SUPPLEMENTAL DATA

Supplemental Table S1: Pathogenicity Predictions for Missense Variants in Human HPS Genes

	mRNA Variant	Amino Acid Variant [1]	Exon/ Intron	dbSNP ID [2] MAF ExAc [3]	ACMG Pathogenicity Prediction [1]	Comments
HPS1 (NM_000195.5)						
1	c.316C>G	p.Arg106Gly	ex 5	rs376557022 0.00001	VUS (PM2 [3], PP3 [4], PP4 [5]) [6]	(Wei et al., 2016)
2	c.344T>C	p.Leu115Pro	ex 5	-	VUS (PM2, PP3, PP4) [6]	(Khan et al., 2016)
3	c.505G>A	p.Glu169Lys	ex 6	-	LP (PS3, PM2, PP1, PP3, PP4)	At splice junction (Kahn et al., 2016). Predicted to create splice defect similar as reported for Glu169Glu (Merideth et al., 2009)
4	c.695C>T	p.Ala232Val	ex 8	rs764420988 0.00006	VUS (PP3, PP4) [6]	(Khan et al., 2016). Despite high MAF, this variant is predicted deleterious to protein function
5	c.716T>C	p.Leu239Pro	ex 8	rs281865080 -	P (PS3, PM2, PM3, PP1, PP3, PP4)	(Hermos et al., 2002; Lasseaux et al., 2018; Thielen et al., 2010). In vitro studies showed that the HPS1 protein with this variant is unstable and prevents proper BLOC-3 formation (Carmona-Rivera, et al., 2013)
6	c.937G>A	p.Gly313Ser	ex 10	-	P (PS3, PM2, PM3, PP3, PP4)	(Lasseaux et al., 2018). At splice junction, a cryptic intronic splice site produces mis-spliced mRNA that includes 144-bp intronic sequence, producing 11 novel amino acids followed by a stop codon (Carmona-Rivera, Hess, et al., 2011)
7	c.1080C>G	p.Ser360Arg	ex 12	-	VUS (PM2, PM3) [6]	Predicted medium deleterious to protein function [7]
8	c.1342T>C	p.Trp448Arg	ex 14	-	VUS (PM2, PP1, PP3, PP4) [6]	(Yousaf et al., 2016). Predicted deleterious to protein function. Predicted to not affect nearby splice site at c.1336
9	c.1639G>T [8]	p.Val547Leu	ex 17	-	LP (PS3, PM2, PP1, PP3, PP4)	In vitro studies showed that the HPS1 protein with this variant was unstable and prevents proper BLOC-3 formation (Carmona-Rivera et al., 2013; Nazarian et al., 2008)
-	*c.1645C>T* [8]	*p.Arg549Cys*	ex 17	rs747984964	VUS (PM2, PP1, PP3, PP4) [6]	(Nazarian et al., 2008)
10	c.1763T>C	p.Leu588Pro	ex 18	-	VUS (PM2, PP3, PP4) [6]	(Okamura et al., 2019)
11	c.1787G>T	p.Gly596Val	ex 18	rs139951191	LP (PM2, PM3, PP3, PP4)	(Okamura et al., 2019; Takeuchi et al., 2014)
12	c.1937A>G	p.Tyr646Cys	ex 19	-	LP (PS3, PM2, PP1, PP3)	In vitro studies showed that the HPS1 protein with this variant was unstable and prevents proper BLOC-3 formation (Carmona-Rivera et al., 2013). Predicted to weaken the nearby splice site at c.1940 [9]
13	c.1996G>A	p.Glu666Lys	ex 20	rs121908385 0.00001	VUS (PM2, PP3, PP4) [6]	(Sim et al., 2019)

14	c.1996G>C	p.Glu666Gln	ex 20	-	VUS (PM2, PP3, PP4) [6]	(Lasseaux et al., 2018)
15	c.2003T>C	p.Leu668Pro	ex 20	rs281865090	LP (PS3, PM2, PP3, PP4)	(Ito et al., 2005; Iwata et al., 2017; Kanazu et al., 2014; Mai et al., 2019; Okamura et al., 2019; Wei et al., 2016). In vitro experiments showed Leu668Pro-HPS1 to be stable, but lacked the ability to stabilize the HPS4 protein, suggesting it cannot assemble into BLOC-3 (Ito et al., 2005)
AP3B1 **(**NM_003664.4)						
1	c.2T>G	p.Met1Arg	ex 1	-	P (PVS1, PM2, PP3)	Occurs in start codon. Predicted to affect protein translation (Cetica et al., 2015)
2	c.305T>C	p.Leu102Pro	ex 4	-	VUS (PM2, PP1, PP3, PP4) [6]	(Jessen et al., 2013)
3	c.1739T>G	p.Leu580Arg	ex 16	rs121908904	LP (PS3, PM2, PP1, PP3, PP4)	Fibroblasts of this subject have decreased AP-3 assembly and function compared to normal cells (Dell'Angelica et al., 1999)
4	c.2702C>G	p.Ser901Cys	ex 23	rs869312835	LP (PS3, PM2, PP3, PP4)	Activates a cryptic splice site (de Boer et al., 2017) [10]
HPS3 (NM_032383.5)						
1	c.1189C>T	p.Arg397Trp	ex 6	rs121908316 0.00002	LP (PS3, PM2, PP3, PP4)	(Huizing et al., 2001; Okamura et al., 2019; Wei et al., 2016). Reported to destabilize BLOC-2 assembly (Nazarian et al., 2008; Wei et al., 2016)
2	c.1509G>A	p.Met503Ile	ex 8	rs780183200 0.00002	VUS (PM2, PP1, PP3, PP4) [6]	At splice junction, predicted but not demonstrated to cause splicing defect, segregates with disease in a large Pakistani family (Yousaf et al., 2016)
3	c.1673T>C	p.Leu558Pro	ex 8	-	VUS (PM2, PP1, PP3) [6]	Occurs homozygous in 1 subject, both unaffected parents are a carrier (Lasseaux et al., 2018)
HPS4 (NM_022081.5)						
1	c.272T>C	p.Leu91Pro	ex 4	-	VUS (PM2, PP1, PP3, PP4) [6]	Occurred homozygous in two siblings. Variant segregated with disease in this family (Bastida et al., 2019)
2	c.461A>G	p.His154Arg	ex 6	rs281865098	LP (PM2, PM3, PP3, PP4)	(Saito et al., 2013). Familial testing of one subject showed occurrence in trans with pathogenic variant p.Arg217* (PM3) (Anderson et al., 2003)
3	c.554G>A	p.Arg185His	ex 7	rs111522254 0.00012	VUS (PP3, PP4) [6]	Relatively high frequency in ExAc (14 mostly South Asian alleles out of 121,412 chromosomes) (Arcot Sadagopan et al., 2016)
4	c.803G>A	p.Arg268Lys	ex 10	-	VUS (PM2, PP3, PP4) [6]	Predicted to cause splicing defect. Occurred homozygous (Lasseaux et al., 2018)
5	c.1856C>T	p.Pro619Leu	ex 13	rs374238081 0.00002	VUS (PM2, PP3, PP4) [6]	Occurred homozygous (Lasseaux et al., 2018)
HPS5 (NM_181507.1)						
1	c.434G>A	p.Gly145Glu	ex 5	rs1355819005	LP (PS3, PM2, PP3, PP4)	In vitro studies showed that this variant prevents proper BLOC-2 formation (Nazarian et al., 2008)
2	c.719G>C	p.Arg240Pro	ex 7	-	LP (PM2, PM3, PP3, PP4)	Parental testing showed that this variant occurs in trans with a pathogenic variant (del1.5kb) (Michaud et al., 2017; Lasseaux et al., 2018)

3	c.1871T>G [7]	p.Leu624Arg [11]	ex 16	rs281865102	LP (PM2, PM3, PP3, PP4)	(Huizing et al., 2004). [11] Parental testing of one subject showed tha this variant is in trans with a pathogenic frameshift variant (p.Leu992Valfs*17) (Michaud et al., 2017; Lasseaux et al., 2018) [7]
4	c.2219T>C	p.Leu740Ser	ex 16	-	VUS (PM2, PP3, PP4) [6]	(Lasseaux et al., 2018; Michaud et al., 2017)
5	c.2234T>C	p.Leu745Ser	ex 16	-	VUS (PM2, PP3, PP4) [6]	(Wei et al., 2016)
-	*c.3293C>T* [7]	*p.Thr1098Ile* [11]	ex 22	rs61884288 0.02362	-	(Huizing et al., 2004). High MAF and low pathogenicity scores classify this variant as a benign SNP [11]
6	c.3346A>G	p.Met1116Val	ex 23	-	VUS (PM2, PP3, PP4) [6]	(Wei et al., 2016)
HPS6 (NM_024747.5)						
1	c.233C>G	p.Pro78Arg	ex 1	-	VUS (PM2, PP4) [6]	(Okamura et al., 2019)
2	c.275T>A	p.Leu92Gln	ex 1	-	VUS (PM2, PP3, PP4) [6]	Occurred homozygous (Lasseaux et al., 2018)
3	c.337C>T	p.Arg113Trp	ex 1	rs371307947 0.00033	VUS (PM2, PP4) [6]	(Lasseaux et al., 2018)
4	c.383T>C	p.Val128Ala	ex 1	-	LP (PM2, PM3, PP3, PP4)	Occurred homozygous. Associated with reduced *HPS6* mRNA and protein expression (Han et al., 2018)
5	c.779G>A	p.Gly260Glu	ex 1	-	VUS (PM2, PP1, PP3, PP4) [6]	Occurred homozygous in 2 siblings (Hull et al., 2016)
6	c.815C>T	p.Thr272Ile	ex 1	rs281865109	LP (PM2, PM3, PP3, PP4)	Shown to occur in trans with pathogenic variant c.238dupG (PM3) (Huizing et al., 2009)
7	c.823C>T	p.Pro275Ser	ex 1	rs756325364 0.00001	VUS (PM2, PP3, PP4) [6]	(Yousaf et al., 2016)
8	c.895C>T	p.Arg299Trp	ex 1	rs201628418 0.00001	VUS (PM2, PP4) [6]	(Wei et al., 2016)
9	c.896G>C	p.Arg299Pro	ex 1	-	VUS (PM2, PP4) [6]	(Lasseaux et al., 2018)
10	c.905G>A	p.Gly302Asp	ex 1	-	VUS (PM2, PP4) [6]	Occurred homozygous (Lasseaux et al., 2018)
11	c.2207T>C	p.Leu736Pro	ex 1	-	LP (PM2, PM3, PP3, PP4)	Occurs in trans with pathogenic variant p.Arg463*(PM3) (Lasseaux et al., 2018)

[1] Pathogenicity predictions following ACMG Standards and Guidelines for interpretation of sequence variants All variants were scored as Pathogenic (P, **Red)**, Likely Pathogenic (LP, **Yellow**) and Variant of Unknown Significance (VUS, **Green**). Pathogenicity criteria for each variant are listed as PVS = Pathologic Very Strong; PS = Pathologic Strong; PM = pathologic Moderate; PS = Pathologic Supporting see (Richards et al., 2015) for more details.

[2] Reference SNP ID number per dbSNP (https://www.ncbi.nlm.nih.gov/snp). Searched in November 2019.

[3] Minor Allele Frequency (MAF) as reported by ExAc Aggregated Populations (121412 chromosomes) (http://exac.broadinstitute.org/). Searched in November 2019.The variant was scored PM2 if MAF <0.001.

[4] A variant was scored PP3, by using the in silico prediction program Mutationtaster (http://www.mutationtaster.org/),which bases pathogenicity on a combination criteria. A MutationTaster prediction of "disease causing" resulted in a PP3 score of the vairant.

[5] A variant was scored PP4 if the affected subjects's phenotype or family history is highly specific for HPS. The references describing PP4 are indicated in the "Comments" column.

[6] To prove pathogenicity of this variant according to ACMG Guidelines, experimental evidence needs to be acquired and can include effect on protein expression, BLOC assembly, mRNA splicing (PS3 score) and in some cases testing parents to demonstrate occurrence in trans with a pathogenic variant (PM3) is sufficient.

7 This *HPS1* variant was identified in one unreported subject of *Canadian-German-Irish-Scottish-Swedish-Ukrainian* descent from the NIH HPS cohort. This subject is compound heterozygous for c.1080C>G and c.1189delC.

8 These 2 HPS1 missense variants occur heterozygous on the same allele in two HPS siblings of our NIH cohort, their cells showed aberrant BLOC-3 assembly (Nazarian et al., 2008). The p.Val547Leu variant is predicted to be more pathogenic than p.Arg549Cys. In vitro studies showed that the HPS1 protein with the p.Val547Leu variant was unstable and prevents proper BLOC-3 formation (Carmona-Rivera et al., 2013). No *HPS1* coding/splice site was detected on the other allele, but that allele appeared to be subject to non-sense mediated mRNA decay (on cDNA analysis), suggesting a (intronic) gene-truncation variant on that allele.

9 This *HPS1* variant was found heterozygous in one unreported subject of *English-Irish-Scottish* in the NIH HPS cohort. This subject is compound heterozygous for c.1189delC and c.1937A>G.

10 This *AP3B1* variant activates a cryptic donor splice and causes a deletion of 112bp within exon 23 on the mRNA level, resulting in a frame shift and a premature termination codon p.Val900Thrfs*63 (de Boer et al., 2017).

11 Two siblings were both homozygous for these 2 missense *HPS5* variants (hemizygosity was excluded) [Huizing et al., 2004]. The high MAF (including homozygotes) low pathogenicity predictions of p.Thr1098Ile in contrast to high pathogenicity predictions of p.Leu624Arg as well as recent identification of this variant in other HPS-5 cases in trans with a pathogenic variant (Michaud et al., 2017; Lasseaux et al., 2018) classifies p.Leu624Arg as likely pathogenic and p.Thr1098Ile as a benign SNP.

Supplemental Table S2: Predicted Splicing Effects of HPS Variants in Proximity of Splice Junctions [1]

No	Variant [1]	Loca-tion	Exp. Splice Effect [2]	Predicted Splice Effect [3]		Comments	References [4]
				wt	var		
Reported Intronic Variants							
HPS1	c.255+5G>A	in 4	Yes	99%	51%	Demonstrated to result in a 17-bp deletion and a frameshift p.Tyr81Leufs*38	(Ghafouri-Fard et al., 2016)
HPS1	c.398+2T>C	in 5	ND	75%	0%	Predicted to cause splicing defect	*novel* [5]
HPS1	c.398+5G>A	in 5	Yes	75%	0%	Demonstrated to result in skipping of exon 5	(Suzuki et al., 2004)
HPS1	c.507+1G>A	in 6	Yes	57%	0%	Demonstrated to result in use of an alternative intronic splice donor site (72%), 43-bp into intron 6, causing a frameshift of the coding region, and premature stop codon 26 amino acids downstream of the variant	(Natsuga et al., 2005)
HPS1	c.868-2A>G	in 9	ND	83%	0%	Predicted to cause splicing defect	(Wei et al., 2019)
HPS1	c.988-1G>T	in 11	Yes	99%	0%	Demonstrated to result in exon 12 in-frame skipping and removing 56 amino acids from the protein	(Vincent et al., 2009)
HPS1	c.1744-2A>C	in 17	Yes	99%	0%	Predicted to cause splicing defect	(Oetting and King, 1999; Hermos et al., 2002)
HPS1	c.1857+2T>C	in 18	ND	91%	0%	Predicted to create an alternative intronic splice site 4-bp into intron 18 (94%), resulting in a frameshift of the coding region	(McElvaney et al., 2018)
HPS1	c.1858-1G>A	in 18	ND	96%	53%	Predicted to create alternative splice site (53%) 1-bp into exon 18, resulting in a frameshift of the coding region	*novel* [5]
HPS1	c.1941-2A>G	in 19	ND	98%	0%	Predicted to cause splicing defect	(Okamura et al., 2019)
AP3B1	c.1095+5G>A	in 10	ND	100%	50%	Predicted to weaken the splice site, a cryptic splice site 19-bp into intron 10 (28%) may get activated	(Chiang et al., 2010)
AP3B1	c.1168-1G>C	in 11	Yes	98%	0%	Demonstrated to cause skipping of exon 12. Initially reported as a 21-amino acid deletion, later found to be caused by skipping of exon 12	(Dell'Angelica et al., 1999; Gochuico et al., 2012)
AP3B1	c.1473+6T>C	in 14	Yes	90%	27%	Demonstrated to activate a cryptic splice site 39-bp into intron 14, resulting in a premature stop codon	(Clark et al., 2003)
HPS3	c.712+2T>C	in 2	Yes	99%	0%	Predicted to cause splicing defect. Cells of this subject showed destabilized BLOC-2 assembly	(Wei et al., 2016)
HPS3	c.885-1G>A	in 3	ND	55%	0%	Predicted to cause a splicing defect	(Thielen et al., 2010)
HPS3	c.1163+1G>A	in 5	Yes	79%	0%	Demonstrated to cause skipping of exon 5	(Huizing et al., 2001)
HPS3	c.1691+1G>A	in 9	ND	81%	0%	Predicted to cause exon 9 skipping, similar as c.1691+2T>G	*novel* [5]
HPS3	c.1691+2T>G	in 9	Yes	81%	0%	Demonstrated to cause skipping of exon 9	(Huizing et al., 2001)
HPS3	c.2482-2A>G	in 13	Yes	92%	0%	Demonstrated to cause skipping of exon 13	(Huizing et al., 2001)
HPS3	c.2589+1G>C	in 14	Yes	100%	0%	Demonstrated to cause skipping of exon 14	(Huizing et al., 2001)
HPS3	c.2589+1G>T	in 14	ND	100%	0%	Predicted to cause exon 14 skipping, similar as c.2589+1G>T	*novel* [5]

HPS3	c.2888-1612G>A	in 16	Yes	0%	87%	This deep-intronic variant creates a strong (87%) consensus splice site, inserting of 89-bp in the subject's *HPS3* mRNA	(Huizing et al., 2001)
HPS4	c.276+5G>A	in 4	ND	99%	61%	Predicted to cause splicing defect	(Yousaf et al., 2016)
HPS4	c.596+1G>A	in 7	ND	81%	20%	Predicted to weaken the splice site	(Okamura et al., 2019)
HPS4	c.597-2A>T	in 7	ND	76%	0%	Predicted to cause splicing defect	(Jones et al., 2012)
HPS4	c.706+1G>A	in 9	ND	99%	5%	Predicted to cause splicing defect	*novel* [5]
HPS4	c.1713+5G>C	in 11	ND	98%	0%	Predicted to cause splicing defect	(Wei et al., 2019)
HPS5	c.285-10A>G	in 4	Yes	23%	26%	Reported to activate a cryptic splice site, leading to an in-frame insertion of 9-bp and reduced expression of HPS5	(Stephen et al., 2017)
HPS5	c.1634+1G>A	in 13	Yes	97%	0%	Reported to result in skipping of exon 13	(Carmona-Rivera et al., 2011)
HPS5	c.3058+3A>G	in 21	ND	99%	78%	Predicted to cause a splicing defect	(Michaud et al., 2017)
Exonic (Missense) Variants in Proximity of Splice Junctions [4]							
HPS1	c.2T>A/. p.Met1Lys	ex 3	ND	92%	75%	Predicted to weaken the nearby splice site at c.1	(Lasseaux et al., 2018)
HPS1	c.505G>A/ p.Glu169Lys	ex 6	ND	57%	7%	Occurs 3-bp from splice junction and predicted to weaken the splice site. No experimental evidence is available. An alternative intronic splice site (72%), inserting 43-bp of intron 6 sequence may be used as reported for variant c.507G>A occurring in the same codon	(Merideth et al., 2009; Khan et al., 2016)
HPS1	c.507G>A/ p.Glu169Glu	ex 6	Yes	57%	0%	Occurs at a 3' splice junction. Reported to result in use of an alternative intronic splice site (72%), inserting 43-bp of intron 6 sequence, resulting in frameshift and 26 novel amino acids followed by a stop codon	(Merideth et al., 2009)
HPS1	c.937G>A/ p.Gly313Ser	ex 10	Yes	100%	86%	Occurs at a 3' splice junction. Reported to result in use of a cryptic intronic splice site 144-bp downstream, producing 11 novel amino acids followed by a stop codon	(Carmona-Rivera et al., 2011)
HPS1	c.1342T>C/ p.Trp448Arg	ex 14	ND	95%	95%	Predicted to not affect nearby splice site at c.1336	(Yousaf et al., 2016)
HPS1	c.1937A>G/ p.Tyr646Cys	ex 19	ND	81%	55%	Predicted to weaken the nearby splice site at c.1940	*novel* [5]
AP3B1	c.2702C>G/ p.Ser901Cys	ex 23	Yes	0%	4%	Demonstrated to activate a cryptic donor splice site and cause a mRNA deletion of 112bp, resulting in a frame shift and a premature termination codon p.Val900Thrfs*63	(de Boer et al., 2017)
HPS3	c.1509G>A/ p.Met503Ile	ex 8	ND	8%	0%	Predicted to affect splicing of exon 8. Note that the exon 8/intron 8 splice site is weak (8%)	(Yousaf et al., 2016)
HPS4	c.272T>C/ p.Leu91Pro	ex 4	ND	99%	99%	Predicted to not affect nearby splice site at c.276	(Bastida et al., 2019)
HPS4	c.803G>A/ p.Arg268Lys	ex 10	ND	92%	0%	Predicted to cause splicing defect	(Lasseaux et al., 2018)

HPS5	c.219G>A/ p.Arg73Arg	ex 3	ND	100%	82%	Predicted to cause splicing defect at c.219	(Michaud et al., 2017)
HPS5	c.1871T>G/ p.Leu624Arg	ex 16	ND	96%	97%	Predicted to not affect nearby splice site at c.1863	(Huizing et al., 2004; Michaud et al., 2017)

[1] Exonic cDNA variants resulting in protein variants located within 10-bp from a splice junction are listed.
[2] Experimental (Exp.) Splice Effect: as reported in literature; ND = Not Done. Yes = Splice site effect was demonstrated experimentally.
[3] Using Human Splice Site Prediction by Neural Network (http://www.fruitfly.org/seq_tools/splice.html), comparing wild type (wt) sequence to variant (var) sequence. The NNSPLICE 0.9 version (January 1997) of this splice site predictor was used (in November 2019) (Reese et al., 1997). Predicted Splice Site Scores are visualized as follows: **Green** (high splice site prediction >85%), **Yellow** (medium splice site prediction 55-85%), **Red** (low splice site prediction <55%).
[4] See main text for full references.
[5] *novel* = previously unreported variant detected in the NIH HPS cohort.

Supplemental Table S3: Frequent Nonsynonymous SNPs (MAF>0.001) in Human HPS Genes

Gene	dbSNP ID [1]	Variant [2]	MAF (gnomAD) [3]
HPS1	rs58548334	c.11T>C; p.Val4Ala	0.0322
	rs7914192	c.27G>C; p.Glu9Asp	0.0017
	rs142893758	c.478C>T; p.Arg160Trp	0.0014
	rs1801286	c.557C>T; p.Ala186Val	0.0042
	rs56378825	c.779G>C; p.Arg260Gln	0.0023
	rs11592273	c.847G>T; p.Gly283Trp	0.0491
	rs74154475	c.848G>C; p.Gly283Ala	0.0017
	rs2296434	c.1472C>G; p.Pro491Arg	0.1071
	rs2296436	c.1808A>G; p.Gln603Arg	0.1014
	rs139061260	c.1888G>A; p.Val630Ile [5]	0.0013
AP3B1	rs142025324	c.1069A>G; p.Ile357Val	0.0018
	rs6453373	c.1754T>A; p.Val585Glu	0.8661
	rs113301033	c.2042A>G; p.Glu681Gly	0.0013
	rs62001050	c.2324T>A; p.Ile775Lys	0.0022
	rs199702315	c.2409_2411del; p.Lys804del [6]	0.0138
	rs146624866	c.2585C>T; p.Thr862Ile	0.0017
	rs139344924	c.2661C>A; p.Phe887Leu	0.0078
	rs146503597	c.2995G>A; p.Val999Met	0.0041
	rs111935323	c.2873_2875del; p.Ala1008del [6]	0.0115
HPS3	rs199663930	c.158A>G; p.Gln53Arg	0.0011
	rs34388030	c.823G>A; p.Glu275Lys	0.0019
	rs149640235	c.1366A>G; p.Ile456Val	0.0015
	rs78336249	c.2215G>A; p.Gly739Arg	0.0099
	rs150765088	c.2527G>A; p.Val843Ile	0.0012
HPS4	rs149830675	c.250A>G; p.Ile84Val	0.0044
	rs713998	c.686A>G; p.Glu229Gly	0.8432
	rs77597168	c.710C>T; p.Ala237Val	0.0015
	rs34962745	c.751A>T; p.Thr251Ser	0.0070
	rs114685298	c.1060T>A; p.Ser354Thr	0.0028
	rs116769827	c.1061C>G; p.Ser354Cys	0.0028
	rs2014410	c.1327C>G; p.Leu443Val	0.3703
	rs147435410	c.1396C>T; p.Arg466Cys	0.0015
	rs5752330	c.1654G>A; p.Val552Met	0.8431
	rs1894706	c.1816C>T; p.His606Tyr	0.8770
	rs1894704	c.1875G>T; p.Gln625His	0.8769
	rs146303784	c.1947G>A; p.Met649Ile	0.0013
HPS5	rs147053126	c.241G>A; p.Ala81Thr	0.0016

	rs7128017	c.1249C>A; p.Leu417Met	0.1359
	rs143784823	c.1501G>A; p.Gly501Arg	0.0047
	rs149677540	c.1609G>T; p.Val537Leu	0.0029
	rs144875223	c.2537C>T; p.Pro846Leu	0.0044
	rs61755718	c.3045G>A; p.Met1015Ile	0.0051
	rs17853184	c.3046G>A; p.Glu1016Lys	0.0013
	rs116394570	c.3217A>G; p.Met1073Val	0.0012
	rs75482179	c.3229C>T; p.Arg1077Trp	0.0015
	rs61884288	c.3293C>T; p.Thr1098Ile [7]	0.0237
HPS6	rs371307947	c.337C>T; p.Arg113Trp [8]	0.0023
	rs199816481	c.398C>T; p.Ala133Val	0.0028
	rs200584437	c.632G>C; p.Gly211Ala	0.0047
	rs36078476	c.698T>G; p.Leu233Arg	0.0072
DTNBP1	rs17470454	c.814C>T; p.Pro272Ser	0.0437
	rs73369534	c.874A>G; p.Arg292Gly	0.0086
	rs74907982	c.886C>T; p.Pro296Ser	0.0041
BLOC1S3	rs75792246	c.322C>G; p.Leu108Val	0.0266
	rs201502372	c.478G>T; p.Val160Leu	0.0016
BLOC1S6	rs145762743	c.34G>A; p.Ala12Thr	0.0027
AP3D1	rs34569645	c.1621G>A; p.Gly541Arg	0.1242
	rs25673	c.3400A>G; p.Ile1134Val	0.1239

[1] Reference SNP ID number per dbSNP (https://www.ncbi.nlm.nih.gov/snp). Searched in November 2019.
[2] Nomenclature according to the longest mRNA splice variant, similar to that used in Tables in the main text.
[3] Minor Allele Frequency as reported by gnomAD (https://gnomad.broadinstitute.org/) and ClinVar (https://www.ncbi.nlm.nih.gov/clinvar/). Searched in November 2019.
[4] This pathogenic *HPS1* frameshift variant occurs frequent in HPS subjects.
[5] This *HPS1* missense variant was found heterozygous in a cohort of familiar pulmonary fibrosis cases (Stearman et al., 2019).
[6] Two in-frame *AP3B1* 3-bp deletions with high MAF (including homozygotes) occur, which should be considered as non-pathogenic polymorphisms when encountered in *AP3B1* genetic analysis.
[7] This *HPS5* variant occurred on the same allele as another *HPS5* missense variant (p.Leu624Arg) in two siblings were both (Huizing et al., 2004). The high MAF (including homozygotes) low pathogenicity predictions of p.Thr1098Ile in contrast to high pathogenicity predictions of p.Leu624Arg as well as recent identification of this variant in other HPS-5 individuals (Michaud et al., 2017) classified p.Leu624Arg as pathogenic and p.Thr1098Ile as a benign SNP.
[8] This *HPS6* variant of uncertain significance was reported as a disease causing variant in one subject (Lasseaux et al., 2018).

Supplemental Table S4: Reported Variants in Human HPS Genes Associated with Traits other than HPS

mRNA Variant	Amino Acid Variant	Exon/ Intron	dbSNP ID [1] MAF gnomAD [2]	Comments
HPS1 (NM_000195.5)				
c.1286G>A	p.Arg429His	ex 13	rs201728087 0.00026	Reported heterozygous in a subject with familial pulmonary fibrosis (Stearman et al., 2019)
c.1395G>A	p.Trp465*	ex 14	-	Reported ***homozygous*** in a Saudi-Arabian subject with absent nails. No other clinical details or reference to the HPS phenotype was reported (Abouelhoda et al., 2016).
c.1888G>A	p.Val630Ile	ex 19	rs139061260 0.00135	Reported heterozygous in a subject with familial pulmonary fibrosis (Stearman et al., 2019)
c.1915G>A	p.Gly639Ser	ex 19	rs116698870 0.00053	Reported heterozygous in a subject with familial pulmonary fibrosis (Stearman et al., 2019)
AP3B1 **(**NM_003664.4)				
c.787G>T	p.Gly263Cys	ex 8	-	Occurs at a splice junction and is predicted to weaken the intron 7/exon 8 spice site. Reported heterozygous in a subject with primary immunodeficiency (Gallo et al., 2016)
c.1075A>G	p.Thr359Ala [4]	ex 10	rs148160411 0.00003	Reported heterozygous in individuals with HLH (Gao et al., 2015; Miao et al., 2019) [4]
c.1254insA	p.Gln419Thrfs*22	ex 13	-	Reported heterozygous in a subject with HLH (Tesi et al. 2015)
c.1393A>G	p.Ile465Val	ex 14	-	Reported heterozygous in two unrelated subjects with primary immunodeficiency disorder (Chi et al., 2018)
c.1468A>G	p.Ile490Val	ex 14	-	Reported heterozygous in a subject with HLH (Mukda et al., 2017)
c.2626C>T	p.Arg876*	ex 23	rs773298750 0.000004	Reported heterozygous in a subject with HLH (Tesi et al. 2015)
c.2671C>T	p.Gln891*	ex 23	rs780503803 0.000004	Reported heterozygous in a subject with HLH (Miao et al., 2019)
c.3197C>T	p.Ser1066Phe	ex 27	rs764100439 0.00007	Reported heterozygous in a subject with HLH (Xu et al., 2017)
HPS3 (NM_032383.5)				
c.796G>A	p.Glu266Lys	ex 3	-	Occurred heterozygous *de novo* in a proband with schizophrenia (Fromer et al., 2014)
HPS4 (NM_022081.5)				
c.1102insG	p.Asp368Glyfs*4	ex 11	-	Reported heterozygous in a subject with sporadic pulmonary fibrosis (Deng et al., 2018)
c.1396C>T	p.Arg466Cys	ex 11	rs147435410 0.00150	Reported heterozygous in a subject with familial pulmonary fibrosis (Stearman et al., 2019)
c.1966_1967insAC	p.Ala657Argfs*46	ex 14	rs752827715 0.000008	Reported heterozygous in a subject with familial pulmonary fibrosis (Stearman et al., 2019)
HPS6 (NM_024747.5)				
c.2326T>C	p.*776Arg	ex 1	rs200206362 0.00014	Reported heterozygous in a subject with *BRCA1* and *BRCA2*-negative breast cancer (Shahi et al., 2019)
DTNBP1 (NM_032122.4)				

c.286G>T	p.Glu96*	ex 5	-	Reported heterozygous in a subject with sporadic pulmonary fibrosis (Deng et al., 2018)
c.814C>T	p.Pro272Ser	ex 10	rs17470454 0.04371	This variant with a high MAF (0.04358, including homozygotes) was reported as a low susceptibility allele for colorectal cancer (Webb et al., 2006)
AP3D1 (NM_001261826.3)				
c.273+1G>T	IVS3+1G>T	in 3	-	Reported de novo in a Japanese proband with autism spectrum disorder (Takata et al., 2018)
c.1217A>G	p.Gln406Arg	ex 13	-	Reported *de novo* in a in a proband with autism spectrum disorder (Iossifov et al., 2014)
c.1815C>G	p.Asn605Lys	ex 16	-	Reported *de novo* in a in a proband with schizophrenia (Fromer et al., 2014)

1 Reference SNP ID number per dbSNP (https://www.ncbi.nlm.nih.gov/snp). Searched in November 2019.
2 Minor Allele Frequency as reported by gnomAD (https://gnomad.broadinstitute.org/) and ClinVar (https://www.ncbi.nlm.nih.gov/clinvar/). Searched in November 2019.
3 The AP3B1 p.Thr359Ala variant occurred heterozygous in one individual in parallel with a heterozygous variant in *UNC13D* (c.1232G>A; p.Arg411Gln). A synergistic function of the heterozygous variants in *AP3B1* and *UNC13D* was suggested to underlie the defect in cytotoxicity of natural killer (NK) cells and cytotoxic T-lymphocytes, which caused a fatal progressive hemophagocytic lymphohistiocytosis (HLH) in this individual (Gao et al., 2015). The same AP3B1 variant p.Thr359Ala was also found heterozygous in 3 Eastern-Asian subjects with HLH, and suggested to contribute to their phenotype (Miao et al., 2019). The same heterozygous *UNC13D* variant (p.Arg411Gln) was previously reported to act synergistically with a heterozygous *PRF1* variant, causing cytotoxic lymphocyte degranulation (K. Zhang et al., 2014).