hum Mutat 28, 897 Thümler (2012) J Inherit Metab Dis 35, 1071	
Exon 2	c.440A>C	p.(His147Pro)	2	Uncertain significance		Giraldo (2016) Meta Gene 7, 83	

Exon 2	c.454C>T	p.(Arg152Trp)	62	Pathogenic		Voskoboeva (1994) Hum Genet 93, 259 Voskoboeva (2000) Genetika 6, 837 Karageorgos (2007) Hum Mutat 28, 897 Jurecka (2011) Cent Eur J Med 6, 163 Jurecka (2011) Mol Genet Metab 104, 695 Jurecka (2012) Mol Genet Metab 105, 237 Thümler (2012) J Inherit Metab Dis 35, 1071 Brands (2013) Orphanet J Rare Dis 8, 51 Jurecka (2013) Am J Med Genet A 161, 1291 Jurecka (2014) Ped Intl 56, 520 Chistiakov (2014) Clin Chim Acta 436C, 112 Ferla (2015) Hum Gene Ther 26, 145 Ebbink (2016) J Inherit Metab Dis 39, 285 Oussoren (2017) Mol Genet Metab 121, 241	
Exon 2	c.464G>A	p.(Cys155Tyr)	3	Uncertain significance		Ittiwut (2017) Genet Test Mol Biomarkers 21, 58	
Exon 2	c.478C>T	p.(Arg160*)	16	Pathogenic		Voskoboeva (1994) Hum Genet 93, 259 Voskoboeva (2000) Genetika 6, 837 Garrido (2007) Mol Genet Metab 92, 122 Karageorgos (2007) Hum Mutat 28, 897 Jurecka (2012) Mol Genet Metab 105, 237 Thümler (2012) J Inherit Metab Dis 35, 1071 Jurecka (2014) Ped Intl 56, 520 Jurecka (2014) Clin Rheumatol 33, 725 Kilic (2017) Am J Med Genet A 173, 2954	
Exon 2	c.479G>A	p.(Arg160Gln)	13	Likely pathogenic		Voskoboeva (1994) Hum Genet 93, 259 Voskoboeva (2000) Genetika 6, 837 Karageorgos (2007) Hum Mutat 28, 897 Garrido (2007) Mol Genet Metab 92, 122 Jurecka (2012) Mol Genet Metab 105, 237 Kantaputra (2014) Am J Med Genet A 164A, 1443 Jurecka (2014) Ped Intl 56, 520 Mathew (2015) Mol Genet Metab Rep 4, 53 Ittiwut (2017) Genet Test Mol Biomarkers 21, 58	
Exon 2	c.489_491del	p.(Thr164del)	1	Uncertain significance		Karageorgos (2007) Hum Mutat 28, 897	

Exon 2	c.498del	p.(Phe166fs*18)	2	Pathogenic		Uttarilli (2015) Indian J Med Res 142, 414	
Exon 2	c.499G>A	p.(Gly167Arg)	5	Uncertain significance		Jurecka (2012) Mol Genet Metab 105, 237 Jurecka (2014) Ped Intl 56, 520 Zheng (2014) Chin J Pediatr 52, 403	
Exon 3	c.509T>G	p.(Leu170Arg)	1	Likely pathogenic		Dou (2006) Clin Chim Acta 374, 171	
Exon 3	c.511G>A	p.(Gly171Ser)	3	Likely pathogenic		Karageorgos (2007) Mol Genet Metab 90, 164 Karageorgos (2007) Hum Mutat 28, 897	
Exon 3	c.523T>G	p.(Tyr175Asp)	1	Uncertain significance		Zheng (2014) Chin J Pediatr 52, 403	
Exon 3	c.532C>G	p.(His178Asp)	2	Likely pathogenic		Zanetti (2014) JIMD Rep 14, 1	
Exon 3	c.533A>T	p.(His178Leu)	29	Likely pathogenic		Karageorgos (2007) Hum Mutat 28, 897 Costa-Motta (2011) Mol Genet Metab104, 603 Costa-Motta (2014) Hum Hered77, 189 Horovitz (2015) Mol Gen Metab Rep 5, 19	
Exon 3	c.571C>T	p.(Arg191*)	7	Pathogenic		Karageorgos (2007) Mol Genet Metab 90, 164 Karageorgos (2007) Hum Mutat 28, 897 Ferla (2015) Hum Gene Ther 26, 145	
Exon 3	c.574T>C	p.(Cys192Arg)	15	Likely pathogenic		Isbrandt (1994) Am J Hum Genet 54, 454 Wu (2000) Hum Mutat 15, 389 Yang (2001) J Formos Med Assoc 100, 820 Karageorgos (2007) Hum Mutat 28, 897 Lin (2008) Clin Chim Acta 394, 89 Wang (2008) World J Pediatr4, 152 Thümler (2012) J Inherit Metab Dis 35, 1071 Jester S (2013) Orphanet J Rare Dis; 8:134. Kilic (2017) Am J Med Genet A 173, 2954	
Exon 3	c.589C>T	p.(Arg197*)	5	Pathogenic	rs118203943	Petry (2005) J Inherit Metab Dis 28, 1027 Dou (2006) Clin Chim Acta 374, 171 Karageorgos (2007) Hum Mutat 28, 897	

Exon 3	c.629A>G	p.(Tyr210Cys)	46	Pathogenic	ClinVar Allele ID: 15924	Litjens (1996) Am J Hum Genet 58, 1127 Voskoboeva (2000) Genetika 6, 837 Bradford (2002) Biochemistry 41, 4962 Karageorgos (2004) Hum Mutat 23, 229 Karageorgos (2007) Hum Mutat 28, 897 Sandberg (2008) Mol Genet Metab 93, S34 Scarpa (2010) J Ped Rehab Med 3, 71 Gottwald (2011) Mol Genet Metab 103, 300 Jurecka (2011) Cent Eur J Med 6, 163 Jurecka (2012) Mol Genet Metab 105, 237 Thümler (2012) J Inherit Metab Dis 35, 1071 Brands (2013) Orphanet J Rare Dis 8, 51 Mendelsohn (2013) JIMD Rep 11, 125 Jurecka (2014) Ped Intl 56, 520 Jurecka (2014) Clin Rheumatol 33, 725 Ferla (2015) Hum Gene Ther 26, 145 Ebbink (2016) J Inherit Metab Dis 39, 285 Oussoren (2017) Mol Genet Metab 121, 241	
Exon 3	c.630_636del	p.(Tyr210*)	1	Likely pathogenic		Karageorgos (2007) Hum Mutat 28, 897	
Exon 3	Not given	p.(Thr212Ile)	2	Uncertain significance		Sandberg (2008) Mol Genet Metab 93, S34	Prediction of c. annotation is c.635C>T
Exon 3	c.659_660del	p.(Ile220fs*5)	1	Likely pathogenic	rs367650121	Uttarilli (2015) Indian J Med Res 142, 414	
Exon 3	c.667A>G	p.(Ile223Val)	2	Likely pathogenic		Karageorgos (2007) Hum Mutat 28, 897	
Exon 4	c.(690+1_691-1)_(898+1_899-1)del	---	2	Pathogenic		Lin (2015) Tohoku J Exp Med 235, 267	Deletion of exon 4 without defined boundaries
Intron 3	c.691-1G>A	---	3	Likely pathogenic	rs6870443	Cobos (2015) JIMD Rep 15, 123	
Exon 4	c.707T>C	p.(Leu236Pro)	2	Uncertain significance	ClinVar Allele ID: 15918	Karageorgos (2004) Hum Mutat 23, 229 Karageorgos (2007) Hum Mutat 28, 897 Jin (1992) Am J Hum Genet 50, 795	
Exon 4	c.710C>A	p.(Ala237Asp)	4	Likely benign		Brands (2013) Orphanet J Rare Dis 8, 51 Uttarilli (2015) Indian J Med Res 142, 414	
Exon 4	c.716A>G	p.(Gln239Arg)	3	Uncertain significance		Wu (2000) Hum Mutat 15, 389 Lin (2008) Clin Chim Acta 394, 89 Wang (2008) World J Pediatr4, 152 Yang (2001) J Formos Med Assoc 100, 820	

Exon 4	c.719C>T	p.(Ser240Phe)	1	Uncertain significance		Garrido (2007) Mol Genet Metab 92, 122	
Exon 4	c.725A>C	p.(His242Pro)	1	Uncertain significance		Di Natale (2008) Biotechnol Appl Biochem 49, 219 Ferla (2015) Hum Gene Ther 26, 145	
Exon 4	c.743del	p.(Pro248Leufs*5)	1	Pathogenic	ClinVar Allele ID: 15921	Isbrandt (1996) Hum Mutat 7, 361	
Exon 4	c.750_754delinsCCTGAAGTCAAG	p.(Glu250Aspfs*9)	2	Likely pathogenic		Jurecka (2012) Mol Genet Metab 105, 237 Jurecka (2012) Pediatr Neurosurg 48, 191 Jurecka (2014) Ped Intl 56, 520	
Exon 4	c.750_754delinsCCTGAAG	p.(Glu250Aspfs*4)	2	Likely pathogenic		Jurecka (2011) Cent Eur J Med 6, 163	
Exon 4	c.753C>G	p.(Tyr251*)	43	Pathogenic		Sillence (2011) JIMD Rep 2, 103 Cobos (2015) JIMD Rep 15, 123 Al-Sannaa (2018) J Community Genet 9, 65	
Exon 4	c.765T>A	p.(Tyr255*)	4	Likely pathogenic	rs749015246	Lam (2004) Chin Med J 117, 1850 But (2011) Hong Kong Med J17, 317 Zheng (2014) Chin J Pediatr 52, 403	
Exon 4	c.785dup	p.(Asn262Lysfs*14)	1	Likely pathogenic		Chistiakov (2014) Clin Chim Acta 436C, 112	
Exon 4	c.797A>C	p.(Tyr266Ser)	7	Uncertain significance		Jurecka (2012) Mol Genet Metab 105, 237 Jurecka (2014) Ped Intl 56, 520	
Exon 4	c.803G>T	p.(Gly268Val)	1	Uncertain significance		Karageorgos (2007) Hum Mutat 28, 897	
Exon 4	c.883_884dup	p.(Ile296Serfs*43)	2	Likely pathogenic		Ferla (2015) Hum Gene Ther 26, 145	
Exon 4	c.887T>A	p.(Ile296Asn)	2	Likely pathogenic		Karageorgos (2007) Hum Mutat 28, 897	
Exon 5	c.(898+1_899-1)_(1142+1_1143-1)del	---	6	Pathogenic		Arlt (1994) J Biol Chem 269, 9638 Garrido (2007) Mol Genet Metab 92, 122 Karageorgos (2007) Hum Mutat 28, 897 Ferla (2015) Hum Gene Ther 26, 145	Deletion of exon 5 without defined boundaries
Exon 5	c.899-1341_1142+1051del	---	1	Pathogenic		Villani (2010) Genet Test MolBiomarkers 14, 113	Deletion of exon 5 with defined boundaries
Exon 5	c.900T>A	p.(Asp300Glu)	1	Uncertain significance		Karageorgos (2007) Hum Mutat 28, 897	
Exon 5	c.900T>G	p.(Asp300Glu)	2	Uncertain significance		Giraldo (2016) Meta Gene 7, 83	

Exon 5	c.903C>G	p.(Asn301Lys)	4	Likely pathogenic	rs779378413	Brands (2013) Orphanet J Rare Dis 8, 51 Zanetti (2014) JIMD Rep 14, 1 Ferla (2015) Hum Gene Ther 26, 145 Ebbink (2016) J Inherit Metab Dis 39, 285	
Exon 5	c.904G>A	p.(Gly302Arg)	10	Uncertain significance		Villani (1997) Hum Mutat 11, 410 Karageorgos (2007) Mol Genet Metab 90, 164 Scarpa (2010) J Ped Rehab Med 3, 71 Jurecka (2012) Mol Genet Metab 105, 237 Jurecka (2014) Ped Intl 56, 520 Giraldo (2016) Meta Gene 7, 83	
Exon 5	c.908G>A	p.(Gly303Glu)	5	Likely pathogenic		Lin (2008) Clin Chim Acta 394, 89 Zheng (2014) Chin J Pediatr 52, 403 Ferla (2015) Hum Gene Ther 26, 145	
Exon 5	c.922G>A	p.(Gly308Arg)	1	Uncertain significance		Garrido (2007) Mol Genet Metab 92, 122	
Exon 5	c.923G>A	p.(Gly308Glu)	1	Uncertain significance	rs749989641	Cobos (2015) JIMD Rep 15, 123	
Exon 5	c.937C>G	p.(Pro313Ala)	11	Likely pathogenic		Brooks (2005) Mol Genet Metab 85, 236 Garrido (2007) Mol Genet Metab 92, 122 Karageorgos (2007) Hum Mutat 28, 897 Jurecka (2013) Am J Med Genet A 161A, 1291 Brands (2013) Orphanet J Rare Dis 8, 51 Ferla (2015) Hum Gene Ther 26, 145 Ebbink (2016) J Inherit Metab Dis 39, 285 Oussoren (2017) Mol Genet Metab 121, 241	
Exon 5	c.937C>T	p.(Pro313Ser)	1	Uncertain significance		Karageorgos (2007) Hum Mutat 28, 897	
Exon 5	c.943C>T	p.(Arg315*)	10	Likely pathogenic	rs727503809	Voskoboeva (2000) Genetika 6, 837 Lin (2008) Clin Chim Acta 394, 89 Di Natale (2008) Biotechnol Appl Biochem 49, 219 Villani (2010) Genet Test Mol Biomarkers 14, 113 Chistiakov (2014) Clin Chim Acta 436C, 112 Jurecka (2014) Ped Intl 56, 520 Ferla (2015) Hum Gene Ther 26, 145	

Exon 5	c.944G>A	p.(Arg315Gln)	22	Likely pathogenic	ClinVar Allele ID: 177363	Villani (1999) Biochim Biophys Acta 1453, 185 Karageorgos (2004) Hum Mutat 23, 229 Petry (2005) J Inherit Metab Dis 28, 1027 Garrido (2007) Mol Genet Metab 92, 122 Karageorgos (2007) Mol Genet Metab 90, 164 Karageorgos (2007) Hum Mutat 28, 897 Di Natale (2008) Biotechnol Appl Biochem 49, 219 Zanetti (2009) Eur J Hum Genet 17, 1160	
Exon 5	c.944G>C	p.(Arg315Pro)	4	Uncertain significance		Mathew (2015) Mol Genet Metab Rep 4, 53	
Exon 5	c.960C>G	p.(Ser320Arg)	3	Uncertain significance		Voskoboeva (2000) Genetika 6, 837 Uttarilli (2015) Indian J Med Res 142, 414	
Exon 5	c.962T>C	p.(Leu321Pro)	60	Pathogenic		Isbrandt (1994) Am J Hum Genet 54, 454 Karageorgos (2004) Hum Mutat 23, 229 Karageorgos (2007) Hum Mutat 28, 897 Chistiakov (2014) Clin Chim Acta 436C, 112 Kantaputra (2014) Am J Med Genet A 164A, 1443 Zanetti (2014) JIMD Rep 14, 1 Cobos (2015) JIMD Rep 15, 123 Ferla (2015) Hum Gene Ther 26, 145	
Exon 5	c.966G>A	p.(Trp322*)	2	Pathogenic	rs398123125	Garrido (2007) Mol Genet Metab 92, 122 Giraldo (2016) Meta Gene 7, 83	
Exon 5	c.971G>T	p.(Gly324Val)	5	Likely pathogenic	ClinVar Allele ID: 98267; rs773492223	Karageorgos (2007) Hum Mutat 28, 897 Brands (2013) Orphanet J Rare Dis 8, 51 Ferla (2015) Hum Gene Ther 26, 145 Ebbink (2016) J Inherit Metab Dis 39, 285	
Exon 5	c.979C>T	p.(Arg327*)	16	Pathogenic	rs201168448	Karageorgos (2004) Hum Mutat 23, 229 Karageorgos (2007) Hum Mutat 28, 897 Brands (2013) Orphanet J Rare Dis 8, 51 Zheng (2014) Chin J Pediatr 52, 403 Ferla (2015) Hum Gene Ther 26, 145 Kaissi (2016) Medicine 95, 32 Ebbink (2016) J Inherit Metab Dis 39, 285 Oussoren (2017) Mol Genet Metab 121, 241	

Exon 5	c.995T>G	p.(Val332Gly)	2	Likely pathogenic		Brands (2013) Orphanet J Rare Dis 8, 51 Ferla (2015) Hum Gene Ther 26, 145 Ebbink (2016) J Inherit Metab Dis 39, 285 Oussoren (2017) Mol Genet Metab 121, 241	
Exon 5	c.1001G>T	p.(Ser334Ile)	3	Uncertain significance		Giraldo (2016) Meta Gene 7, 83	
Exon 5	c.1028A>T	p.(Lys343Met)	1	Uncertain significance		Karageorgos (2007) Hum Mutat 28, 897	
Exon 5	c.1032C>G	p.(Asn344Lys)	1	Uncertain significance		Karageorgos (2007) Hum Mutat 28, 897	
Exon 5	c.1036del	p.(Glu346Serfs*11)	13	Pathogenic		Karageorgos (2007) Hum Mutat 28, 897 Zanetti (2014) JIMD Rep 14, 1 Ferla (2015) Hum Gene Ther 26, 145 Kilic (2017) Am J Med Genet 173A, 2954	
Exon 5	c.1048A>T	p.(Ile350Phe)	2	Pathogenic		Uttarilli (2017) Gene 599, 19	
Exon 5	c.1052C>T	p.(Ser351Phe)	2	Pathogenic		Pollard (2013) J Inherit Metab Dis 36, 179	
Exon 5	c.1057T>A	p.(Trp353Arg)	2	Uncertain significance		Karageorgos (2007) Mol Genet Metab 90, 164 Karageorgos (2007) Hum Mutat 28, 897 Zanetti (2014) JIMD Rep 14, 1	
Exon 5	c.1059G>A	p.(Trp353*)	2	Pathogenic		Uttarilli (2015) Indian J Med Res 142, 414	
Exon 5	c.1079T>C	p.(Leu360Pro)	6	Likely pathogenic		Voskoboeva (2000) Genetika 6, 837 Jurecka (2013) Am J Med Genet A 161A, 1291 Jurecka (2014) Ped Intl 56, 520 Zanetti (2014) JIMD Rep 14, 1	
Exon 5	Not given	p.(Asp372Gly)	1	Uncertain significance		But (2011) Hong Kong Med J17, 317	Prediction of c. annotation is c.1115A>G
Exon 5	c.1127T>A	p.(Val376Glu)	4	Likely pathogenic		Kantaputra (2014) Am J Med Genet A 164A, 1443 Cobos (2015) JIMD Rep 15, 123	
Exon 5	c.1130G>A	p.(Trp377*)	1	Likely pathogenic		Karageorgos (2007) Hum Mutat 28, 897	
Exon 5	c.1142+1G>T	---	2	Pathogenic		Karageorgos (2007) Hum Mutat 28, 897	
Exon 5	c.1142+2T>A	p.(Asp300Valfs*193)	2	Likely pathogenic		Garrido (2007) Mol Genet Metab 92, 122	
Exon 5	c.1142+2T>C	---	4	Pathogenic		Brands (2013) Am J Med Genet A 161A, 2550 Brands (2013) Orphanet J Rare Dis 8, 51 Ferla (2015) Hum Gene Ther 26, 145 Ebbink (2016) J Inherit Metab Dis 39, 285 Oussoren (2017) Mol Genet Metab 121, 241	

Intron 5	c.1143-1G>C	p.(Ser381Argfs*12)	16	Pathogenic	ClinVar Allele ID: 15926	Garrido (2007) Mol Genet Metab 92, 122 Karageorgos (2007) Hum Mutat 28, 897 Giraldo (2016) Meta Gene 7, 83	
Intron 5	c.1143-8T>G	p.(Ser381Argfs*12)	24	Likely pathogenic	ClinVar Allele ID: 15927; rs431905496	Petry (2005) J Inherit Metab Dis 28, 1027 Garrido (2007) Mol Genet Metab 92, 122 Karageorgos (2007) Hum Mutat 28, 897 Garcia (2010) J Ped Rehab Med 3, 63 Leal (2014) Cardiol Young 24, 229 Horovitz (2015) Mol Gen Metab Rep 5, 19 Franco (2016) Genet Mol Res 15, gmr.15017850	
Exon 6	c.1151G>A	p.(Ser384Asn)	9	Benign	ClinVar Allele ID: 98263; rs25414	Voskoboeva (2000) Genetika 6, 837 Karageorgos (2004) Hum Mutat 23, 229 Petry (2005) J Inherit Metab Dis 28, 1027 Karageorgos (2007) Hum Mutat 28, 897 Karageorgos (2007) Mol Genet Metab 90, 164 Chistiakov (2014) Clin Chim Acta 436C, 112	
Exon 6	c.1161dup	p.(Arg388Glnfs*3)	1	Likely pathogenic		Karageorgos (2007) Hum Mutat 28, 897	
Exon 6	c.1163G>C	p.(Arg388Thr)	1	Uncertain significance		Ittiwut (2017) Genet Test Mol Biomarkers 21, 58	
Exon 6	c.1168G>A	p.(Glu390Lys)	6	Likely pathogenic		Kantaputra (2014) Am J Med Genet A 164A, 1443 Ferla (2015) Hum Gene Ther 26, 145 Kilic (2017) Am J Med Genet 173A, 2954	
Exon 6	c.1178A>C	p.(His393Pro)	10	Uncertain significance	ClinVar Allele ID: 15925	Litjens (1996) Am J Hum Genet 58, 1127 Bradford (2002) Biochemistry 41, 4962 Karageorgos (2007) Hum Mutat 28, 897 Karageorgos (2007) Mol Genet Metab 90, 164 McGill (2010) Clin Genet 5, 492	
Exon 6	c.1178A>G	p.(His393Arg)	3	Uncertain significance		Ferla (2015) Hum Gene Ther 26, 145 Uttarilli (2015) Indian J Med Res 142, 414	
Exon 6	c.1195T>C	p.(Phe399Leu)	1	Uncertain significance	rs762979755	Pollard (2013) J Inherit Metab Dis 36, 179	

Exon 6	c.1197C>G	p.(Phe399Leu)	17	Likely pathogenic	rs200793396	Yang (2001) J Formos Med Assoc 100, 820 Lam (2004) Chin Med J 117, 1850 Lin (2008) Clin Chim Acta 394, 89 But (2011) Hong Kong Med J17, 317 Pollard (2013) J Inherit Metab Dis 36, 179 Zheng (2014) Chin J Pediatr 52, 403	
Exon 6	c.1208C>G	p.(Ser403*)	1	Pathogenic		Zheng (2014) Chin J Pediatr 52, 403	
Exon 6	c.1208del	p.(Ser403Tyrfs*171)	2	Pathogenic		Kantaputra (2014) Am J Med Genet A 164A, 1443	
Intron 6	c.1213+5G>A	---	2	Uncertain significance		Karageorgos (2007) Mol Genet Metab 90, 164 Karageorgos (2007) Hum Mutat 28, 897	
Intron 6	c.1213+6T>C	---	3	Pathogenic		Di Natale (2008) Biotechnol Appl Biochem 49, 219 Ferla (2015) Hum Gene Ther 26, 145	
Intron 6	c.1214-2A>G	---	1	Likely pathogenic		Karageorgos (2007) Mol Genet Metab 90, 164 Karageorgos (2007) Hum Mutat 28, 897 Zanetti (2014) JIMD Rep 14, 1	
Exon 7	c.1214G>A	p.(Cys405Tyr)	3	Uncertain significance	ClinVar Allele ID: 15919; rs118203941	Jin (1992) Am J Hum Genet 50, 795 Karageorgos (2007) Hum Mutat 28, 897	
Exon 7	c.1261G>T	p.(Glu421*)	2	Pathogenic		Xu (1996) Hokkaido Igaku Zasshi 71, 359	
Exon 7	c.1279del	p.(Thr427Hisfs*147)	1	Likely pathogenic		Petry (2005) J Inherit Metab Dis 28, 1027	
Exon 7	c.1286dup	p.(His430Profs*5)	2	Likely pathogenic		Isbrandt (1994) Am J Hum Genet 54, 454	
Exon 7	c.1288C>A	p.(His430Asn)	1	Uncertain significance		Lin (2008) Clin Chim Acta 394, 89	
Exon 7	c.1289A>G	p.(His430Arg)	3	Likely pathogenic		Karageorgos (2007) Mol Genet Metab 90, 164 Karageorgos (2007) Hum Mutat 28, 897	
Exon 7	c.1301G>T	p.(Arg434Ile)	1	Uncertain significance		Karageorgos (2007) Hum Mutat 28, 897	
Exon 7	c.1315A>G	p.(Lys439Glu)	1	Uncertain significance		Karageorgos (2007) Hum Mutat 28, 897	
Exon 7	c.1325C>T	p.(Thr442Met)	3	Uncertain significance	ClinVar Allele ID: 368534	Karageorgos (2007) Hum Mutat 28, 897 Zheng (2014) Chin J Pediatr 52, 403	
Exon 7	c.1334C>T	p.(Pro445Leu)	2	Uncertain significance		Kantaputra (2014) Am J Med Genet A 164A, 1443	

Intron 7	c.1336+2T>G		7	Pathogenic	rs768012515	Karageorgos (2004) Hum Mutat 23, 229 Karageorgos (2007) Hum Mutat 28, 897 Chistiakov (2014) Clin Chim Acta 436C, 112	
Exon 7	c.1336G>A	p.(Gly446Ser)	3	Uncertain significance		Garcia (2010) J Ped Rehab Med 3, 63 Giraldo (2016) Meta Gene 7, 83	
Exon 7	c.1336G>C	p.(Gly446Arg)	1	Uncertain significance		Karageorgos (2007) Mol Genet Metab 90, 164 Karageorgos (2007) Hum Mutat 28, 897	
Exon 8	c.1340G>C	p.(Cys447Ser)	1	Uncertain significance		Karageorgos (2007) Hum Mutat 28, 897	
Exon 8	c.1340G>T	p.(Cys447Phe)	4	Uncertain significance		Garrido (2007) Mol Genet Metab 92, 122 Karageorgos (2007) Hum Mutat 28, 897 Giraldo (2016) Meta Gene 7, 83	
Exon 8	c.1349G>T	p.(Trp450Leu)	4	Uncertain significance		Uttarilli (2015) Indian J Med Res 142, 414	
Exon 8	c.1350G>C	p.(Trp450Cys)	11	Likely pathogenic	rs555785323	Kantaputra (2014) Am J Med Genet A 164A, 1443 Uttarilli (2015) Indian J Med Res 142, 414 Mathew (2015) Mol Genet Metab Rep 4, 53	
Exon 8	c.1366C>T	p.(Gln456*)	4	Pathogenic	rs200188234	Villani (1997) Hum Mutat 11, 410 Karageorgos (2007) Hum Mutat 28, 897	
Exon 8	c.1391C>A	p.(Ser464*)	1	Likely pathogenic		Zheng (2014) Chin J Pediatr 52, 403	
Exon 8	c.1394C>G	p.(Ser465*)	1	Likely pathogenic		Lin (2008) Clin Chim Acta 394, 89	
Exon 8	c.1415T>C	p.(Leu472Pro)	2	Likely pathogenic		Garrido (2007) Mol Genet Metab 92, 122 Karageorgos (2007) Hum Mutat 28, 897	
Exon 8	c.1442C>T	p.(Pro481Leu)	1	Uncertain significance		Brooks (2005) Mol Genet Metab 85, 236	
Exon 8	c.1449A>T	p.(Glu483Asp)	1	Uncertain significance	ClinVar Allele ID: 406764	Pollard (2013) J Inherit Metab Dis 36, 179	
Exon 8	c.1450A>G	p.(Arg484Gly)	2	Uncertain significance	ClinVar Allele ID: 187113	Karageorgos (2004) Hum Mutat 23, 229 Karageorgos (2007) Hum Mutat 28, 897	
Exon 8	c.1457A>T	p.(Asp486Val)	6	Uncertain significance		Nouri (2012) Iranian Biomed J 16, 169	
Exon 8	c.1475del	p.(Pro492Lysfs*80)	1	Likely pathogenic		Di Natale (2008) Biotechnol Appl Biochem 49, 219	
Exon 8	c.1482del	p.(Ile494Metfs*80)	1	Likely pathogenic		Karageorgos (2007) Hum Mutat 28, 897	
Exon 8	c.1493T>C	p.(Leu498Pro)	1	Likely pathogenic	rs774358117	Litjens (1996) Am J Hum Genet 58, 1127	

Exon 8	c.1507C>T	p.(Gln503*)	2	Likely pathogenic	rs771113472	Villani (1999) Biochim Biophys Acta 1453, 185	
Exon 8	c.1515C>T	p.(Tyr505Tyr)	1	Uncertain significance		Karageorgos (2007) Hum Mutat 28, 897	
Exon 8	c.1534_1556del	p.(Val512Profs*3)	13	Uncertain significance		Petry (2005) J Inherit Metab Dis 28, 1027 Karageorgos (2007) Hum Mutat 28, 897 Garcia (2010) J Ped Rehab Med 3, 63 Giraldo (2016) Meta Gene 7, 83	
Exon 8	c.1539C>G	p.(Tyr513*)	1	Likely pathogenic		Voskoboeva (2000) Genetika 6, 837 Jurecka (2014) Ped Intl 56, 520	
Exon 8	c.1562G>A	p.(Cys521Tyr)	9	Uncertain significance		Isbrandt (1994) Am J Hum Genet 54, 454 Voskoboeva (2000) Genetika 6, 837 Jurecka (2013) Am J Med Genet A 161A, 1291 Jurecka (2014) Ped Intl 56, 520 Jurecka (2014) Clin Rheumatol 33, 725	
Exon 8	c.1577del	p.(Thr526Metfs*48)	8	Pathogenic		Isbrandt (1994) Am J Hum Genet 54, 454 Kantaputra (2014) Am J Med Genet A 164A, 1443 Zanetti (2014) JIMD Rep 14, 1	
Exon 8	c.1582_1596del	p.(Val528_Trp532del)	2	Uncertain significance		Karageorgos (2007) Hum Mutat 28, 897	
Exon 8	c.1592C>G	p.(Pro531Arg)	2	Uncertain significance		Villani (1999) Biochim Biophys Acta 1453, 185	
Exon 8	c.1600T>C	p.(*534Glnext*50)	1	Uncertain significance		Arlt (1994) J Biol Chem 269, 9638	
Exon 8	c.1601A>G	p.(*534Trpext*50)	1	Uncertain significance		Giraldo (2016) Meta Gene 7, 83	

Supplemental Material S5. Most common *ARSB* variants obtained from gnomAD (.xls file)