SUPPLEMENTARY TABLES

Genome-wide linkage and haplotype sharing analysis implicates the MCDR3 locus as a candidate region for a developmental macular disorder in association with digit abnormalities

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Supplementary Table 1 Primer sequences used for segregation analysis of candidate variants identified in the whole-exome sequencing analysis.

Gene	Primer sequence		Length (bp)
ZNF774	F	5’ - GTTGGGGAGGAAACTGGGAG - 3’	402
	R	5’ - ACTCTGGGCACTCATAGGGT - 3’	
TTC31	F	5’ - GAAGGATGGGTGGAATGAGA - 3’	554
	R	5’ - GATGTGGGGCTCCTTTCTCT - 3’	
SH3RF1	F	5’ - GGATTTTAGCAGATGTAGACATGG - 3’	494
	R	5’ - CAGCAAAACCTCTTTCAATGG - 3’	
ANKRD33B	F	5’ - TTCACGTCTAGGCCCTCACT - 3’	559
	R	5’ - GGAGCTTGATCTGCCCATAC - 3’	
PCDHA8	F	5’ - TGTACACGGGCGAGATCAG - 3’	606
	R	5’ - CGGTGAAAAACTAAATCTGAAACA - 3’	
IKBKB	F	5’ - AGCGATGGGTGTGTGATGTA - 3’	621
	R	5’ - GTGAAGGCTCAGAATCCACA - 3’	
SMARCA2	F	5’ - ATGAGACCTCGGTCCCTCTT - 3’	599
	R	5’ - CTATTAAAAAGGCAATAAACAAAGC - 3’	
NEK3	F	5’ - TGGTTGCACAATATTTTGAATGT - 3’	691
	R	5’ - TCCGCAAATATTCCCTCTTG - 3’	
MPI	F	5’ - CAAGGGTCACGATGTGGAG - 3’	699
	R	5’ - GAGAGGGAAGACAAAGGGAGT - 3’	
CCNF	F	5’ - GGGTGTTAGAGGCAGGTGTG - 3’	567
	R	5’ - ACTCCAGACAGGGTCTCTGC - 3’	
RAX2	F	5’ - ACGGTTGCTCCATGACCTC - 3’	576
	R	5’ - GAAGCAGCAGGTAGGAGTCG - 3’	
CAPS	F	5’ - CCAGTCACCACCTCCTGTC - 3’	674
	R	5’ - TGCAAGATCTCTGGTCAGCA - 3’	
C22orf15	F	5’ - TGGGCAACTCCCTACTGAAG - 3’	561
	R	5’ - ACCTTTCTGGGCCTTGAAGT - 3’	

HIST1H2BJ	F R	5’ – TGAGAACATGGGTGGCTCTT - 3’ 5’ – CCTGACCTCTGACGTTACCC - 3’	600
EPHX2	F R	5’ - AGACACACCCATCTGCCTTC- 3’ 5’ - AAAGCCAGCACAATGAAACC- 3’	205

Primers were designed using Primer3 software.

Supplementary Table 2 Linkage analysis in four individuals (3 affected, 1 unaffected) from family GC16334.

	Genetic position (cM)		Physical position (bp)		SNP		Linkage analysis
Chr	Start	End	Start	End	Start	End	max LOD
1	3.63	13.18	3245399	7408904	rs2483280	rs12088178	0.60
1	14.13	23.92	8278054	13832868	rs3850464	rs12060059	0.60
1	232.26	242.21	227235445	233057127	rs7517398	rs883278	0.60
2	37.03	100.32	16318056	75634513	rs4099911	rs11126476	0.60
3	49.68	50.38	27204290	27802737	rs7653480	rs9817112	0.26
3	181.85	211.30	177528430	194817287	rs2220099	rs7646250	0.60
4	5.64	5.64	3552449	3552449	rs6817919	rs6817919	0.06
4	34.11	40.61	17281982	24403895	rs1558379	rs2284659	0.60
4	67.05	70.76	53686267	56537631	rs10016091	rs2593082	0.60
4	71.79	73.84	57154247	58710633	rs4864589	rs12649436	0.60
4	74.76	84.94	60177989	75798477	rs7683528	rs3923243	0.60
4	155.59	168.16	162726680	174890618	rs4691773	rs3890767	0.60
5	12.24	28.30	4976629	10970489	rs489095	rs17789185	0.60
5	120.12	141.29	114940545	141448040	rs256994	rs12655443	0.60
5	151.57	172.82	148347836	166491185	rs4705303	rs1432944	0.60
6	6p-telomere	52.74	6p-telomere	33867268	6p-telomere	rs6929696	0.60
6	167.81	168.49	159039967	159356582	rs6901469	rs2057061	0.60
6	169.76	181.23	159944835	166707233	rs2053949	rs4305699	0.60
7	7p-telomere	1.26	7p-telomere	257228	7p-telomere	rs10268225	0.24
7	6.12	16.09	2652585	8202431	rs10950811	rs2882042	0.60
7	19.30	22.39	9400633	11452052	rs2350842	rs10262052	0.60
7	33.67	34.86	19539376	20382351	rs2080222	rs3807945	0.52
7	122.61	161.07	115935144	148576210	rs4727833	rs886674	0.60
8	15.50	16.05	6542966	6682255	rs11137056	rs2977802	0.30
8	33.13	65.88	19320961	53931920	rs6990357	rs6473757	0.60
8	89.56	99.57	78881129	95274293	rs2139324	rs10956904	0.60
9	9p-telomere	22.15	9p-telomere	10078517	9p-telomere	rs413553	0.60
9	55.74	85.62	33684161	88362487	rs855427	rs913356	0.60
9	111.17	111.70	109712194	109967341	rs10816586	rs510082	0.17
9	153.13	154.71	136762744	137046552	rs3128606	rs11103632	0.35
10	47.91	94.70	24640014	77233106	rs12258036	rs1004603	0.60
10	95.70	140.95	78063962	120418771	rs751770	rs17097926	0.60
10	142.87	143.41	121678217	121927920	rs7895684	rs2039347	0.60
10	145.08	146.00	122985131	123219616	rs12220647	rs2420941	0.22
10	151.52	151.52	126144789	126144789	rs1254947	rs1254947	0.25
11	11p-telomere	13.56	11p-telomere	8051078	11p-telomere	rs6578921	0.60
11	14.58	17.99	8546224	11148063	rs9736791	rs12363497	0.60
11	64.95	65.50	59656682	60188058	rs4939312	rs10897105	0.31
11	125.45	155.09	121299396	134449982	rs17337467	rs11224232	0.60
12	38.63	44.39	20372259	24186749	rs10770641	rs10505937	0.60
12	105.59	112.57	93671268	100144673	rs7296947	rs2673689	0.60
12	127.37	130.79	111585377	113881331	rs17824620	rs2077395	0.60
13	54.25	129.42	50537801	113957543	rs9596434	rs10467349	0.60
14	45.18	47.62	46643032	50069943	rs10145984	rs3783408	0.31

14	76.83	80.82	76403716	80018586	rs2242629	rs7143237	0.60
14	101.92	102.48	94873609	95013301	rs999986	rs8020368	0.25
15	73.08	85.21	67777591	78616704	rs919054	rs4238523	0.60
15	95.92	100.91	88193157	90579071	rs11635652	rs1080865	0.60
16	16p-telomere	12.61	16p-telomere	5221560	16p-telomere	rs10459837	0.60
16	59.10	99.81	48233308	78227563	rs1861657	rs7189933	0.60
17	13.19	14.01	5263952	5630509	rs1806269	rs17645516	0.32
17	87.67	101.21	53180700	65237250	rs12949688	rs2947870	0.60
17	104.93	133.24	67349312	76876404	rs757992	rs10445407	0.60
18	85.58	113.52	57163169	72656141	rs11152292	rs6420510	0.60
19	19p-telomere	33.55	19p-telomere	13283724	19p-telomere	rs2419244	0.60
19	107.31	113.08	61287529	63749895	rs11672395	rs7249714	0.60
20	20p-telomere	49.37	20p-telomere	20131966	20p-telomere	rs16981689	0.60
21	18.14	18.94	20478347	20801025	rs2826065	rs6517967	0.19
22	22p-telomere	47.97	22p-telomere	37883718	22p-telomere	rs139413	0.60
22	60.78	75.64	44616787	49576671	rs4823324	rs9616985	0.60

Genomic coordinates refer to GRCh37/hg19 assembly.

Supplementary Table 3 Shared exonic variants by affected individuals III:2 and III:3 in family GC16334 after variant filtering.

Chrom	Pos	Ref allele	Alt allele	HGVS variant	Gene	Variant type	Linkage (max LOD in family GC16334)	Does segregate? (Y/N)
2	**74720283**	**G**	**C**	**c.1498G>C:p.(Asp500His)**	***TTC31***	**missense**	**0.60**	**N**
4	129776852	A	G	c.764A>G:p.(Gln255Arg)	*PHF17*	missense	< -2	
4	**170042051**	**T**	**C**	**c.1436A>G:p.(Gln479Arg)**	***SH3RF1***	**missense**	**0.60**	**Y**
5	**10618520**	**G**	**A**	**c.442G>A:p.(Val148Ile)**	***ANKRD33B***	**missense**	**0.60**	**Y**
5	36608576	A	T	c.51A>T:p.(Arg17Ser)	*SLC1A3*	missense	< -2	
5	**140223103**	**C**	**G**	**c.2197C>G:p.(Arg733Gly)**	***PCDHA8***	**missense**	**0.60**	**N**
5	179292977	T	G	c.48A>C:p.(Glu16Asp)	*TBC1D9B*	missense	< -2	
6	**27100363**	**G**	**A**	**c.167C>T:p.(Ser56Leu)**	***HIST1H2BJ***	**missense**	**0.60**	**Y**
6	71190714	A	G	c.524A>G:p.(Lys175Arg)	*FAM135A*	missense	< -2	
8	**27401706**	**C**	**A**	**c.1534C>A:p.(Pro512Thr)**	***EPHX2***	**missense**	**0.60**	**Y**
8	**42166476**	**G**	**A**	**c.625G>A:p.(Gly209Ser)**	***IKBKB***	**missense**	**0.60**	**Y**
9	**2191340**	**A**	**G**	**c.4669A>G:p.(Arg1557Gly)**	***SMARCA2***	**missense**	**0.60**	**N**
10	5246413	A	C	c.326A>C:p.(Asp109Ala)	*AKR1C4*	missense	< -2	
11	22363102	G	A	c.115G>A:p.(Glu39Lys)	*SLC17A6*	missense	< -2	
11	67787217	G	A	c.511G>A:p.(Glu171Lys)	*ALDH3B1*	missense	< -2	
12	9095025	C	G	c.698G>C:p.(Gly233Ala)	*M6PR*	missense	< -2	
12	50188846	G	A	c.1576C>T:p.(Arg526Cys)	*NCKAP5L*	missense	< -2	
12	120652735	TCTC	T	c.1168_1170del:p.(Glu390del)	*PXN*	inframe deletion	< -2	
13	41941590	A	T	c.1555A>T:p.(Thr519Ser)	*NAA16*	missense	< -2	
13	46619120	C	T	c.197G>A:p.(Arg66His)	*ZC3H13*	missense	< -2	
13	**52722555**	**G**	**A**	**c.661C>T:p.(His221Tyr)**	***NEK3***	**missense**	**0.60**	**N**
14	24975419	G	A	c.415C>T:p.(Pro139Ser)	*CMA1*	missense	< -2	
15	41192795	G	C	c.1779G>C:p.(Gln593His)	*VPS18*	missense	< -2	
15	42169070	C	T	c.3788G>A:p.(Arg1263Gln)	*SPTBN5*	missense	< -2	
15	51975596	A	G	c.362A>G:p.(Asp121Gly)	*SCG3*	missense	< -2	
15	**75189982**	**G**	**A**	**c.1183G>A:p.(Val395Met)**	***MPI***	**missense**	**0.60**	**N**
16	**2505557**	**A**	**G**	**c.1877A>G:p.(Glu626Gly)**	***CCNF***	**missense**	**0.60**	**Y**
16	29996679	G	A	c.1568G>A:p.(Arg523Gln)	*TAOK2*	missense	< -2	

17	8215425	G	A	c.68G>A:p.(Arg23His)	*ARHGEF15*	missense	< -2	
17	42273441	T	A	c.505A>T:p.(Asn169Tyr)	*ATXN7L3*	missense	< -2	
18	48327850	C	T	c.454G>A:p.(Ala152Thr)	*MRO*	missense	< -2	
19	**3770858**	**G**	**T**	**c.454C>A:p.(Leu152Met)**	***RAX2***	**missense**	**0.60**	**Y**
19	**5915299**	**T**	**G**	**c.536T>G:p.(Phe179Cys)**	***CAPS***	**missense**	**0.60**	**N**
22	**24106847**	**C**	**G**	**c.287C>G:p.(Thr96Ser)**	***C22orf15***	**missense**	**0.60**	**Y**

Genomic coordinates refer to GRCh37/hg19 assembly. Highlighted in bold are the variants in a linkage region of maximum LOD score of 0.60 on which segregation analysis was performed.

Supplementary Table 4 Human Phenotype Ontology (HPO) terms used in the Exomiser variant prioritisation analysis (Robinson et al. 2014) to describe the phenotypic abnormalities seen in patients from family GC16500 and family GC16334.

HPO term	Description
Family GC16500	
HP:0000567	Chorioretinal coloboma
HP:0100490	Camptodactyly of finger
HP:0100257	Ectrodactyly
HP:0001159	Syndactyly
Family GC16334	
HP:0000567	Chorioretinal coloboma
HP:0005831	Type B brachydactyly
HP:0005848	Bifid thumb distal phalanx
HP:0100490	Camptodactyly of finger
HP:0001159	Syndactyly
HP:0000104	Renal agenesis

Supplementary Table 5 Variant prioritisation analysis using Exomiser[1] and the Human Phenotype Ontology (HPO) terms in Supplementary Table S4 for the variants identified in family GC16334.

Variant (Gene)	Exomiser score	Exomiser phenotypic score	Exomiser variant score	Human phenotypic score	Mouse phenotypic score	Fish phenotypic score	Walker score	Exomiser phenotypic similarity
p.Gly209Ser (*IKBKB*)	**0.7491**	0.50	1	0	0	0	0.50	Proximity in interactome to *PCSK5* and phenotypic similarity to mouse mutant of *PCSK5* [persistent truncus arteriosis (MP:0002633), polydactyly (MP:0000562), syndactyly (MP:0000564), absent kidney (MP:0000520)]
p.Gln479Arg (*SH3RF1*)	**0.4621**	0.50	0.86	0	0	0	0.50	Proximity in interactome to *ILK* and phenotypic similarity to mouse mutant of *ILK* [MP:0000520, absent kidney]
p.Pro512Thr (*EPHX2*)	**0.4620**	0.50	0.86	0	0.30	0.16	0.50	Phenotypic similarity to mouse mutant involving *EPHX2* [abnormal retinal vasculature morphology (MP:0002792)]; Phenotypic similarity to zebrafish mutant involving *HGNC:3402* [ZP:0003348, abnormal(ly) mislocalised anteriorly pancreas]; Proximity in interactome to *DHCR7* and phenotypic similarity to Smith-Lemli-Opitz syndrome associated with *DHCR7* [Iris coloboma (HP:0000612), Brachydactyly syndrome (HP:0001156), Postaxial hand polydactyly (HP: 0001162), Finger syndactyly (HP:0006101), Renal agenesis (HP:0000104)] and to mouse mutant of *DHCR7* [syndactyly (MP:0000564)]
p.Glu626Gly (*CCNF*)	**0.4619**	0.50	0.86	0	0.31	0	0.50	Phenotypic similarity to mouse mutant involving *CCNF* [abnormal vitelline vasculature morphology (MP:0003229), small hindlimb buds (MP:0013169)]; Proximity in interactome to *GLI3* and phenotypic similarity to Pallister-Hall syndrome associated with *GLI3* [Preductal coarctation of the aorta (HP:0005151), Brachydactyly syndrome (HP:0001156), Mesoaxial hand polydactyly (HP:0006159), Finger syndactyly (HP:0006101), Renal hypoplasia/aplasia (HP:0008678)]; Proximity in interactome to *GLI3* and phenotypic similarity to mouse mutant of *GLI3* [polydactyly (MP:0000562), camptomelia (MP:0011505), syndactyly (MP:0000564), single kidney (MP:0003604)]
p.Leu152Met (*RAX2*	**0.1902**	0.26	1	0.26	0	0	0	Phenotypic similarity to Cone-rod dystrophy 11 associated with *RAX2* [Cone-rod dystrophy (HP:0000548)]
p.Val148Ile (*ANKRD33B*)	**0.0162**	0	1	0	0	0	0	No phenotype or Protein-Protein-Interaction evidence

p.Ser56Leu (*HIST1H2BJ*)	**0.0047**	0	0.86	0	0	0	0	No phenotype or Protein-Protein-Interaction evidence
p.Thr96Ser (*C22orf15*)	**0.0002**	0	0.50	0	0	0	0	No phenotype or Protein-Protein-Interaction evidence

REFERENCES

1. Robinson PN, Köhler S, Oellrich A, et al. Improved exome prioritization of disease genes through cross-species phenotype comparison. *Genome Res*. 2014;24(2):340-348. doi:10.1101/gr.160325.113.