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CRB1-associated Retinal Dystrophies: Genetics, Clinical Characteristics and Natural History.

Running head: *CRB1* Retinal Dystrophy Natural History

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Abstract

Purpose: To analyse the clinical characteristics, natural history, and genetics of *CRB1*-associated retinal dystrophies.

Design: Multicenter international retrospective cohort study.

Methods: Review of clinical notes, ophthalmic images, and genetic testing results of 104 patients (91 probands) with disease-causing *CRB1* variants. Macular optical coherence tomography (OCT) parameters, visual function, fundus characteristics, and associations between variables were our main outcome measures.

Results: The mean age of the cohort at the first visit was 19.8 ± 16.1 (median 15) years of age, with a mean follow-up of 9.6 ± 10 years. Based on history, imaging, and clinical examination, 26 individuals were diagnosed with retinitis pigmentosa (RP, 26%), 54 with early-onset severe retinal dystrophy/Leber Congenital Amaurosis (EOSRD/LCA, 51%), and 24 with macular dystrophy (MD, 23%). Severe visual impairment was most frequent after 40 years of age for patients with RP and after 20 years of age for EOSRD/LCA.

Longitudinal analysis revealed a significant difference between baseline and follow up best corrected visual acuity in the three sub-cohorts. Macular thickness decreased in most patients with EOSRD/LCA and MD, whereas the majority of patients with RP had increased perifoveal thickness.

Conclusions: A subset of individuals with *CRB1* variants present with mild, adult-onset RP. EOSRD/LCA phenotype was significantly associated with null variants, and 167_169 deletion was exclusively present in the MD cohort. The poor OCT lamination may have a degenerative component, as well as being congenital. Disease symmetry and reasonable window for intervention highlight *CRB1* retinal dystrophies as a promising target for trials of novel therapeutics.

INTRODUCTION

Biallelic disease-causing variants in Crumbs homolog 1 (*CRB1,* MIM# 604210) have been associated with a wide and complex range of phenotypes. The most commonly reported is Leber congenital amaurosis (LCA)/early onset severe retinal dystrophy (EOSRD), where *CRB1* accounts for around 10% of all cases.[1] This is followed in frequency by retinitis pigmentosa (RP),[2,3] in which *CRB1* represents up to 6.5%.[4] Other phenotypes include cone-rod (CRD),[5,6] macular dystrophy (MD),[7,8] foveal retinoschisis,[9] and fenestrated slit maculopathy.[10]

One of the distinctive features of *CRB1*-retinopathy can be the presence of nummular pigmented deposits,[11] admixed with small yellow-white dots.[12] Also, *CRB1* is commonly associated with preserved para-arteriolar retinal pigment epithelium (PPRPE),[2,13] abnormally laminated and thickened retina,[14] and peripheral exudative retinal telangiectasia (Coats-like vasculopathy)[15,16] - which can ultimately lead to retinal detachment and neovascular glaucoma.[5] Non-retinal features have also been linked to this gene such as nanophthalmos,[17,18] hyperopia,[13,19] narrow anterior chamber,[20] and optic disc drusen.[18]

CRB1 was first identified in several unrelated individuals with RP and PPRPE.[21,22] *CRB1* encodes a transmembrane protein with multiple epidermal growth factor-like and laminin A globular-like domains;[15] and is believed to have a role in retinal development as well as in long-term retinal integrity. Its primary function is in the maintenance of the zonula adherens junctions between photoreceptors, Müller glial cells and the external limiting membrane (ELM).[23ï 25] It also has essential roles in epithelial cell polarity and in the scaffolding complex, in vascular integrity, and is key to the preservation of an organized photoreceptor layer.[26]

CRB1 is frequently reported as one of the most common causative genes for LCA/EOSRD. [27ï 29] This has driven increasing efforts to develop animal models and treatments.[30,31] As the preclinical work moves forward, it becomes imperative to understand the natural history of the disease. In this retrospective international study, we undertake deep phenotyping of the largest *CRB1* cohort to date, report disease natural history and explore potential endpoints for future interventional clinical trials.

METHODS

The study protocol adhered to the tenets of the Declaration of Helsinki and was approved by the ethics committees of the participating institutions.

Patient Selection and Genetics

The inclusion criterion for the current study was to have molecularly confirmed *CRB1*-associated retinopathy. This was defined as patients with an inherited retinal dystrophy (IRD) harbouring 2 or more disease-causing *CRB1* variants. The patients were identified by reviewing the genetics database of Moorfields Eye Hospital (London, UK) and St. John of Jerusalem Eye Hospital group (Jerusalem), and their records were subsequently studied.

Genetic testing was performed with various available methods, such as direct Sanger sequencing, next-generation sequencing (NGS)-based retinal dystrophy gene panels, whole exome sequencing (WES), and whole genome sequencing (WGS). *In silico* molecular genetic analysis was performed for all detected *CRB1* variants (transcript reference: NM_201253.3: ENST00000367400.3) and the detailed description is provided in the supplemental material (**Supplementary Methods, available at AJO.com**). Pathogenicity of each variant was classified mainly according to the guidelines of the American College of Medical Genetics and Genomics (ACMG).[32,33] The cut off value of allele frequency to apply PM2 (absence or very rare in the general population database) was 0.001. For the purpose of this study, an additional specification (Likely pathogenic: 1 Moderate (PM1-PM6) AND 3 Supporting (PP1-PP5)) to determine the verdict assessment results was applied to the ACMG classification.

Clinical Assessment and Retinal Imaging

All participants were seen by specialists in IRDs at referral sites. Clinical notes were reviewed, including family, medical and ophthalmic history, best corrected visual acuity (BCVA), refraction, slit-lamp biomicroscopy findings, and fundoscopy. BCVA was

converted to logarithmic minimum angle of resolution (LogMAR) for statistical analysis. Count fingers vision was given a value of LogMAR 1.98 and hand motion, LogMAR 2.28, light perception and no light perception were LogMAR 2.7 and 3, respectively.[34,35] Patients were categorised using the World Health Organization (WHO) visual impairment criteria, that defines no or mild visual impairment as BCVA $\leq$ 0.48 (6/18, 20/60), moderate impairment as BCVA > 0.48 and $\leq$ 1.0 (6/60, 20/200), severe as BCVA >1.0 and $\leq$ 1.3 (3/60, 20/400), and blindness as BCVA > 1.3. Records of visual field were limited within our cohort; therefore, we only took into consideration central vision based on BCVA to classify patients. 'Low vision' corresponds to patients with moderate and severe impairment. Asymmetric BCVA was defined as a difference greater than Ó0.3 LogMAR (equivalent to 15 ETDRS letters) between eyes. Refraction was undertaken by an optometrist for both adults and children, and spherical equivalent was calculated for refractive error.

When available, we also assessed additional testing such as color and autofluorescence retinal imaging, near-infrared reflectance, and OCT (details in **Supplementary Methods**). Fovea-centred macular volume scans were performed in a 6 mm^2 area that included the standard 1, 3, and 6 mm grid template from the ETDRS. Inner limiting membrane and Bruchôs membrane were automatically segmented by the manufacturer software (Heyex version 1.9.14.0; Heidelberg Engineering) or adjusted manually as needed by a trained ophthalmologist (M.D.V.). Macular OCTs were divided into three categories regarding their qualitative features and associations subsequently explored: group 1, characterized by normal lamination; group 2, where the retinal layers are generally discernible but appear ill-defined; and group 3, defined by a disorganised retina with coalescent layers (particularly within the inner retina) and a degree of increased reflectivity of the nuclear layers (**Figure 1**).[36,37] To allow direct comparison between normal and abnormal retinal architecture, we also compared normal (group 1) and abnormal OCT lamination (groups 2 and 3). Patients with macular cysts, edema, and/or only line scans due to poor fixation were excluded from quantitative assessments (details in **Supplementary Methods**). Normative data regarding OCT thickness in the general population was extracted from Grover et al.,[38] and volume parameters were taken from Roshandel et al.[10] Both eyes from each patient were analysed.

Electrophysiological assessment

Pattern and full-field electroretinogram (PERG; ff-ERG) testing was performed in a subset of patients, incorporating the standards of the International Society for Clinical Electrophysiology of Vision (ISCEV) and included additional dark-adapted (DA) red flash ERGs.[39ï 41] The PERG and ff-ERG were performed using gold foil electrodes, except in 9 young children who underwent testing with lower eyelid skin electrodes using a shorter ERG protocol.[42] The quantitative ERG data analysis was limited to recordings from Moorfields Eye Hospital, to optimise consistency of methods and to minimise variability due to different types of recording electrode. The patient ERG data were compared with those from a control group of healthy subjects (age range: 10-79 years).[43] Further details can be found in the **Supplementary Methods**.

Statistics

Statistical analysis was carried out with GraphPad Prism 8.0.2 (GraphPad Software, San Diego, CA, USA). The threshold of significance for all statistical tests was set at $p < 0.05$. Linear regressions and t-test were used for parametric variablesôassessment. Welch's t-test variation was employed when the sample sizes were significantly different. Chi-square was undertaken to assess possible association between two categorical variables.

RESULTS

Demographics, phenotypic category, and visual acuity

One hundred and four patients (91 probands) with multiple *CRB1* variants were included in this cohort and ascertained for phenotyping, after a multidisciplinary team of ophthalmologists and clinical geneticists excluded other possible genotypes. Eighty-seven (84%) were seen at Moorfields Eye Hospital and 17 (16%) at St John of Jerusalem Eye Hospital. Seven patients had a typical phenotype for the disease

(nummular pigmented deposits, admixed with small yellow-white dots, preserved para-arteriolar retinal pigment epithelium (PPRPE), abnormally laminated and thickened retina), however a single disease-causing variant in *CRB1* was identified. These 7 cases with presumed *CRB1*-associated disease were excluded from further analysis. **Supplementary Table 1 (available at AJO.com)** summarizes the genetics and the clinical phenotype of these patients.

Sixty-two were male (60%) and 42 female (40%). The mean age ± standard deviation (SD) at the first visit was 19.8 ± 16.1 years of age, with a median of 15 years. Fifty-three participants had their first visit as children (below the age of 16). The mean follow-up time of the cohort was 9.6 ± 10 years and the overall age at their latest visit was 29.6 ± 17.2 years of age. The clinical findings from the cohort are summarized in **Table 1**.

Based on ophthalmic history, imaging, and clinical examination, 54 presented with EOSRD/LCA (51%), 26 individuals were diagnosed with RP (26%), and 24 with MD (23%). Within the EOSRD/LCA sub-cohort, the mean age of onset was 2.4 ± 2.8 years old (median 1), with poor central vision and secondly nystagmus as the most prevalent initial symptoms/signs. Among the RP group, the mean age of onset was 13.2 + 10.8 years old (median 10) and the most common presenting symptom was nyctalopia, followed by constricted field. Lastly, the patients from the MD sub-cohort had a mean age of onset of 16.8 + 10.8 years of age (median 15) and primarily complained of decreased acuity.

Baseline BCVA was 1.6 ± 0.8 LogMAR in those with EOSRD/LCA (mean age 16.2 ± 15.3 years), 0.9 ± 0.8 LogMAR in patients with RP (mean age 23.9 ± 18.6 years), and 0.6 ± 0.4 LogMAR in MD patients (23.2 + 13.7 years). Seven infants with EOSRD/LCA did not have accurate vision recorded (e.g., fix and follow) and 1 patient with RP did not have BCVA detailed in the medical records. The number of patients in each WHO category of visual impairment is displayed in **Table 1** and **Supplementary Figure 1A (available at AJO.com)**. Asymmetric BCVA was seen in 20 patients (19%); 9 with EOSRD/LCA, 5 with RP, and 6 with MD. There was a significant association between age and BCVA in all EOSRD/LCA ($p < 0.0001$), RP ($p < 0.0001$), and MD sub-cohorts ($p = 0.047$).

The mean spherical equivalent in the RP cohort was +1.75 ± +1.75 (n=1 myopic); in the EOSRD/LCA, +5.75 ± +3.5 (n=2 myopic), and +0.75 ± +2.5 among the MD sub-cohort (n=7 myopic, 29%). High hyperopia (spherical equivalent >+5.00 dioptres) was found in 1 patient with RP, 1 with MD, and in 21 with EOSRD/LCA (39%).

Clinical findings - anterior segment

One individual with RP and four with EOSRD/LCA were diagnosed with keratoconus. Fifteen patients with RP had lens opacities (58%), diagnosed at 34 ± 13 years of age; 17 patients among the EOSRD/LCA group (31%) at age 34.5 ± 14; and only two patients in the MD cohort, at ages 54 and 71 respectively. Only four patients among the RP sub-cohort had glaucoma; one neovascular at age 41, two open angle at ages 32 and 35, and one acute angle closure at 29 years of age.

Clinical findings - posterior segment

All EOSRD/LCA patients presented with diffuse, dense pigment in the retinal periphery, with both spicules and nummular pigment. They all had macular involvement, with a pigmented ring in the posterior pole in 16 patients, and coloboma-like severe atrophy in four (**Figure 2A and B**). All patients in the RP sub-cohort presented with peripheral retinal pigmentation and a range of phenotypes at the posterior pole: seven patients had a normal appearing macula, ten had a blunted/opaque macular reflex, and 12 had signs of atrophy and pigmented deposits (**Figure 2C and D**). Sixteen patients with MD had normal retina outside the arcades, whereas eight had peripheral areas of pigmented bone spicules or nummular lesions, and/or vessel thinning. The macula reflex was blunted in 12 patients, with mottled RPE and signs of atrophy in the remaining 12; the latter often accompanied by pigmented bone spicules and affecting the nasal peripapillary area (**Figure 2E and F**). Four individuals with MD presented with foveal sparing and therefore good central vision. Macular involvement (functional and/or

structural) was present in 25 RP patients (first documented at mean age of 23.9 + 18.6 years), and in all EOSRD/LCA (2.4 ± 2.8 years) and MD patients (19 ± 10 years).

Thirty-four individuals with EOSRD/LCA (mean age 24.1 ± 16.6 years), 11 with RP (23 ± 18 years), and 3 with MD (37.3 ± 11.1 years) had nummular pigment clumps. White/yellow dots were seen in 16 EOSRD/LCA patients (mean age 24 ± 9 years), in 3 patients with RP (19 ± 7.5 years), and in 2 MD patients, at the same timepoint where nummular pigment was present (25 and 35 years of age). Sixteen patients with EOSRD/LCA (mean age 22 ± 13.5 years) presented with PPRPE; ten with RP (23 ± 12 years), and three with MD (38 ± 10.5 years). PPRPE was more readily identified with autofluorescence (AF) imaging, likely given the RPE-basis of AF imaging.[10]

Seven EOSRD/LCA patients had retinal telangiectasia (mean age 30 ± 10 years), six of which were associated with exudation, with two resulting in vitreous haemorrhage(s). Retinal telangiectasia was seen in 4 patients with RP, diagnosed at a mean age of 28 ± 8 years, and resulted in a range of complications including exudation, vitreous haemorrhage, and retinal detachment (RD). Optic disc drusen was the most common optic nerve abnormality; affecting 7 patients with LCA, 4 with RP, and 1 with MD. Two patients with EOSRD/LCA had gliosis on the optic disc.

Ocular complications were seen in twelve individuals with EOSRD/LCA (21%); in 4 they were related to telangiectasia, while the remaining eight corresponded to RD, iris nodules, anterior segment synechiae, retinal hamartoma, and corneal hydrops. Ocular complications were also reported in six patients with RP (22%); 4 were associated with retinal telangiectasia, the remaining two were uveitis and asteroid hyalosis. Only one patient with MD was found to have unusual vessel sheathing at age 8, of unknown cause.

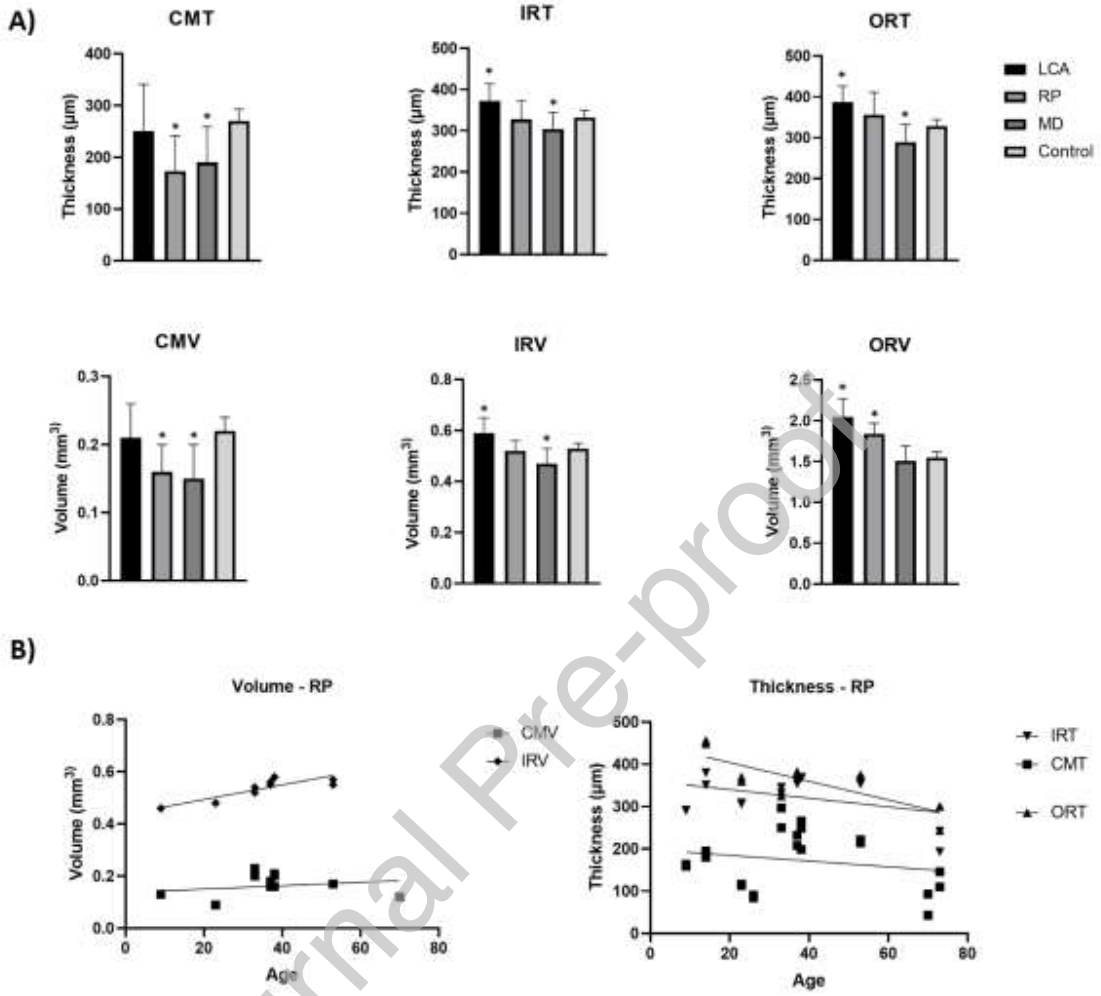
Macular OCT analysis

Eighty-five patients from our cohort had macular OCT scans (82%); 38 (45%) with EOSRD/LCA, 25 (29%) with RP, and 22 (26%) with MD; with all being included in the qualitative analysis. Quantitative assessment was possible in 15 patients with

EOSRD/LCA, 8 with RP, and 10 with MD, due to image quality and sufficient scans being available. Eleven individuals from the EOSRD/LCA sub-cohort had follow up scans (over 7 ± 3 years), 7 from the RP group (over 7.5 ± 1.52 years), and 10 with MD (7 ± 3 years), which enabled additional longitudinal analysis. Baseline and follow up structural parameters are described on **Supplementary Table 2**.

The EOSRD/LCA sub-cohort had significantly increased inner ring thickness (IRT, p= 0.002), outer ring thickness (ORT, p <0.0001), inner ring volume (IRV, p=0.002), and outer ring volume (ORV, p=0.0004) compared to the normal population (**Figure 3**). The RP group had significantly decreased central macular thickness (CMT, p=0.0008) and central macular volume (CMV, p=0.0037), however the ORV was increased (p=0.0004). Lastly, patients with MD showed significant thinning in all CMT (0.003), IRT (0.004), ORT (0.01), CMV (0.0017), and IRV (0.01; **Figure 3A**). No association was found between thickness or volume metrics and age in EOSRD/LCA (p between 0.08 ï 0.95) and MD subgroups (p between 0.4 and 0.8). However, a significant association was found in patients with RP between age and ORT (negative slope, p=0.003) and IRV (positive slope, p=0.0003, **Figure 3B**). Longitudinal analysis demonstrated no statistically significant differences between baseline and follow up parameters in all sub-cohorts. Sixty percent of patients with EOSRD/LCA had decreased CMT over follow up (mean -3 µm/year), 54% had decreased IRT (-1.5 µm/year), and 50% had decreased ORT (-0.6 µm/year). Within the RP sub-cohort, 67% had decreased CMT (-1.9 µm/year), 49% had decreased IRT (with an overall increase however of 0.3 µm/year), and 43% had decreased ORT (increase of 1.5 µm/year). Lastly, 59% patients with MD had decreased CMT over follow up (-0.5 µm/year), 70% had decreased IRT (-1.1 µm/year), and 49% had decreased ORT (-1.8 µm/year).

Macular cystic spaces were present in 29% of our cohort as a whole, and in 52% and 42% of the RP and MD subgroups, respectively. The majority had the INL affected only (24 eyes), followed by both INL and ONL involved (19 eyes), and then ONL only (13 eyes). There was a significant difference in the age of patients with and without cysts, both analysing the cohort as a whole (0.007) and excluding the EOSRD/LCA group (p= 0.002), with a mean age of 22.3 ± 15.4 for those having cysts and 34.6 ± 18.2 for those



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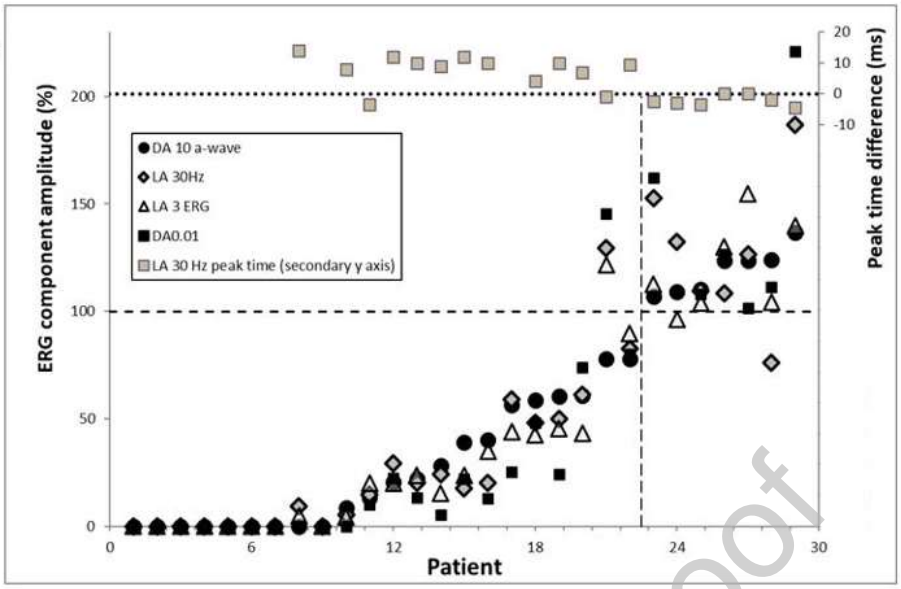

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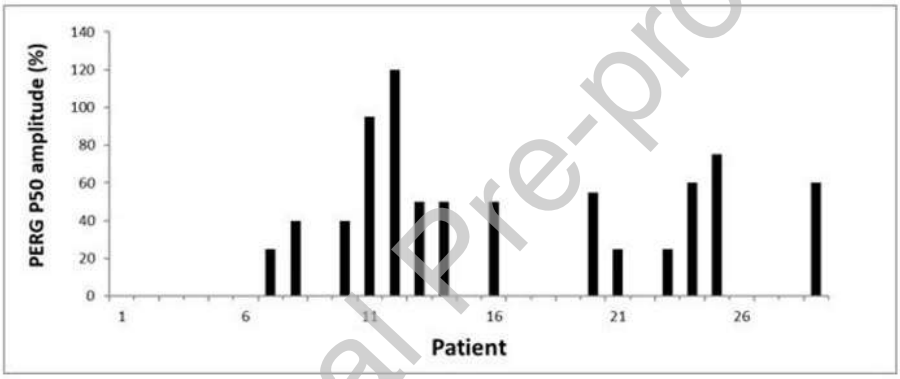

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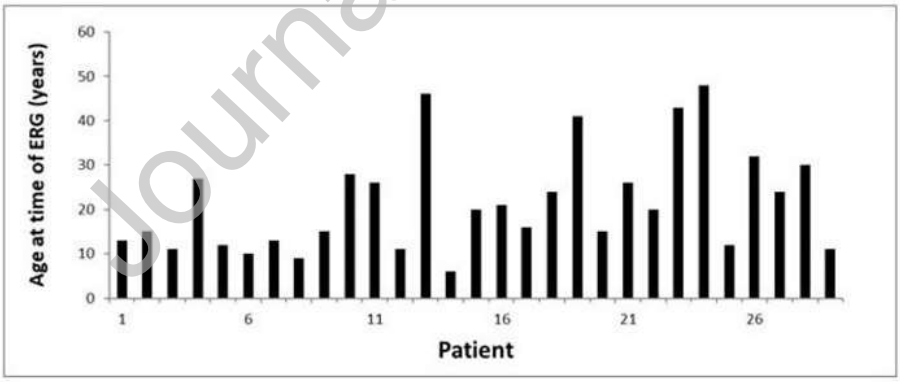

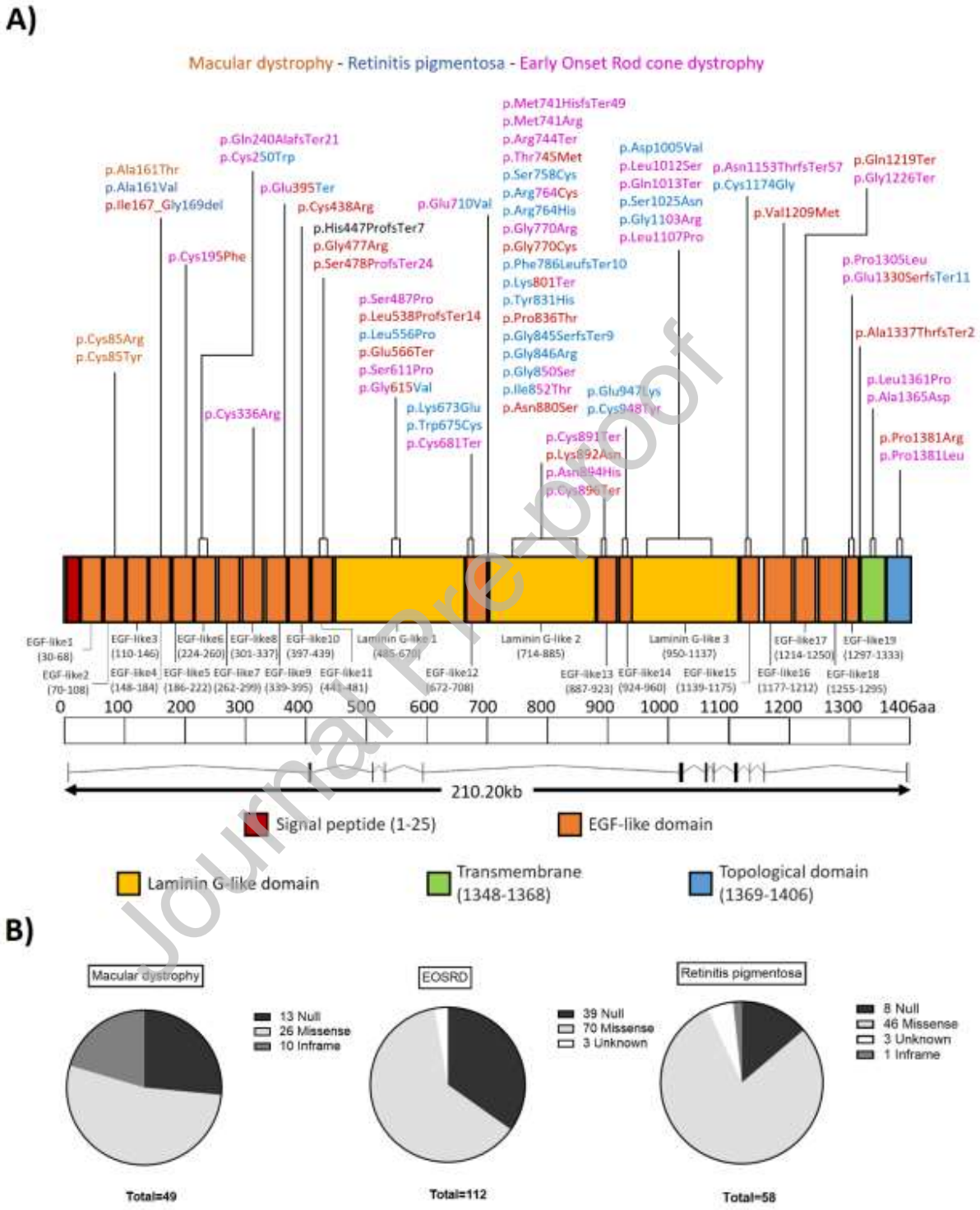

Table 1: Clinical characteristics of *CRB1* disease.

	EOSRD/LCA (n=54, 52%)	RP (n= 26, 25%)	MD (n= 24, 23%)
Age at baseline, mean ± SD (years)	16.2 ± 15.3	23.9 ± 18.6	23.2 ± 13.7
Gender, n (%)			
Male	32 (56)	19 (66)	17 (68)
Female	25 (44)	10 (34)	8 (32)
Age of onset, mean ± SD (years)	2 ± 2.2	13.7 ± 10.5	16.3 ± 10.8
Infancy (birth – 2 years old)	37	0	0
Childhood (3 – 11 years old)	20	14	10
Adolescence (12 – 16 years old)	0	5	6
Adulthood (over 16 years old)	0	10	9
Baseline best corrected visual acuity, mean ± SD (LogMAR)	1.6 ± 0.8	0.9 ± 0.8	0.6 ± 0.4
Final best corrected visual acuity, mean ± SD (LogMAR)	1.9 ± 0.7	1.3 ± 1	0.8 ± 0.5
Baseline WHO visual impairment category, n= (%)*			
No or mild impairment	4 (7)	10 (38)	14 (58)
Moderate impairment	15 (28)	10 (38)	10 (42)
Severe impairment	8 (15)	0	0
Blindness	20 (37)	5 (21)	0
Spherical equivalent, mean ± SD	+5.75 ± +3.5	+1.75 ± +1.75	+0.75 ± +2.5
High hyperopia	21 (39)	1 (3)	1 (4)
Myopia	2 (4)	1 (3)	7 (29)
Lens opacity, n (%)	17 (31)	15 (58)	2 (8)
Keratoconus, n (%)	4 (7)	1 (4)	0
Nummular pigment, n (%)	34 (63)	11 (42)	3 (12)
Macular involvement, n (%)	54 (100)	25 (96)	24 (100)
Baseline OCT categories, eyes n (%)			
Normal lamination and organisation	0	7 (16)	11 (28)
Abnormal lamination	42 (54)	37 (75)	32 (70)
Disorganisation	34 (46)	6 (9)	1 (2)
Yellow/white dots, n (%)	16 (30)	3 (11)	2 (8)
PPRPE, n (%)	16 (30)	10 (38)	3 (12)
Retinal telangiectasia, n (%)	7 (13)	4 (15)	0

EOSRD/LCA: Early Onset Severe Retinal Dystrophy/ Leber Congenital Amaurosis; RP: Retinitis Pigmentosa; MD: Macular Dystrophy; SD: Standard Deviation; OCT: Optical Coherence Tomography; PPRPE: Preserved Paraarteriolar Retinal Pigment Epithelium.

*: the patients that do not appear in this classification correspond to 7 babies with LCA with non ETDRS measured vision (e.g., fix and follow) and 1 patient with RP with no details of acuity.

This is multicentre international retrospective cohort study.

Clinical notes, ophthalmic images, and genetic testing results of 104 patients with disease-causing CRB1 variants were reviewed.

EOSRD/LCA is the most common phenotype, often associated with null variants.

Individuals with CRB1 variants can present with adult-onset RP.

OCT lamination may have a degenerative component.

CRB1-retinopathy is often symmetric and has a reasonable window for intervention.