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Supplemental Data

A Population-Based Study of Autosomal-Recessive Disease-Causing Mutations in a Founder Population

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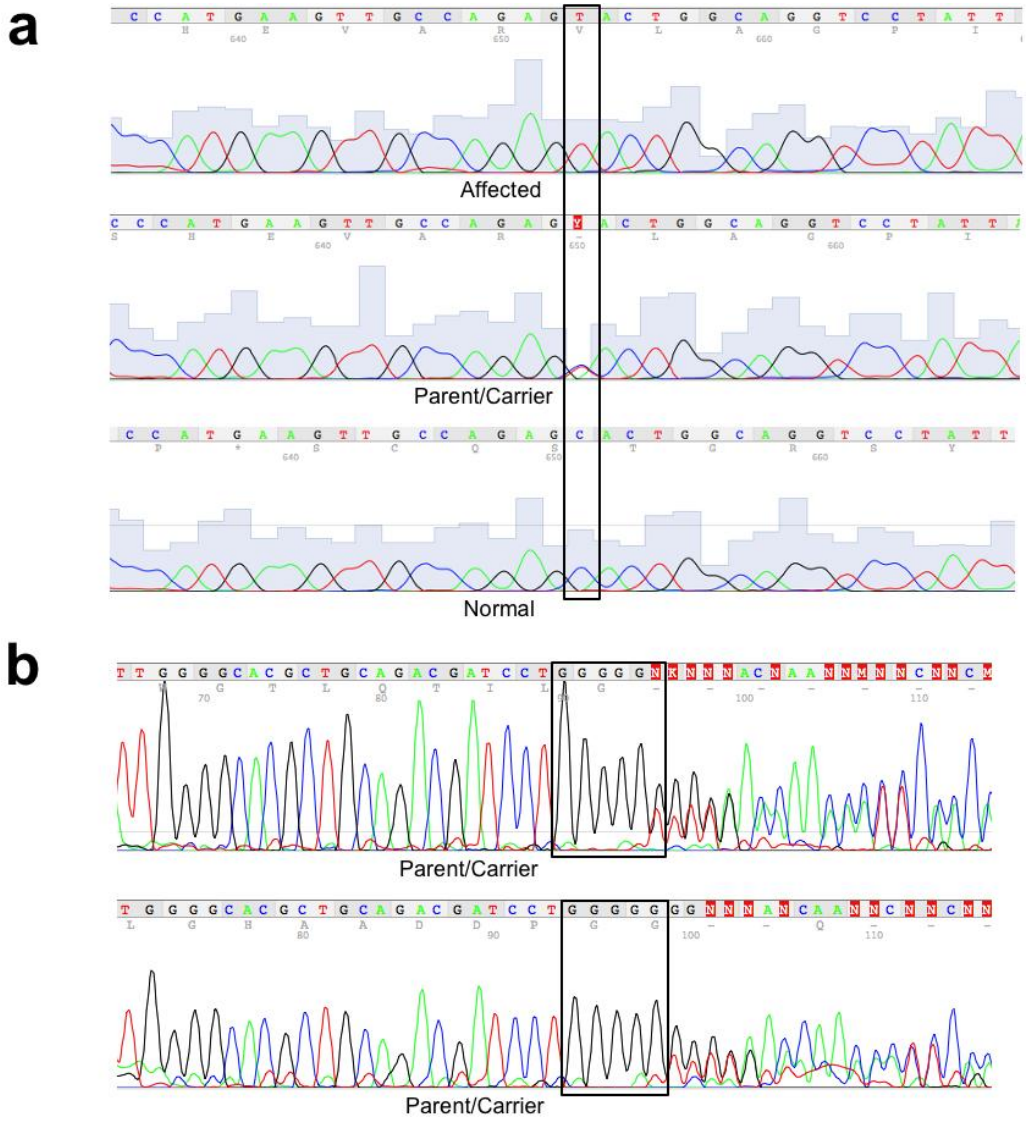
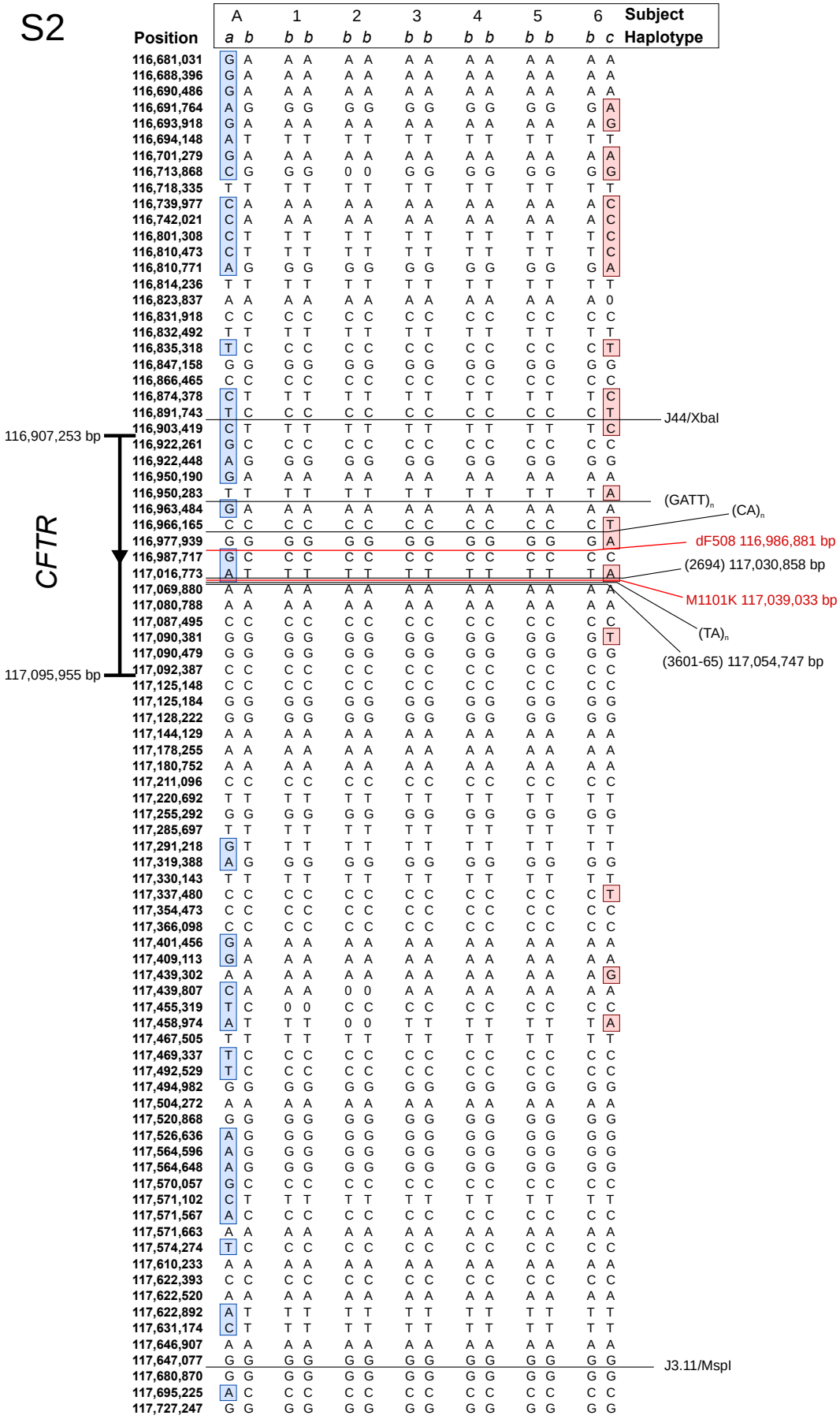


Figure S1. Sanger Sequencing Traces for (A) *TYR* p.Cys91Tyr in an Adult with Albinism, a Parent of Children with Albinism, and a Normal Control and (B) *GJB2* c.35delG in Both Parents of Deaf Children

TYR p.Cys91Tyr is novel, although Chaki et al. reported an albinism-causing mutation, p.Cys91Ser, at the same amino acid.[1] This residue is highly conserved and may disrupt disulfide bond formation. The GJB2 c.35delG mutation is the most common cause of nonsyndromic AR deafness in Europeans.[2]

S2


A 1 2 3 4 5 6 Subject
Position a b b b b b b b b b b b c Haplotype
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116,690,486 G A A A A A A A A A A A A
116,691,764 A G G G G G G G G G G G A
116,693,918 G A A A A A A A A A A A G
116,694,148 A T T T T T T T T T T T T
116,701,279 G A A A A A A A A A A A A
116,713,868 C G G G 0 0 G G G G G G G
116,718,335 T T T T T T T T T T T T T
116,739,977 C A A A A A A A A A A A C
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116,801,308 C T T T T T T T T T T T C
116,810,473 C T T T T T T T T T T T C
116,810,771 A G G G G G G G G G G G A
116,814,236 T T T T T T T T T T T T T
116,823,837 A A A A A A A A A A A A 0
116,831,918 C C C C C C C C C C C C C
116,832,492 T T T T T T T T T T T T T
116,835,318 T C C C C C C C C C C C T
116,847,158 G G G G G G G G G G G G G
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J44/XbaI
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(GATT)n
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(CA)n
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CFTR
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(TA)n
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(3601-65) 117,054,747 bp
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117,354,473 C C C C C C C C C C C C C
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117,409,113 G A A A A A A A A A A A A
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J3.11/MspI
117,680,870 G G G G G G G G G G G G G
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117,727,247 G G G G G G G G G G G G G

Figure S2. Haplotypes of One *CFTR* p.Met1101Lys + p.Phe508del Compound Heterozygote (A) and Six *CFTR* p.Met1101Lys Homozygotes (1–6) across a ~1 Mb Region Surrounding *CFTR*

Positions (build36/hg18) of the two Hutterite CF mutations, p.Met1101Lys and p.Phe508del, as well as the approximate positions of polymorphic markers used in an early haplotype analysis of Met1101Lys haplotypes[3] are shown on the right. The haplotypes are designated *a*, *b*, and *c* to maintain consistency with Zielenski et al. Subject A is a compound heterozygote for p.Met1101Lys and p.Phe508del (on haplotype *a*), subjects 1-5 are homozygous for p.Met1101Lys on haplotype *b*, and subject 6 is homozygous for p.Met1101Lys on haplotypes *b* and *c*. Blue boxes highlight the SNPs at which haplotype *a* differs from haplotype *b*, and red boxes highlight differences between haplotypes *c* and *b*. Zielenski et al. proposed that haplotype *c* was derived from haplotype *b* through a recombination within *CFTR* between marker 2694 and p.Met1101Lys because the markers distal to p.Met1101Lys that were used in their study were identical on haplotypes *b* and c.[3] However, the additional SNP genotypes in our study revealed four mismatches between *b* and *c* distal to p.Met1101Lys, suggesting that *c* is either the result of two recombination that left almost none of *b* on the new haplotype, or that *c* is a distinct p.Met1101Lys -bearing haplotype that was independently introduced by a second Hutterite founder.

S3

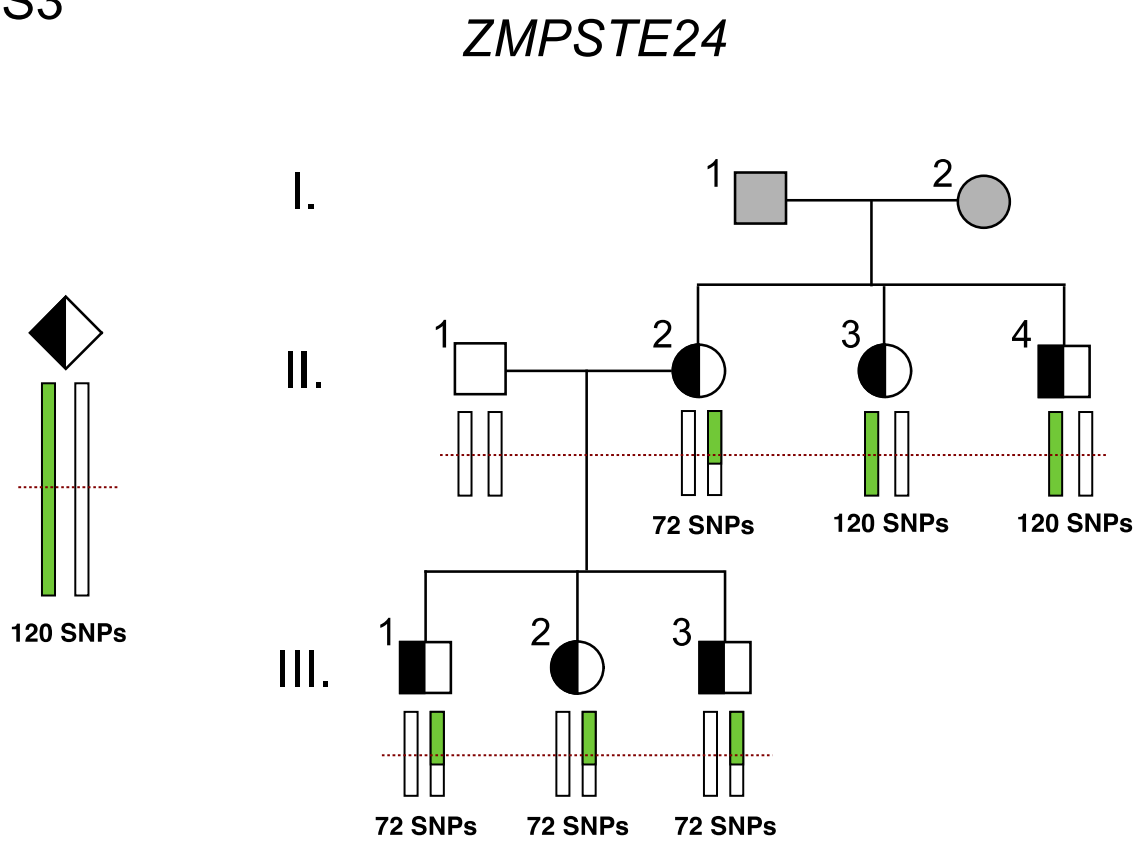

Figure S3. Pedigree and Haplotypes of Family Carrying *ZMPSTE24* c.1085dupT on a Recombinant Haplotype

The diamond carrier on the left represents the consensus haplotype (green) shared IBS≥1 by all carriers of this deletion except the individuals shown in this figure. White chromosomes represent unknown haplotypes. The dashed lines represent the approximate location of the mutation on the haplotype. In this family, the mother (II.2) inherited a small portion of the consensus haplotype while two of her siblings (II.3, II.4) inherited the full consensus haplotype, allowing us to infer that she inherited a recombinant version of the shared haplotype that bears the deletion and passed it on to three of her children (III.1-3).

Table S1. Summary of AR Diseases Reported in the Hutterites (Modified and Updated from Boycott et al. 2008)

Name of Disease	Abbrev.	OMIM	Gene/Locus	Chr	Mutation (Common Name)	HGVS Name(s)	rsID	In This Study	Refs.
Bardet-Biedl syndrome	BBS	209900	BBS2	16	IVS3-2A>G	NM_031885.3:c.472-2A>G	rs137854887	Yes	[4]
Bowen-Conradi syndrome	BCS	211180	EMG1	12	p.D86G	NM_006331.7:c.257A>G NP_006322.4:p.Asp86Gly	rs74435397	No	[5]
Carnitine Palmitoyltransferase I deficiency	CPT1	255120	CPT1A	11	p.G710E	NM_001876.3:c.2129G>A NP_001867.2:p.Gly710Glu	rs80356780	No	[6,7]
Cataracts (juvenile)	JC	212500	-	-	-	-	-	No	[8,9]
Cerebro-osteo-nephrodysplasia	COND	236450	-	-	-	-	-	No	[10-12]
Combined pituitary hormone deficiency	CPHD	262600	PROP1	5	c.301_302delAG	NM_006261.4:c.301_302delAG NP_006252.3:p.Ser101=fs	rs193922688	No	[13,14]
Cystic fibrosis	CF	219700	CFTR	7	p.F508del	NM_000492.3:c.1521_1523delCTT NP_000483.3:p.Ile507_Phe508?	rs113993960	Yes	[3,15]
					p.M1101K	NM_000492.3:c.3302T>A NP_000483.3:p.Met1101Lys	rs36210737	Yes	[3,15]
Dilated cardiomyopathy with ataxia syndrome	DCMA	610198	DNAJC19	3	IVS3-1G>C	NM_145261.3:c.130-1G>C	rs137854888	Yes	[16]
Dihydropyrimidine dehydrogenase deficiency	DPD	274270	-	-	-	-	-	No	[17]
Dopa-responsive dystonia	DRS	605407	TH	11	p.T494M	NM_199292.2:c.1481C>T NP_954986.2:p.Thr494Met	rs45471299	No	personal observation[18]
Dysequilbrium syndrome	DES-H	224050	VLDLR	9	deletion (199 kb)	-	-	No	[19,20]
Forehead, Abnormal Heart, Renal, Rhino	FARR	613680	16p13.3	-	-	-	-	No	[21]
Hypophosphatasia		241500	ALPL	1	p.G317D	NM_000478.4:c.1001G>A NP_000469.3:p.Gly334Asp	rs121918009	No	personal observation[18]
Iodide transporter defect	ITD	274400	SLC5A5	19	p.G395R	NM_000453.2:c.1183G>A NP_000444.1:p.Gly395Arg	rs121909180	No	[22,23]
Joubert syndrome/Meckel syndrome	JBTS	614424	TMEM237	2	p.R18X	NM_001044385.1:c.52C>T NP_001037850.1:p.Arg18Ter	rs199469707	Yes	[24]
Leigh disease		256000	-	-	-		-	No	[25]
Limb girdle muscular dystrophy 2H/Sarcotubular myopathy	LGMD2H	254110	TRIM32	9	p.D487N	NM_001099679.1:c.1459G>A NP_001093149.1:p.Asp487Asn	rs111033570	Yes	[26]
Limb girdle muscular dystrophy 2I	LGMD2I	607155	FKRP	19	p.L276I	NM_024301.4:c.826C>A NP_077277.1:p.Leu276Ile	rs28937900	Yes	[27]
Mandibulofacial dysostosis		248390	-	-	-	-	-	No	[28]
Maple syrup urine disease	MSUD	248600	-	-	-	-	-	No	personal observation[18]
Methylmalonic aciduria	MMA	251000	-	-	-	-	-	No	[29]
Morquio syndrome		253000	-	-	-	-	-	No	[30]
Nephronophthisis - juvenile	JNPHP	256100	NPHP1	2	290 kb deletion	-	-	No	personal

									observation[18]
Nonsyndromic mental retardation	MRT14	614020	TECR	19	p.P182L	NM_138501.5:c.545C>T NP_612510.1:p.Pro182Leu	rs199469705	Yes	[31]
Oculocutaneous albinism (type 1A)	OCA1A	203100	TYR	11	p.C91Y	NM_000372.4:c.272G>A NP_000363.1:p.Cys91Tyr	rs137854890	Yes	this study
Restrictive Dermopathy	RD	275210	ZMPSTE24	1	c.1085dupT	NM_005857.3:c.1078dupT NP_005848.2:p.Cys359_Phe360?fs	rs137854889	Yes	this study, [32]
Sensorineural deafness	DFNB1A	220290	GJB2	13	c.35delG	NM_004004.5:c.35delG NP_003995.2:p.Gly12Valfs	rs80338939	Yes	this study
Sitosterolemia	STSL	210250	ABCG8	2	p.S107X	NM_022437.2:c.320C>G NP_071882.1:p.Ser107Ter	rs137854891	Yes	[33]
Spinal muscular atrophy type III	SMA	253400	SMN1	5	del. including exon 7	-	-	Yes	[34]
Usher syndrome Type 1F	USH1F	602083	PCDH15	10	c.1471delT	NM_001142763.1:c.1101delT NP_001136235.1:p.Leu368fs*	rs199469706	Yes	[35]

Both the "common" mutation names are provided as well as HGVS names; in some cases the common name has become outdated as the coding sequence of the genes have been revised since the original mutation publication.

Table S2. List of AR Mutations and Genotyping Method Used for Carrier Screening in This Study

Disease	**Gene**	**Mutation**	**Genotyping Method**
Bardet-Biedl syndrome (BBS)	*BBS2*	IVS3-2A>G	SNaPshot
Cystic fibrosis (CF)	*CFTR*	p.Met1101Lys	SNaPshot and [36]
		p.Phe508del	SNaPshot and [36]
Dilated cardiomyopathy with ataxia syndrome (DCMA)	*DNAJC19*	IVS3-1G>C	SNaPshot
Joubert syndrome (JBTS)	*TMEM237*	p.Arg18Ter	Taqman[24]
Limb girdle muscular dystrophy 2H (LGMD2H)	*TRIM32*	p.Asp487Asn	SNaPshot
Limb girdle muscular dystrophy 2I (LGMD2I)	*FKRP*	p.Leu276Ile	TaqMan
Nonsyndromic deafness (DFNB1A)	*GJB2*	c.35delG	fluorescent PCR and fragment size analysis
Nonsyndromic mental retardation (NSMR)	*TECR*	p.Pro182Leu	TaqMan[31]
Oculocutaneous albinism Type 1A (OCA1A)	*TYR*	p.Cys91Tyr	OpenArray
Restrictive dermopathy (RD)	*ZMPSTE24*	c.1085dupT	fluorescent PCR and fragment size analysis
Sitosterolemia (STSL)	*ABCG8*	p.Ser107Ter	SNaPshot
Spinal muscular atrophy Type III (SMA)	*SMN1*	exon 7 del.	haplotype analysis[34]
Usher syndrome Type 1F (USH1F)	*PCDH15*	c.1471delT	SNaPshot

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