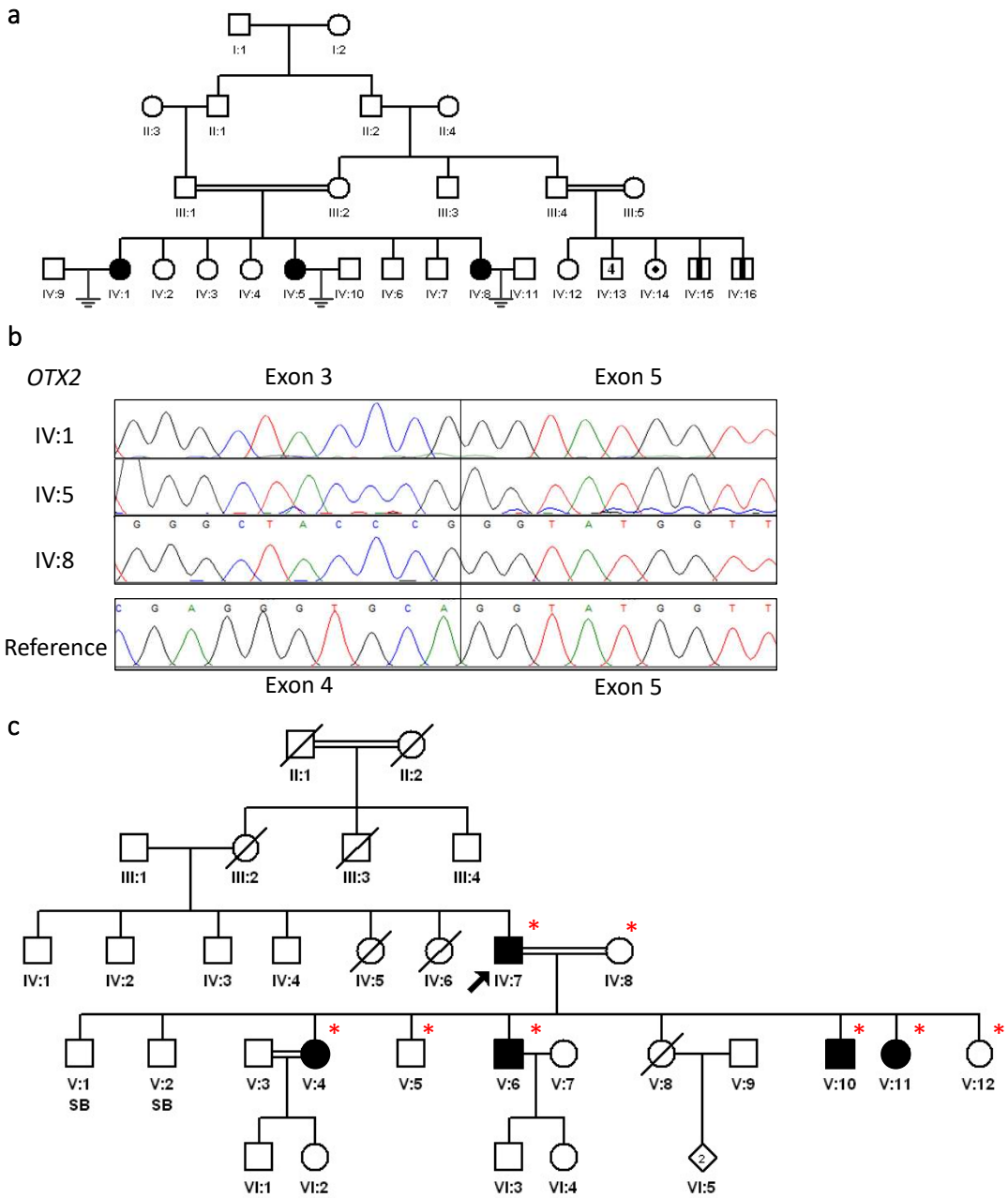
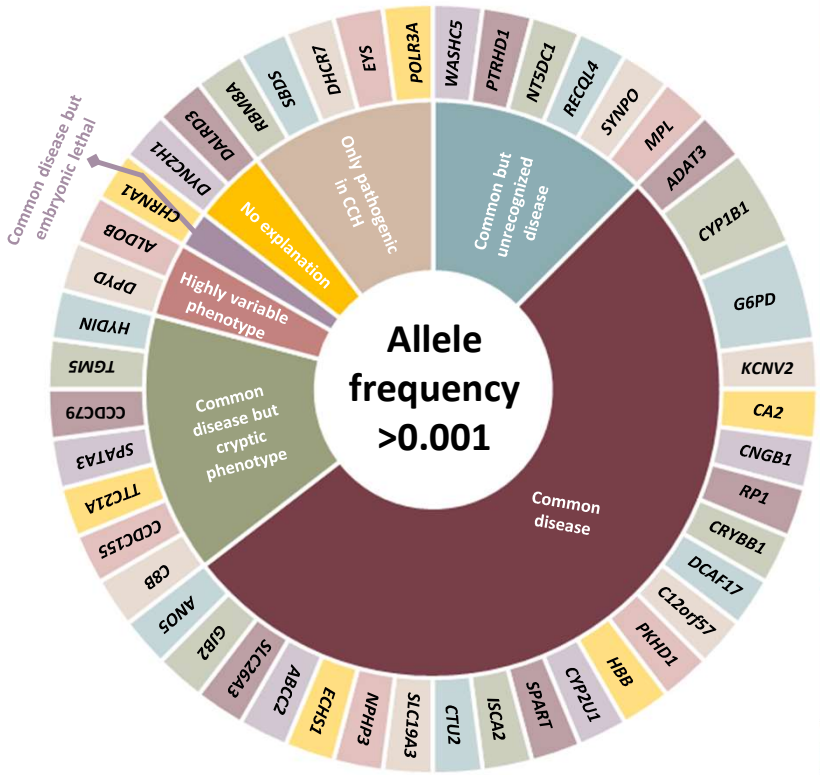


Supplementary Figure 1: Examples of families with novel allelic disorders and highly variable phenotypes.

a) Pedigree of F141 with three sisters (IV:1, IV:5, and IV9) affected with retinal dystrophy and infertility. Their maternal cousins have two brothers (IV:15 and IV:16) affected with Usher syndrome and a sister with epilepsy (IV:12). b) RT-PCR experiment using RNA extracted from the three affected sisters showed aberrant transcript in *OTX2* compared to control. Sequencing revealed that in the three affected sisters, there is skipping of exon 4 in *OTX2* compared to control. c) Pedigree of F7902 with a variant in *ALDOB*:NM_000035.4:c.448G>C;p.(Ala150Pro) displaying a surprisingly mild form of fructose intolerance (* indicates individuals with available DNA for testing).

a

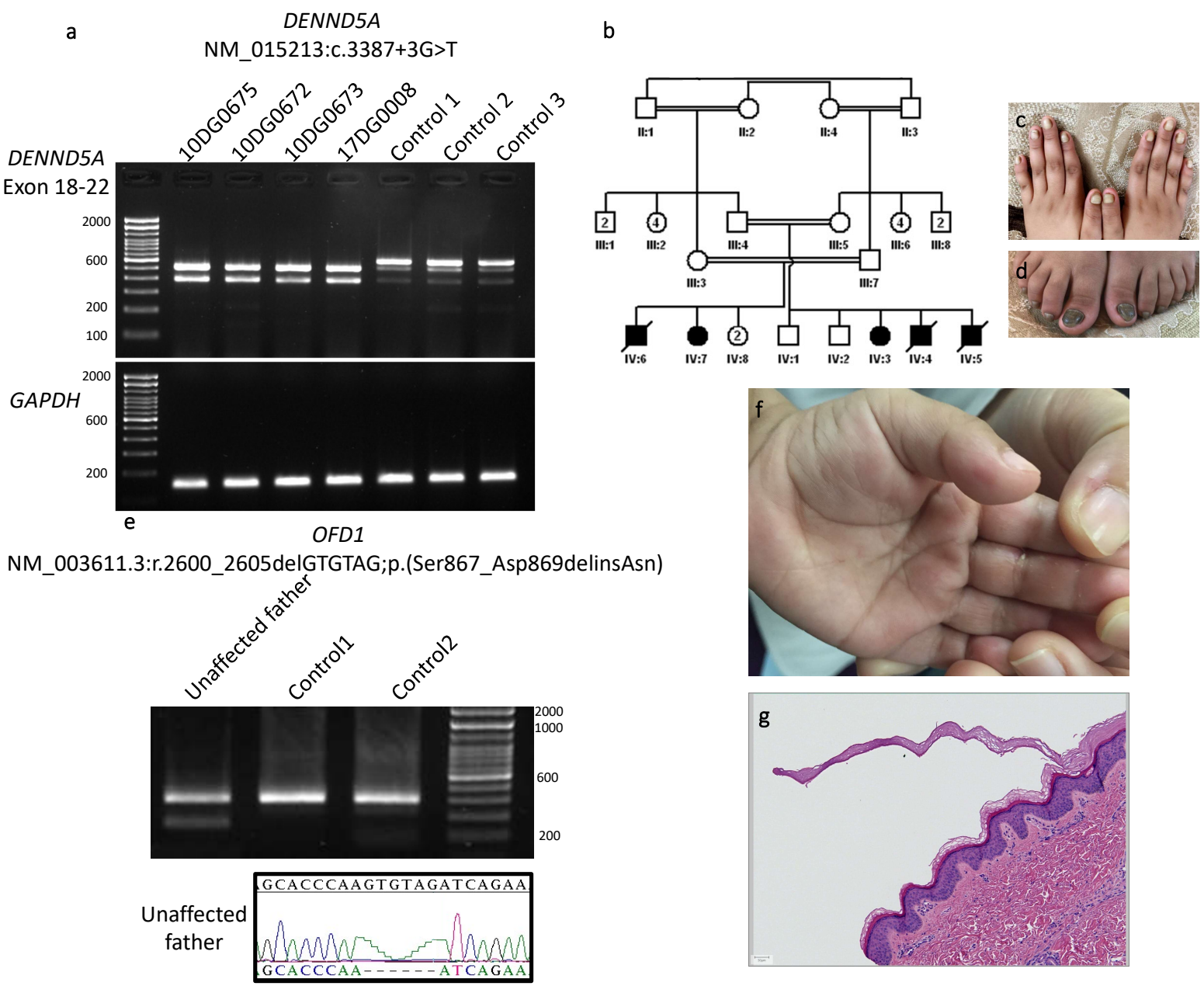


b

Justification	Allele frequency	Gene	Variant	# of families	Family IDs
Common but unrecognized disease	0.002435	*PTRHD1*	NM_001013663.1:c.365G>A;p.(Arg122Gln)	2	F1060, F5150
	0.001623	*RECQL4*	NM_004260.2:c.3128T>A;p.(Leu1043*)	1	F8226
	0.001127	*WASHC5*	NM_014846.3:c.2849A>G;p.(Lys950Arg)	1	F408
	0.001037	*SYNPO*	NM_001166209.1:c.2540C>T;p.(Pro847Leu)	1	F5878
	0.018073	*MPL*	NM_005373.3:c.317C>T;p.(Pro106Leu)	1	F9145
	0.001127	*NT5DC1*	NM_152729.3:c.1114T>C;p.(Ser372Pro)	1	F6301
Common disease	0.017931	*HBB*	NM_000518.4:c.20A>T;p.(Glu7Val)	3	F527, F4367, F4691
	0.012548	*G6PD*	NM_000402.4:c.653C>T;p.(Ser218Phe)	4	F5495, F8565, F6291, F8214
	0.012146	*CYP1B1*	NM_000104.3:c.182G>A;p.(Gly61Glu)	82	F76, F193, F205, F273, F368, F373, F375, F437, F438, F449, F457, F503, F504, F505, F514, F516, F517, F552, F553, F554, F562, F565, F566, F567, F569,F570, F579, F580, F597, F601, F608, F609, F643, F647,F649, F705, F785, F792, F806, F812, F843, F884, F923, F981, F1029, F1040, F4982, F1056, F1069, F1121, F1122, F1123, F1220, F1222,F1225, F1244, F1357, F1371, F1416, F1434, F1744, F1748, F1754, F1774, F1795, F1805, F1834, F1870, F1890, F1891, F2082, F2249, F2298, F2486, F2570, F2578, F2725, F3200, F4392, F4750, F4838, F8304
	0.009972	*G6PD*	NM_000402.3:c.233T>C; p.(Ile78Thr)	12	F900, F1793, F3182, F3310, F3432, F3612, F3908, F3924, F4138, F4424, F5028, F6352
	0.006765	*CNGB1*	NM_001297.4:c.2957A>T;p.(Asn986Ile)	4	F55, F2577, F2674, F2943
	0.005097	*ANO5*	NM_213599.2:c.172C>T;p.(Arg58Trp)	1	F6401
	0.002944	*ADAT3*	NM_138422.2:c.430G>A;p.(Val144Met)	19	F4, F72, F387, F619, F771, F1321, F2053, F2247, F2282, F2752, F3052, F3190, F3592, F4845, F5467, F8487, F6307, F6337, F6422
	0.002618	*CA2*	NM_000067.2:c.232+1G>A	9	F37, F1338, F2563, F2790, F3964, F4904, F5381, F5453, F6429
	0.002618	*SLC26A3*	NM_000111.2:c.559G>T;p.(Gly187*)	2	F6300, F7894
	0.002616	*PKHD1*	NM_138694.3:c.4870C>T;p.(Arg1624Trp)	6	F3304, F3680, F6585, F6732, F7541, F7542
	0.0023	*CYP2U1*	NM_183075.2:c.947A>T;p.(Asp316Val)	3	F590, F1104, F4124
	0.002074	*ABCC2*	NM_000392.3:c.2273G>T;p.(Gly758Val)	2	F5988, F6359
	0.001849	*RP1*	NM_006269.1:c.606C>A;p.(Asp202Glu)	4	F121, F537, F5841, F4277
	0.001713	*GJB2*	NM_004004.6:c.35delG;p.(Gly12Valfs*2)	1	F6386
	0.001489	*C12orf57*	NM_138425.4:c.1A>G;p.?	9	F342, F1086, F1418, F1841, F4311, F4334, F5516, F5954, F6281
	0.001488	*CRYBB1*	NM_001887.3:c.171delG;p.(Asn58Thrfs*107)	17	F23, F950, F1175, F1372, F1417, F1716, F1749, F1761, F1766, F1833, F1861, F3255, F3374, F4864, F4945, F5135, F5136
	0.001353	*SLC19A3*	NM_025243.3:c.1264A>G;p.(Thr422Ala)	4	F2830, F5413, F6400, F7923
	0.001263	*KCNV2*	NM_133497.3:c.427G>T;p.(Glu143*)	14	F185, F260, F543, F671, F702, F869, F915, F1229, F1348, F2327, F2694, F3356, F3392, F6460
	0.001263	*DCAF17*	NM_025000.4:c.436delC;p.(Ala147Hisfs*9)	7	F953, F1319, F2270, F2959, F3412, F3862, F8505
	0.001263	*NPHP3*	NM_153240.4:c.2694-2_2694-1delAG	10	F3637, F4198, F5994, F6592, F6676, F6928, F7524, F7531, F7532, F7533
	0.001127	*CYP1B1*	NM_000104.3:c.1405C>T;p.(Arg469Trp)	7	F449, F504, F566, F1122, F1222, F1779, F4838
	0.001127	*ECHS1*	NM_004092.4:c.88+5G>A	1	F5351
	0.001082	*SPART*	NM_001142294.1:c.988A>G;p.(Met330Val)	4	F1095, F4944, F5317, F5887
	0.001082	*CTU2*	NM_001012762.1:c.873G>A;r.738_873del;p.(Thr247Alafs*21)	5	F2713, F4238, F4491, F5528, F7794
	0.001039	*ISCA2*	NM_194279.4:c.229G>A;p.(Gly77Ser)	3	F1794, F3950, F8747
Common disease but cryptic phenotype	0.001983	*HYDIN*	NM_001270974.1:c.15217A>G;p.(Lys5073Glu)	1	F7426
	0.001533	*TTC21A*	NM_145755.2:c.1997A>G;p.(Asn666Ser)	1	F7166
	0.001443	*SPATA3*	NM_139073.3:c.373C>A;p.(Arg125Ser)	1	F7276
	0.001398	*CCDC155*	NM_144688.5:c.302T>C;p.(Met101Thr)	1	F6517
	0.001127	*CCDC79*	NM_001136505.1:c.733G>A;p.(Gly245Arg)	2	F7337, F7361
	0.010242	*TGM5*	NM_201631.4:c.1335G>C;p.(Lys445Asn)	1	F9185
	0.002615	*C8B*	NM_000066.2:c.1282C>T;p.(Arg428*)	1	F8448
Common disease but embryonic lethal	0.001262	*CHRNA1*	NM_000079.3:c.254T>C;p.(Leu85Pro)	2	F8595, F5922
Highly variable phenotype	0.003066	*DPYD*	NM_000110.3:c.257C>T;p.(Pro86Leu)	2	F169, F3966
	0.002705	*ALDOB*	NM_000035.3:c.448G>C;p.(Ala150Pro)	1	F7902
No explanation	0.001397	*DYNC2H1*	NM_001080463.1:c.1151C>T;p.(Ala384Val)	1	F5904
	0.001082	*DALRD3*	NM_001276405.1:c.1251C>A;p.(Tyr417*)	1	F6574
Only pathogenic in CCH	0.014411	*RBM8A*	NM_005105.4:c.*6C>G	1	F5228
	0.003652	*DHCR7*	NM_001163817.2:c.1A>G;p.?	1	F6277
	0.001082	*SBDS*	NM_016038.2:c.258+2T>C	1	F4212
	0.007348	*EYS*	NM_001142800.2:c.2137+1G>A	2	F8348 and F2084
	0.005418	*POLR3A*	NM_007055.4:c.1909+22G>A	1	F274

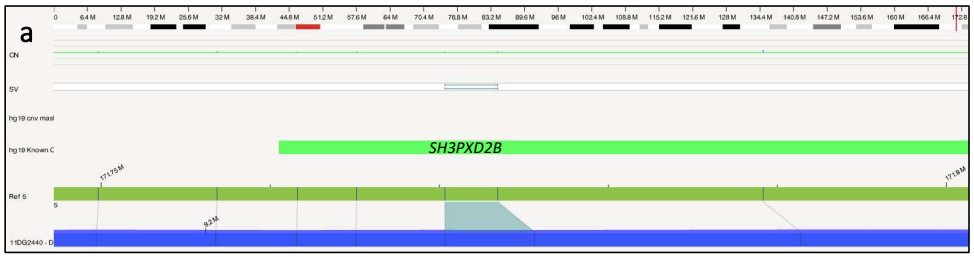
Supplementary Figure 2: Classification of disease-causing variants with Allele frequency above cut-off identified in our cohort.

a) Donut plot showing the contribution of each class of variants with AF above cut-off and the genes within these classes. b) Table detailing the local frequency of each variant, number of families identified with this variant, and the family IDs.



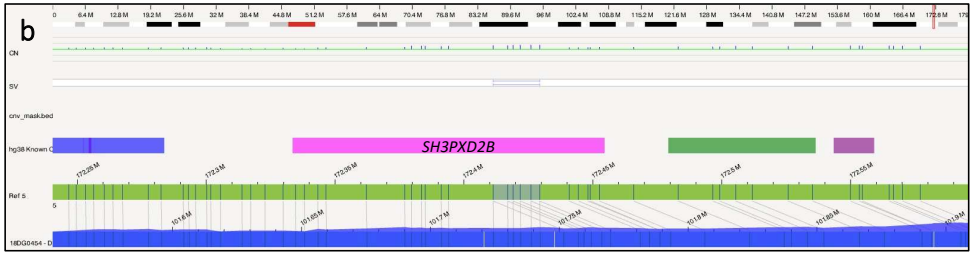
Supplementary Figure 3: Examples of families with variant-related challenges.

a) RT-PCR gel image showing aberrant transcript in individuals with a homozygous *DENND5A* splice variant compared to controls. The same aberrant transcript is observed in the unaffected sister 10DG0675. b) pedigree of family F5409 showing a deceiving penetrance situation where some affected individuals (IV:3 and IV:7) were diagnosed with club nails (c and d) and others were NIHF (IV:4, IV:5, and IV6). e) RT-PCR experiment using an unaffected individual with hemizygous splicing variant in *OFD1*. Compared to control, there is an aberrant transcript that was shown to cause a small in-frame deletion. f and g) Clinical images of patient F9185 showing the skin phenotype and typical intra-epidermal cleft on histopathology, respectively. All data presented in a, e, and g are representative images of at least two experiments.



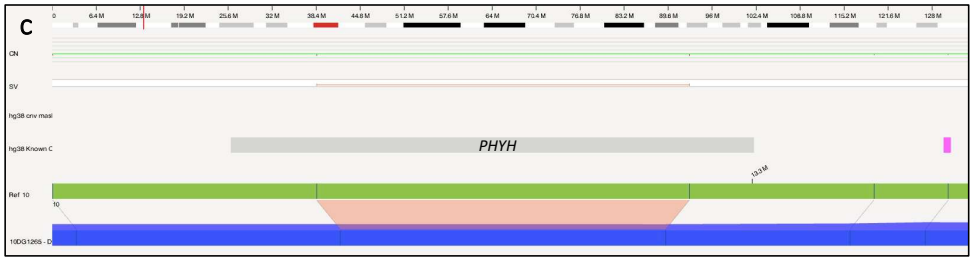
11DG2440

Type of SV	Insertion
Location	chr5:171,770,324 - 171,773,463
Size	2,157 bp
Zygosity	Homozygous
Overlapping Gene(s)	*SH3PXD2B*



18DG0454

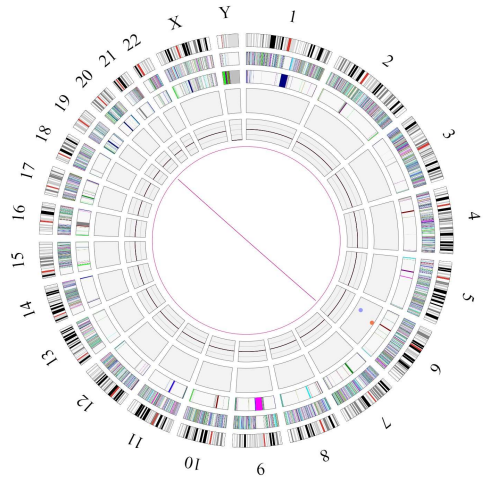
Type of SV	Duplication
Location	chr5:172,411,368 - 172,429,362
Size	17,994 bp
Zygosity	Homozygous
Overlapping Gene(s)	*SH3PXD2B*



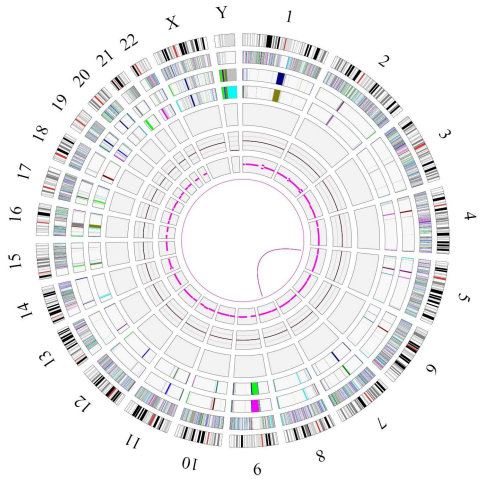
10DG1265

Type of SV	Deletion
Location	chr10:13,281,451 - 13,297,324
Size	2,019 bp
Zygosity	Homozygous
Overlapping Gene(s)	*PHYH*

d 11DG1685

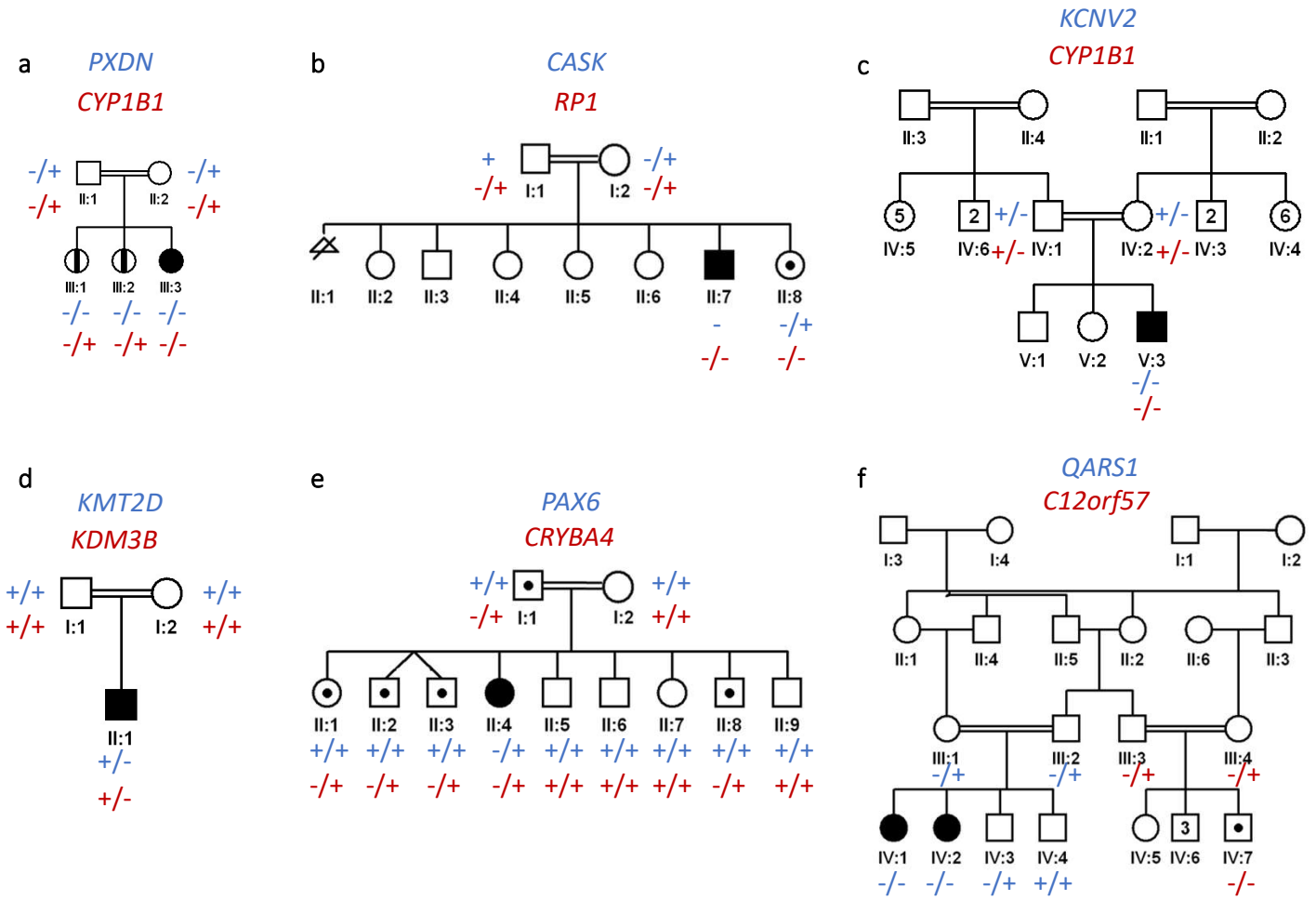


e 22DG0746



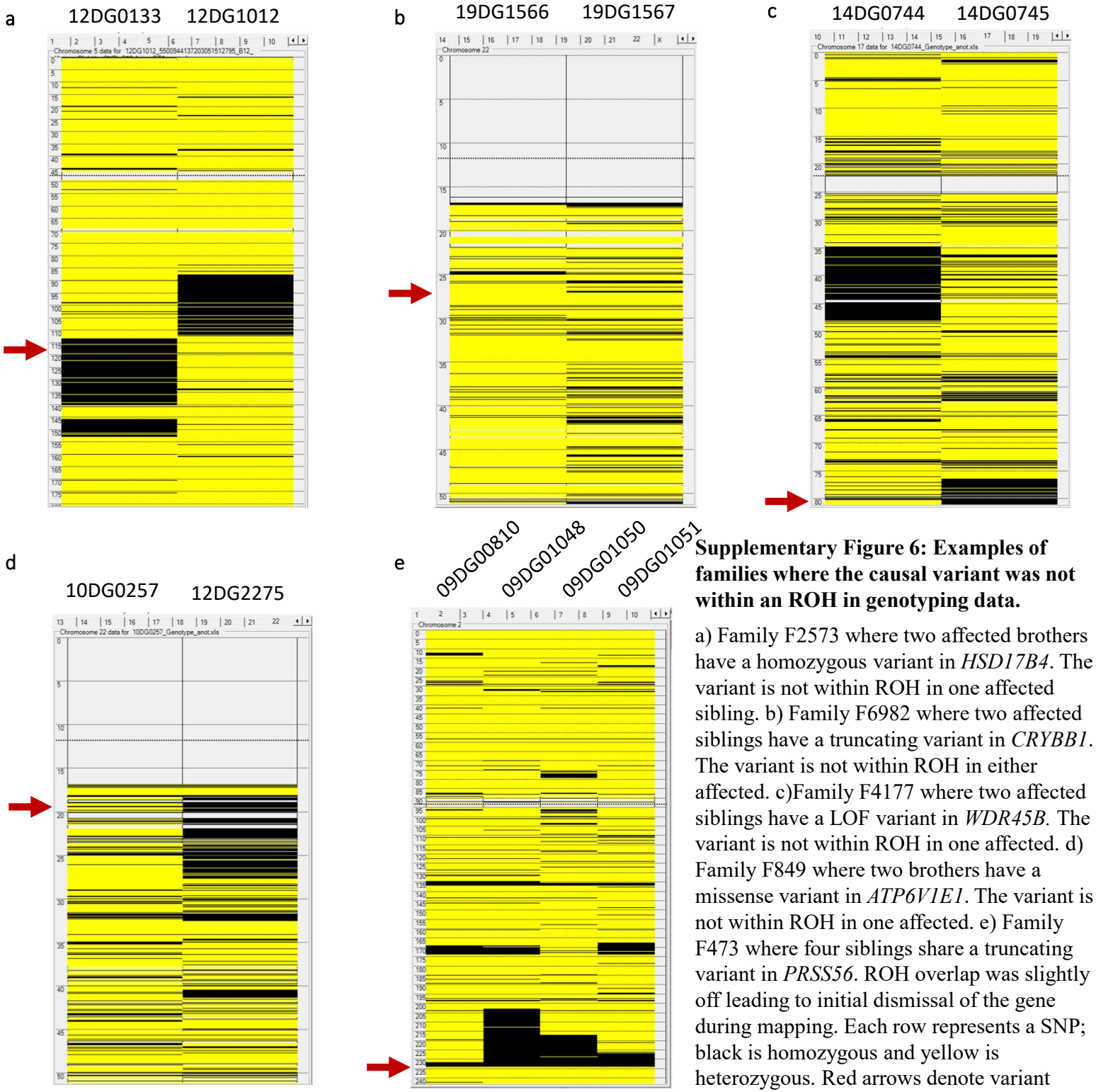
Supplementary Figure 4: Structural variants identified by optical genome mapping.

a) Family F2493 with ~2kb insertion disrupting *SH3PXD2B*. b) Family F6158 with a large duplication (~18kb) disrupting *SH3PXD2B*. *c*) Family F1221 with ~2kb deletion in *PHYH*. d) Family F2242 with interchromosomal translocation [GRCh37] t(6:20)(q25.1;p13) disrupting *TAB2*. e) Family F9257 solved with interchromosomal translocation [GRCh38] t(5;8)(p13.2;q13.3) disrupting *EYA1*.



Supplementary Figure 5: Example of pedigrees showing genetic heterogeneity.

a) Pedigree of family F656 comprising three affected sisters with a homozygous variant in *PXDN* and one sister who is also homozygous for a pathogenic variant in *CYP1B1*. b) Pedigree of family F4277 where the affected index is hemizygous for *CASK*:NM_001367721.1:c.1116C>G;p.(His372Gln) and homozygous for *RP1*:NM_006269.2:c.606C>A;p.(Asp202Glu) while his sister (II:8) is homozygous for the *RP1* variant. c) Pedigree for family F3200 where individual (V:3) has homozygous pathogenic variants in *KCNV2* and *CYP1B1*. d) Pedigree of family F6353 where one affected individual has two de novo variants: *KMT2D*:NM_003482.4:c.1661delT;p.(Leu554Cysfs*376) and *KDM3B*:NM_016604.4:c.5056G>A;p.(Gly1686Arg). e) Pedigree of F4771 where one (II:4) affected has a de novo LOF variant in *PAX6* and she is also heterozygous (together with individuals I:1, II:1, II:2, II:3, and II:8) for a pathogenic variant in *CRYBA4*. f) Pedigree of family F5516 where two sisters (IV:1 and IV:2) are homozygous for *QARS1*:NM_005051.3:c.1058G>T;p.(Gly353Val) while their paternal cousin (IV:7) is homozygote for LOF variant in *C12orf57*:NM_138425.4:c.1A>G;p.?. («+» denotes WT and «-» denotes mutant allele).



Supplementary Figure 6: Examples of families where the causal variant was not within an ROH in genotyping data.

a) Family F2573 where two affected brothers have a homozygous variant in *HSD17B4*. The variant is not within ROH in one affected sibling. b) Family F6982 where two affected siblings have a truncating variant in *CRYBB1*. The variant is not within ROH in either affected. c)Family F4177 where two affected siblings have a LOF variant in *WDR45B*. The variant is not within ROH in one affected. d) Family F849 where two brothers have a missense variant in *ATP6V1E1*. The variant is not within ROH in one affected. e) Family F473 where four siblings share a truncating variant in *PRSS56*. ROH overlap was slightly off leading to initial dismissal of the gene during mapping. Each row represents a SNP; black is homozygous and yellow is heterozygous. Red arrows denote variant location for each family.

Supplementary Methods

Ion Torrent

Select cases underwent Ion Torrent analysis using one or more of the previously designed Gene panels as in [293]. Briefly, DNA samples amplified using gene panel Primer Pools, AmpliSeq HiFi mix (Thermo Fisher, Carlsbad, CA, USA). PCR pools were combined and subjected to primer digestion with FuPa reagent (Thermo Fisher, Carlsbad, CA, USA). Pooled amplicons were ligated with universal adapters and then purified. Libraries were quantified by quantitative PCR. Normalized libraries were barcoded and pooled in equal ratios for emulsion PCR (ePCR) on an Ion OneTouch System. Then, templated Ion Sphere particles were enriched using the Ion OneTouch ES enrichment system as per manufacturer's instructions (Thermo Fisher, Carlsbad, CA, USA). The Ion PI Ion Sphere particles were processed for sequencing on the Ion Proton instrument (Thermo Fisher, Carlsbad, CA, USA).

Whole Exome Sequencing (WES)

Whole exome sequencing was performed as described previously [123]. The exome target regions were captured using platform-specific capture kits according to the recommended manufacturer's protocol. Libraries were made and were enriched for the desired target using the Illumina Exome Enrichment protocol. The final libraries were then sequenced their respective platforms to an average read depth of 81.8X. Reads were mapped against UCSC hg19 by BWA. GATK package was used for calling SNVs and Indels.

Molecular Karyotyping

The majority of simplex cases underwent Molecular Karyotyping as described [271]. Briefly, genome-wide SNP CytoScan HD array was used to perform microarray analysis to assess for genomic gains or losses. This array platform contains 2.6 million markers for CNV detection (Affymetrix). Chromosome Analysis Suite version Cyto 2.0.0.195(r5758) was used for analysis based on UCSC hg19.

Optical Genome Mapping

High molecular weight (HMW) DNA was extracted from 1.5 million patient-derived lymphoblastoid cell lines (LCLs) using the Bionano Prep SP Blood and Cell DNA Isolation Kit (Bionano Genomics, CA, USA, #80030), according to the manufacturer's recommendations. DNA quantification was performed using the Qubit dsDNA BR assay kit with a Qubit 2.0 Fluorometer (Thermo Fisher Scientific). A total of 750ng of HMW DNA was labelled using the Bionano Prep Direct Label and Stain DLS DNA Kit (Bionano Genomics, #80005), following the manufacturer's protocol. The HMW-labelled DNA was loaded onto the Saphyr Chip (Bionano Genomics, #20319) flow cell at a concentration of 12 ng/µl and the samples were run on Bionano Saphyr instrument, according to the manufacturer's instructions, targeting 300× human genome coverage by collecting 500 GB of data per sample [294]. All data were analyzed using Bionano Access software (v1.5) featuring both de novo variant bioinformatics pipelines (hg19 and hg38), according to the manufacturer's recommendations.

Supplementary Table 1

Primers used in this study:

Target	Forward primer	Tm	Reverse Primer	Tm	Size	Type
ABL1	CCTGAATGAAGATGAGCGCC	59.1	TCAAACTGTCTTCCCGTGGA	58.9	495	PCR
OTX2	CTGAACCTGTCCACCCCG	59.7	TGGCCACTTGTTCCACTCTC	59.9	500	RT-PCR
DKK1	CCTTGGATGGGTATTCCAGA	59.7	CCTGAGGCACAGTCTGATGA	60.0	221	qRT-PCR
DENND5A	TGGCTGGTGGAGTATGTGAT	59.0	TGAAACTTGCCATCCTTGCC	63.4	578	RT-PCR
OFD1	AATCTGCAGGGAACATGC	59	TCTCTAAAGGATTTTCAC	59	343	RT-PCR
GAPDH	GGTGAAGGTCGGAGTCAAC	59	ATGGGTGGAATCATATTGGA	58	140	RT-PCR and qRT-PCR

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