Supplementary Data C

A:II.3 and A:II.1 WES data filtering	
Filter	**Number of Variants**
Rare Shared	301
Rare shared PAV	204
Rare shared PAV, known IRD genes	7

Variants of Interest	**Interpretation**	**Justification**
NM_000186.3(CFH):c.1243del, p.(Ala415ProfsTer39) het	Likely pathogenic mutation	Not present on gnomAD Null variant in gene where LOF is a known mechanism of disease Not previously reported as disease-causing
ENST00000264448.6(ALMS1):c.2033A>G, p.(Tyr678Cys)	Carrier of VUS	High allele frequency in European (non-Finnish) population (293/125986) Heterozygous change in recessive gene Gene does not correlate with patient phenotype Predicted deleterious *in silico* (SIFT: Deleterious (0); Polyphen22 (probably damaging (0.997)) Not previously reported as disease-causing
NM_178857.5(RP1L1):c.6992C>T, p.(Thr2331Met) het	Benign	High allele frequency in European (non-Finnish) population (gnomAD: 353/126708) Predicted benign *in silico* (SIFT: Tolerated (0.15); Polyphen22: benign (0.002)) Gene does not correlate with patient phenotype ClinVAR status: Likely benign (RCV000296962.1)
NM_014956.4(CEP164):c.3869C>T, p.(Pro1290Leu)	Carrier of VUS	Rare variant in European (non-Finnish) population (10/126624, 0.00007897) Equivocal *in silico* results (SIFT: Del (0); Polyphen22: Benign: 0.045)

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				Heterozygous change in recessive gene Gene does not correlate with patient phenotype Not previously reported as disease-causing
		NM_014336.3(AIPL1):c.737A>C, p.(Tyr246Ser) het	Carrier of VUS	Rare variant in European (non-Finnish) population (gnomAD: 21/1266694, 0.0001658) Predicted deleterious *in silico* (SIFT: Deleterious (0.01); Polyphen2 (Probably damaging (0.991)) Highly conserved amino acid (GERP: 5.15) Heterozygous change in recessive gene Gene does not correlate with patient phenotype Not previously reported as disease-causing
		NM_000554.4(CRX):c.196G>A, p.(Val66Ile) het	Benign	High frequency in European (non-Finnish) population (225/257790, 0.00724) Equivocal *in silico* result (SIFT: Deleterious (0); Polyphen22: Benign (0.033)) Gene does not correlate with patient phenotype ClinVAR status: Benign (RCV000297047.1)
		NM_001042472.2(ABHD12):c.787+3G>A, p.(splice) het	Carrier of VUS	Moderately high allele frequency in European (non-Finnish) population (34/24942, 0.001363) Not predicted to affect splicing *in silico* Heterozygous change in recessive gene Gene does not correlate with patient phenotype Not previously reported as disease-causing

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B:II.2 Focused exome data filtering	
Filter	**Number of Variants**
All	8,935
All PAV	1,439
Rare PAV	199

Rare PAV, known IRD genes	5	**Variants of Interest**	**Interpretation**	**Justification**
		NM_005559.3(LAMA1):c.2515C>T, p.(Pro839Ser) het	Carrier of VUS	High allele frequency in European (non-Finnish) population (gnomAD: 149/126698). Predicted deleterious *in silico* (SIFT: Deleterious (0); Polyphen22: Probably damaging (1.0)) Heterozygous change in recessive gene. Not previously reported as disease-causing
		NM_000186.3(CFH):c.350+1G>T, p.(splice) het	Likely Disease Causing	Mutation of canonical splice site. Predicted to result in loss of donor splice-site *in silico* Very rare allele in European (non-Finnish) population (gnomAD: 1/22296) Consistent with retinal phenotype and mode of inheritance Not previously reported as disease-causing
		NM_032119.3(ADGRV1):c.5785G>T, (p.Ala1929Ser) het	Benign	High allele frequency in European (non-Finnish) population (gnomAD: 173/126388). ClinVAR status: Likely Benign (SCV000063285.4) Equivocal *in silico* results (SIFT: Tolerated (0.16); Probably damaging 0.99) Heterozygous change in recessive gene. Gene does not correlate with patient phenotype
		NM_018942(HMX1):c.100C>A, p.(Arg34Ser) het	Benign	Absent from gnomAD Predicted benign *in silico* (SIFT: Tolerated (0.76); Polyphen22: Benign (0)) Heterozygous change in recessive gene.

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				Gene does not correlate with patient phenotype. Not previously reported as disease-causing
		NM_006702.4(PNPLA6):c.2945_2961del, p.(Arg983ProfsTer31) het	Benign	Absent from gnomAD Heterozygous change in recessive gene. Gene does not correlate with patient phenotype. Not previously reported as disease-causing

E:II.2 and E:III.11 WES data filtering	
Filter	**Number of Variants**
Rare shared	119
Rare shared PAV	106
Rare PAV, known IRD genes	4

Variants of Interest	**Interpretation**	**Justification**
NM_000186.3(CFH):c.1291T>A, p.(Cys431Ser) het	Pathogenic mutation	Ultra-rare variant (MAF: 0.000004) Predicted deleterious *in silico* (SIFT: Deleterious (0); Polyphen22 (1.0)) Same mutation reported as disease-causing on multiple occasions (Saunders *et al*., 2007; Dragon-Durey *et al*., 2003)
ENST00000264448.6(ALMS1):c.1267G>A, p.(Val423Ile) het	Benign	High allele frequency (gnomAD: 783/276990) Heterozygous change in recessive gene Gene does not correlate with patient phenotype Predicted benign in silico (SIFT: tolerated (ClinVAR status: Benign (RCV000234139.2)

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		NM_178857.5(RP1L1):c.568C>T, p.(Arg190Cys) het	Benign	High allele frequency (gnomAD: 542/277010) Equivocal *in silico* results (SIFT: Deleterious (0); Polyphen22: Benign (0.297)) ClinVAR status: Likely Benign (RCV000389130.1) Gene does not correlate with patients phenotype Not previously reported as disease-causing
		NM_001004334.3(GPR179):c.5563C>G, p.(Leu1855Val) het	Benign	High allele frequency (gnomAD: 725/276738) Heterozygous change in recessive gene Gene does not correlate with patient phenotype Equivocal *in silico* results (SIFT: Tolerated (0.13); Polyphen22: Possibly damaging (0.657)) Not previously reported as disease-causing