

REPORT

Dominant Mutations in *RP1L1* Are Responsible for Occult Macular Dystrophy

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Occult macular dystrophy (OMD) is an inherited macular dystrophy characterized by progressive loss of macular function but normal ophthalmoscopic appearance. Typical OMD is characterized by a central cone dysfunction leading to a loss of vision despite normal ophthalmoscopic appearance, normal fluorescein angiography, and normal full-field electroretinogram (ERGs), but the amplitudes of the focal macular ERGs and multifocal ERGs are significantly reduced at the central retina. Linkage analysis of two OMD families was performed by the SNP High Throughput Linkage analysis system (SNP HiTLink), localizing the disease locus to chromosome 8p22-p23. Among the 128 genes in the linkage region, 22 genes were expressed in the retina, and four candidate genes were selected. No mutations were found in the first three candidate genes, methionine sulfoxide reductase A (*MSRA*), GATA binding 4 (*GATA4*), and pericentriolar material 1 (*PCMI*). However, amino acid substitution of p.Arg45Trp in retinitis pigmentosa 1-like 1 (*RP1L1*) was found in three OMD families and p.Trp960Arg in a remaining OMD family. These two mutations were detected in all affected individuals but in none of the 876 controls. Immunohistochemistry of *RP1L1* in the retina section of cynomolgus monkey revealed expression in the rod and cone photoreceptor, supporting a role of *RP1L1* in the photoreceptors that, when disrupted by mutation, leads to OMD. Identification of *RP1L1* mutations as causative for OMD has potentially broader implications for understanding the differential cone photoreceptor functions in the fovea and the peripheral retina.

Occult macular dystrophy (OMD) is an autosomal-dominant form of inherited macular dystrophy characterized by progressive decrease of visual acuity due to macular dysfunction, which was first reported by Y.M. et al. in 1989.^{1–3} The disorder was called “occult” because of the fact that the macular dysfunction of this disease is hidden by a normal fundus appearance. Typical OMD, as described by Y.M. et al., is characterized by central cone dysfunction and in some cases rod dysfunction, leading to a loss of vision despite normal ophthalmoscopic appearance, normal fluorescein angiography, and normal full-field electroretinograms (ERGs). However, the amplitudes of the focal macular ERGs and multifocal ERGs are significantly reduced, indicating dysfunction of the central retina.^{1,2,4} OMD is known for its broad range of age at disease onset, from 6 to 81 yrs. Brockhurst et al. have reported age at onset of four out of eight OMD patients at over 65 yrs⁵ and similar findings have also been observed in earlier cases.^{1,2} The patient III-3 in family 1 did not notice any visual disturbance in her right eye even at the age of 81 yrs.

The four families shown in [Figure 1](#) demonstrate dominant inheritance of the OMD phenotype. None of the patients had ocular diseases other than OMD, except senile cataract or diabetic retinopathy. Control family members were confirmed to be normal via a complete ophthalmic examination including focal macular ERGs or multifocal

ERGs. For this study, the ethics review committees of the National Hospital Organization Tokyo Medical Center, the Niigata University Graduate School of Medical and Dental Sciences, and the Nagoya University Medical School approved the study, and written informed consent was obtained from both affected and unaffected subjects.

Linkage analysis of OMD families 1 and 2 was performed. Eighteen individuals from family 1 and eleven individuals from family 2 were genotyped by Affymetrix's Genome-Wide Human SNP array 6.0 in accordance with the manufacturer's instructions (Affymetrix, Santa Clara, CA). DNA samples from family 2 were subjected to whole-genome amplification with the use of REPLI-g (QIAGEN, Tokyo, Japan) prior to SNP genotyping. With SNP HiTLink⁶ used as a pipeline, SNPs with a Hardy-Weinberg p value $> f$ 0.001, a call rate of 1, and a maximum confidence score > 0.02 were used for the analysis. SNPs with the minor allele frequency of 0 in controls were eliminated from the analysis. Parametric multipoint linkage analysis (autosomal-dominant model with a setting of liability classes; age-dependent penetrance of 0.19, 0.55, and 0.91 for 0–20, 21–40, and > 41 yrs old, respectively, and disease frequency of 0.000001) was performed with Allegro version 2,⁷ intermarker distance from 80 kb to 120 kb with the use of SNP HiTLink. Because of the limitation of computational capacity, family 1 was divided into two branches (branch 1-1: descendants of II-1; branch

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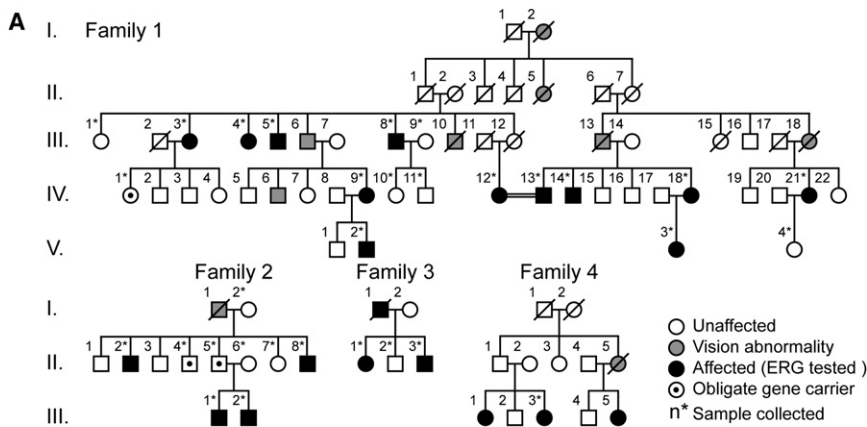
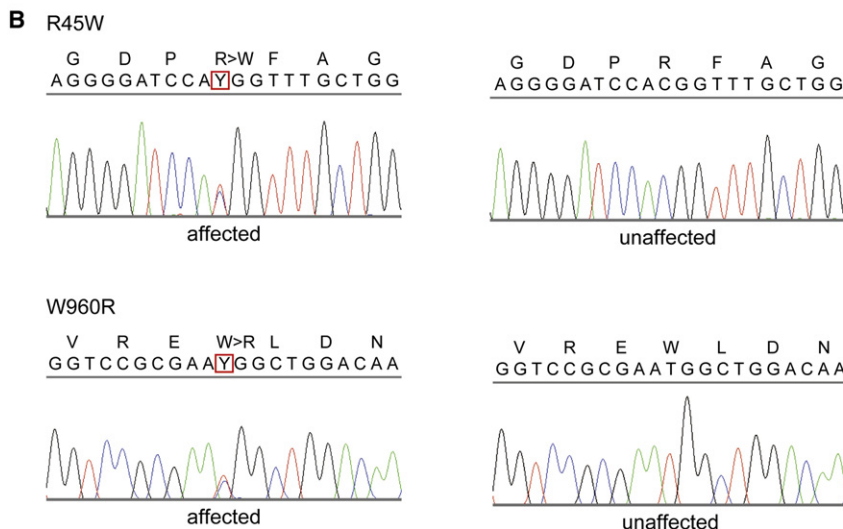


Figure 1. Autosomal OMD Families and DNA Sequencing of *RP1L1*

(A) The four families shown demonstrate dominant inheritance of the OMD phenotype. In all presented families, none of the patients had ocular diseases other than OMD, except senile cataract and diabetic retinopathy. Control family members were confirmed to be normal via a complete ophthalmic examination including focal macular ERGs or multifocal ERGs.

(B) DNA sequencing of both p.Arg45Trp and p.Trp960Arg mutations found in four independent families.



a c.3107T>C (p.Trp960Arg) mutation in family 3 (Table 2). Additionally, known and unknown natural variants were found in *RP1L1*, as shown in Table S2. Unknown SNPs were submitted to the dbSNP database.

In these four families, all of the affected individuals carried one of the two mutations identified in this study, c.362C>T or c.3107T>C. We identified three apparently unaffected individuals carrying the p.Arg45Trp mutation, which suggest a reduced penetrance of the mutation or possibility a later onset of the disease for these individuals. Both mutations were absent in 1752 Japanese control chromosomes.

1-2: descendants of II-7) for multipoint linkage analysis. Haplotypes were reconstructed by Allegro.

The parametric linkage study of family 1 using SNP microarrays and SNP HiTLink mapped the disease locus to an approximately 10 Mb region of chromosome 8p22-p23 with a maximum LOD score of 3.77 (Figure 2). Parametric linkage analysis of affected individuals only produced similar results (Figure 3 and Figure S2 available online). A common haplotype between rs365309 and rs2632841 was shared by all of the affected individuals (Table 1). With the additional linkage study of family 2, the cumulative parametric multipoint LOD score rose to over 4 (Figure S1). A total of 128 known genes were found within the approximately 10 Mb linkage-associated region, containing 22 retina-expressed genes as candidates for mutational analyses. No mutations were found in the first three candidate genes, methionine sulfoxide reductase A (*MSRA*), GATA binding 4 (*GATA4*), and pericentriolar material 1 (*PCMI*). However, a c.362C>T (p.Arg45Trp) substitution in retinitis pigmentosa 1-like 1 (*RP1L1* [MIM 608581]) was found in all affected individuals in family 1. We further extended the mutational analysis of *RP1L1* to three other families with autosomal OMD, and we identified the p.Arg45Trp alteration in families 2 and 4 and

Immunohistochemistry of *RP1L1* in the macula section of primate *Cynomolgus* monkeys (*Macaca fascicularis*) was performed. The eyes from a 6-yr-old normal male cynomolgus monkey were obtained from Tsukuba Primate Research Center, National Institute of Biomedical Innovation, Japan. All experimental procedures were approved by the Animal Welfare and Animal Care Committee of the National Institute of Biomedical Innovation, in compliance with guidelines of the Association for Research in Vision and Ophthalmology. *Cynomolgus* eyes were removed and immediately fixed overnight with 4% paraformaldehyde in 0.1 M phosphate buffer, pH 7.4. After washing in PBS, eyes were cryoprotected in the gradient sucrose dissolved in PBS and embedded into optimal cutting temperature (OCT) compound (Tissue Tek, Miles, IL, USA). Frozen retinal sections cut at 8 μ m thickness with cryostat were incubated at 4°C with a 1:500 dilution of human *RP1L1* polyclonal antibody raised against the N terminus of human *RP1L1* (Santa Cruz Biotechnology, Santa Cruz, CA, USA). Immunofluorescence was visualized with Alexa 568 goat anti-rabbit IgG (Invitrogen, Carlsbad, CA, USA), Alexa 488 PNA (Invitrogen) for detection of cone photoreceptor, and DAPI (Invitrogen) for nuclear staining. Fluorescence images were analyzed with a confocal laser

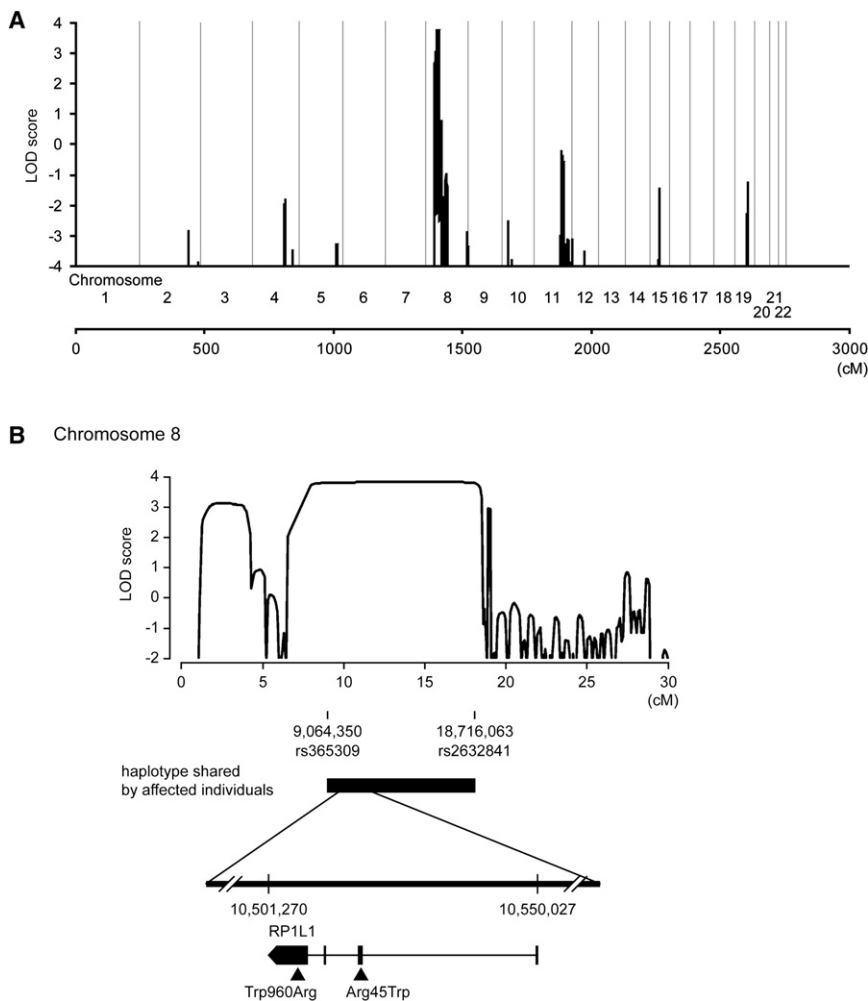


Figure 2. Linkage Analysis and Haplotype Analysis of Family 1

(A) Parametric multipoint linkage analysis of family 1. Horizontal axis indicates cumulative position (cM) from the short arm of chromosome 1. As a result of computational capacity, family 1 was divided into two branches for calculation of LOD scores. No other chromosomes except chromosome 8 yielded a positive LOD score.

(B) Parametric multipoint linkage analysis of family 1 and mutations in *RP1L1*. A maximum LOD score of 3.77 was obtained at 8p32.1-8p22. A haplotype bounded by rs365309 (physical position: 9,064,350 in the hg18 assembly of the UCSC Genome Browser) and rs2632841 (18,716,063) was shared by all affected individuals. Horizontal axis indicates the position (cM) on the short arm of chromosome 8. Vertical axis indicates the parametric multipoint LOD score. Mutations (p.Arg45Trp and p.Trp960Arg) are demonstrated.

patients.^{1,2} It is likely that the initial event may be macular cone specific but may later extend to rod abnormality. Further investigation of *RP1L1* function is required in order to answer these clinical observations.

RP1L1 was originally cloned as a gene derived from common ancestor as retinitis pigmentosa 1 (*RP1* [MIM 180100]) on the same chromosome 8.^{11,12} *RP1L1* shares 35% amino acid

microscope (Radiance 2000, Bio-Rad Laboratories, Hercules, CA, USA).

To our surprise, the immunohistochemistry of *RP1L1* in the macula section of *Cynomolgus* monkeys revealed expression in retinal rod and cone photoreceptors by human *RP1L1* antibody (Figure 3). This expression pattern is significantly different from the previous study of mouse *RP1L1*, in which *RP1L1* was localized exclusively in axoneme of rods.⁸ Furthermore, the human amino acid sequence is only 39% identical to that of the mouse, due to a lack of both polymorphic 16 amino acid repeats or a lack of the highly repetitive Glu-rich region, making mouse *RP1L1* protein considerably shorter than the human protein, which may lead to different functional roles in the primate retina. Recent investigation of photoreceptor structure in OMD patients using advanced optical coherence tomography suggests that the predominant defect involves the cone photoreceptor.^{9,10} Our optical coherence tomography observations also show loss of the cone outer segment tip and irregularity of the inner segment/outer segment junction in the center of the macula of all examined case individuals in family 1 (data not shown). Y.M. et al. have observed that not only cone but also rod sensitivity in the macula was abnormal in some of the older

patients.¹³⁻¹⁵ When *RP1L1* was first identified, a number of attempts were made to identify mutations in *RP1L1* in various RP patients, with no success. The present study demonstrates that *RP1L1* mutation is responsible for OMD, but not for RP. Patients with RP carrying the most common RP1 alteration, p.Arg677X, exhibit night and peripheral vision disturbance beginning in the third decade of life. RP1 is found exclusively in the retina and is localized to both rods and cones. Rod-cone functional comparison in RP patients has indicated that rod sensitivity loss is at least 2 log units greater than cone sensitivity loss.¹³ Thus phenotypic characteristics of RP caused by *RP1* mutations and those of OMD caused by *RP1L1* mutations perfectly agree with the different localizations of *RP1* and *RP1L1* in retina.

The outer segments of rod and cone photoreceptors are highly specialized cilia containing hundreds of disc membranes stacked in an orderly array along the photoreceptor axoneme. Previous studies have shown that *RP1* is part of the axoneme and is required for this correct orientation and higher-order stacking of outer segment discs.¹⁶ This is achieved by the interaction of *RP1* with the

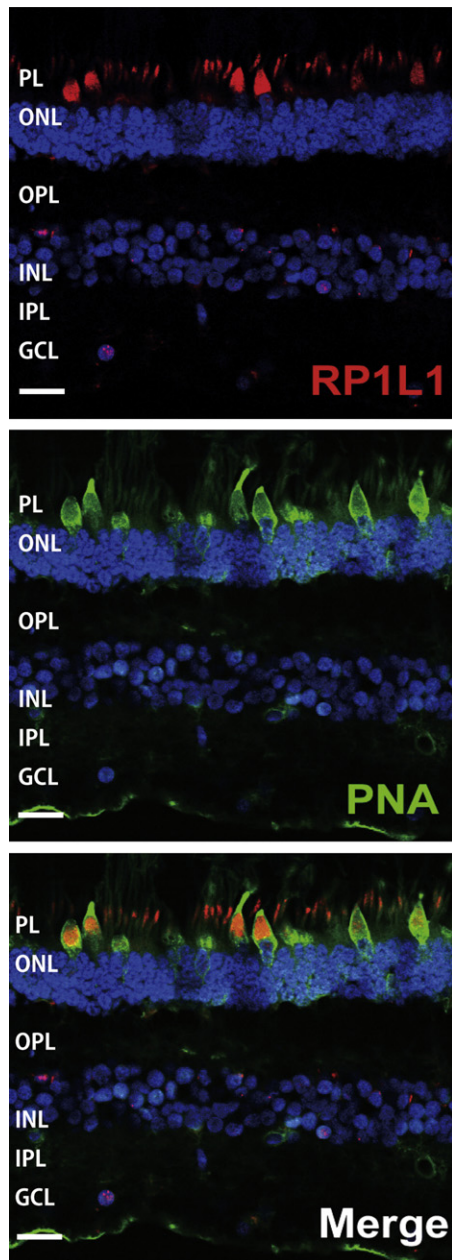


Figure 3. Immunohistochemistry of RP1L1 in the Cynomolgus Monkey Retina

Localization of RP1L1 in the rod and cone photoreceptors in the Cynomolgus monkey (*Macaca fascicularis*). Retina labeled with anti-human RP1L1 (red, top); same section labeled with retinal cone specific marker, peanut agglutinin lectin (PNA, green, middle); merged image (bottom). Yellow signal present in cone photoreceptor resulted from combination of the red signal of RP1L1 and the green signal of PNA. Cell nuclei were stained with DAPI (blue). PL, photoreceptor layer; ONL, outer nuclear layer; OPL, outer plexiform layer; INL, inner nuclear layer; IPL, inner plexiform layer; GCL, ganglion cell layer, Scale bars represent 20 μm .

microtubule in the connecting cilia.¹⁷ RP1 contains microtubule-binding domains (amino acids 28–228) of neuronal microtubule-associated protein (MAP) doublecortin (DCX), which is required to maintain axoneme length

and stability.¹⁸ The RP1L1 p.Arg45Trp alteration resides in one of the two DCX domains (amino acids 33–113 and 147–228), which is required for interaction with RP1 to assemble and stabilize axonemal microtubules.⁸ In primates, both RP1L1 and RP1 proteins may cooperatively function in the rod and cone photoreceptors to perform this task. The mutation in *RP1L1* is likely to dominantly affect the cooperative function with RP1 in rod and cone photoreceptors, given that in a previous publication, the *RP1L1* heterozygous knockout mice were reported to be normal whereas homozygous knockout mice were reported to develop subtle retinal degeneration. Our findings in OMD may shed light for further investigation of patients with cone dystrophy.

In conclusion, we identified *RP1L1* mutations that cause autosomal-dominant OMD, and furthermore, our findings revealed that *RP1L1* plays essential roles in the cone functions in human and that disruption of *RP1L1* function leads to OMD.

Supplemental Data

Supplemental Data include three figures and one table can be found with this article online at <http://www.cell.com/AJHG/>.

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Web Resources

The URLs for data presented herein are as follows:

dbSNP, www.ncbi.nlm.nih.gov/projects/SNP/

SNP HiTLink software, <http://www.dynacom.co.jp/u-tokyo.ac.jp/snphitlink/>

Accession Numbers

The dbSNP accession numbers for the SNPs reported in this paper are ss252841181 and ss252841182.

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Table 1. Disease-Linked Haplotypes in Families 1 and 2

Probe Set ID	dbSNP rs ID	Position	Family 1					Family 2	
			Branch 1-1		Branch 1-2			II-2	III-2
			III-8	IV-9	IV-13	IV-18	IV-21		
SNP_A-8338925	rs365309	9,064,350	(A)	(A)	A	A	B	A	A
SNP_A-8281994	rs1530483	9,065,671	B	B	B	B	B	B	B
SNP_A-8360926	rs10086673	10,342,727	B	B	(B)	B	B	(A)	A
SNP_A-2082488	rs9329223	10,369,164	A	A	A	A	A	(B)	B
SNP_A-2013182	rs6601491	10,453,427	B	B	B	B	B	(A)	A
<i>RP1L1</i> p.Arg45Trp	c.133C>T	10,517,989	T	T	T	T	T	T	T
SNP_A-8345504	rs10097570	10,586,268	A	A	A	A	(A)	(B)	B
SNP_A-1790165	rs10111051	10,590,882	A	A	A	A	(A)	(B)	B
SNP_A-8587750	rs2163379	10,769,460	A	A	A	(A)	A	(B)	B
SNP_A-8500791	rs7460507	11,006,485	B	B	B	B	B	A	A
SNP_A-8525908	rs9772321	12,536,010	A	A	A	A	A	A	A
SNP_A-8283296	rs1021087	13,500,502	A	(A)	(A)	A	A	B	B
SNP_A-8441723	rs6987209	14,501,302	B	B	B	B	B	B	B
SNP_A-2044287	rs7818067	15,580,087	A	A	A	A	A	A	A
SNP_A-4273924	rs6992112	16,689,526	A	A	A	A	A	A	(A)
SNP_A-8447659	rs471041	17,707,836	B	B	B	B	B	B	B
SNP_A-8399664	rs2638658	18,713,620	A	(A)	(A)	A	A	(B)	B
SNP_A-4233785	rs2632841	18,716,063	B	B	(B)	B	A	B	B

Disease-linked haplotypes of the two patients (IV-9 and III-8) who are descendants from II-1 (branch 1-1 of family 1), the three patients (IV-13, IV-18, and IV-21) who are descendants from II-7 (branch 1-2 of family 1), and the two patients (II-2 and III-2) from family 2 are shown. Haplotypes are unequivocally determined, except those with brackets that are inferred to minimize the number of recombination events. Disease-linked haplotypes of the two branches of family 1 are the same, confirming that all affected individuals in family 1 share the same haplotype. Recombination events in the family was observed at rs365309 (telomeric boundary) and at rs2632841 (centromeric boundary). When disease haplotypes are compared between families 1 and 2, who share the p.Arg45Trp mutation in *RP1L1* in common, disease-linked haplotypes flanking the *RP1L1* locus are different between these families, suggesting that the p.Arg45Trp mutation originated independently.

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Table 2. Summary of RP1L1 Mutations in Families with OMD

ID in Pedigree	Clinical Stage	Sex	Age at Diagnosis	Age at Onset in Estimation	Mutation	Best Corrected Visual Acuity (Right / Left)
1 III3	affected	F	81	50	c.362C>T	1.2 / 0.1
1 III4	affected	F	71	25	c.362C>T	0.4 / 0.5
1 III5	affected	M	74	30	c.362C>T	0.2 / 0.3
1 III8	affected	M	82	20	c.362C>T	0.2 / 0.2
1 IV1	unaffected	F	60	-	c.362C>T	1.2 / 1.2
1 IV9	affected	F	49	unknown	c.362C>T	1.2 / 1.2
1 IV12	affected	F	69	50	c.362C>T	0.1 / 0.07
1 IV13	affected	M	70	20	c.362C>T	0.1 / 0.1
1 IV14	affected	M	66	30	c.362C>T	0.2 / 0.3
1 IV18	affected	F	58	12	c.362C>T	0.1 / 0.1
1 IV21	affected	F	58	47	c.362C>T	0.1 / 0.4
1 V2	affected	M	20	13	c.362C>T	0.3 / 0.3
1 V3	affected	F	19	6	c.362C>T	0.2 / 0.15
2 II2	affected	M	69	unknown	c.362C>T	0.2 / 0.2
2 II4	unaffected	M	58	-	c.362C>T	1.0 / 1.0
2 II5	unaffected	M	55	-	c.362C>T	1.0 / 1.0
2 II8	affected	M	52	unknown	c.362C>T	0.2 / 0.3
2 III1	affected	M	23	23	c.362C>T	0.2 / 0.3
2 III2	affected	M	20	20	c.362C>T	0.3 / 0.3
3 II1	affected	F	29	12	c.3107T>C	0.2 / 0.2
3 II3	affected	M	19	13	c.3107T>C	0.2 / 0.3
4 III3	affected	F	52	30	c.362C>T	0.15 / 0.15

Summary of individuals from autosomal OMD families 1–4, in whom p.Arg45Trp or p.Trp960Arg mutations of *RP1L1* were found. Three unaffected individuals at the age of 55–60 were found with the mutation. These individuals suggest a reduced penetrance of the mutation or a possible onset at a later age.

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