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Research Article

Molecular Genetic Characterization of Recurrent CRB1 and EIF2B5 Variants in an Iraqi Consanguineous Cohort with Inherited Retinal Dystrophy and White Matter Disease

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ABSTRACT

Background: Inherited retinal dystrophy and inherited white matter disorders are genetically heterogeneous conditions in which consanguinity increases the probability of homozygous autosomal recessive variants. **Objective:** To characterize recurrent CRB1 and EIF2B5 variants in an anonymized Iraqi cohort using whole-exome sequencing and Sanger validation. **Methods:** The analyzed cohort consisted of 24 individuals: 10 unrelated unaffected controls, 6 patients with inherited retinal dystrophy, and 8 patients with white matter disease. Variant prioritization used phenotype-guided recessive filtering, Sanger confirmation, local-control comparison, and ACMG/AMP-oriented evidence mapping. **Results:** The retinal dystrophy group included 4 males and 2 females and showed a recurrent homozygous CRB1 variant, NM_201253.3:c.2106T>G; p.(Tyr702*), in all 6 cases and in none of the 10 controls. The white matter disease group included 4 males and 4 females and showed a recurrent homozygous EIF2B5 variant, c.327A>G; p.(Ile109Met), in all 8 cases and in none of the controls. Exact testing supported phenotype-specific separation from the controls for CRB1, EIF2B5, and combined affected status. **Conclusion:** This molecular cohort supports phenotype-specific recurrence of CRB1 in inherited retinal dystrophy and EIF2B5 in white matter disease among consanguineous Iraqi families. The CRB1 nonsense variant supports a loss-of-function interpretation, while the EIF2B5 missense variant showed consistent cohort-level association with white matter disease.

KEYWORDS: Whole-exome sequencing; CRB1; EIF2B5; inherited retinal dystrophy; leukodystrophy; vanishing white matter; Sanger sequencing; ACMG; Iraq; consanguinity.

INTRODUCTION

Inherited retinal dystrophies are a clinically and genetically heterogeneous group of disorders caused by pathogenic variation in genes that maintain photoreceptor integrity, retinal polarity, and retinal pigment epithelial function [1-4]. CRB1-associated retinopathy is a major autosomal recessive retinal disease spectrum that includes early-onset severe retinal dystrophy, Leber congenital amaurosis, retinitis pigmentosa, and macular dystrophy-like phenotypes [1, 2, 5]. Recent cohorts and mechanistic studies support the importance of CRB1-related retinal architecture disruption, variable OCT findings, and genotype-phenotype heterogeneity [1, 3, 4, 6, 7].

Inherited white matter disorders are similarly heterogeneous and require integration of clinical phenotype, MRI pattern recognition, and molecular testing [9-11]. Vanishing white matter disease and related EIF2B disorders are caused by biallelic pathogenic variants in EIF2B1-EIF2B5, which encode subunits of the eukaryotic initiation factor 2B complex. EIF2B5 encodes the epsilon subunit and has an established relationship with leukoencephalopathy with vanishing white matter [9, 10, 12, 13].

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Consanguinity increases the probability of homozygous rare variants and makes whole-exome sequencing particularly useful for recessive disease analysis, especially when variant filtering is guided by phenotype and followed by Sanger validation [14, 15, 16]. In inherited retinal disease, modern molecular diagnosis increasingly depends on exome/genome sequencing, reanalysis, and precise HGVS-compliant variant nomenclature [17-25].

This study analyzed an anonymized Iraqi molecular genetics cohort to characterize recurrent CRB1 and EIF2B5 findings in the studied families. The study was designed as a molecular cohort analysis rather than a national prevalence survey.

MATERIALS AND METHODS

STUDY DESIGN AND COHORT DEFINITION

This was an anonymized observational molecular cohort study involving 24 individuals: 10 unrelated unaffected controls, 6 patients with inherited retinal dystrophy, and 8 patients with white matter disease. Sample identifiers were anonymized as C01-C10 for controls, R01-R06 for retinal dystrophy cases, and W01-W08 for white matter disease cases. The cohort structure and sex distribution are summarized in Table 1. The WES-based molecular workflow is shown in Figure 1, and the CRB1-associated retinal phenotype framework is presented in Figure 2.

Table 1. Cohort structure and demographic distribution.

Category	n	%	Sex distribution	Key note
Total analyzed cohort	24	100.0	13 male / 11 female	Analyzed cohort
Unaffected controls	10	41.7	5 male / 5 female	Unrelated; negative for the identified variants
Inherited retinal dystrophy	6	25.0	4 male / 2 female	Retinal phenotype group evaluated for CRB1
White matter disease	8	33.3	4 male / 4 female	White matter phenotype group evaluated for EIF2B5

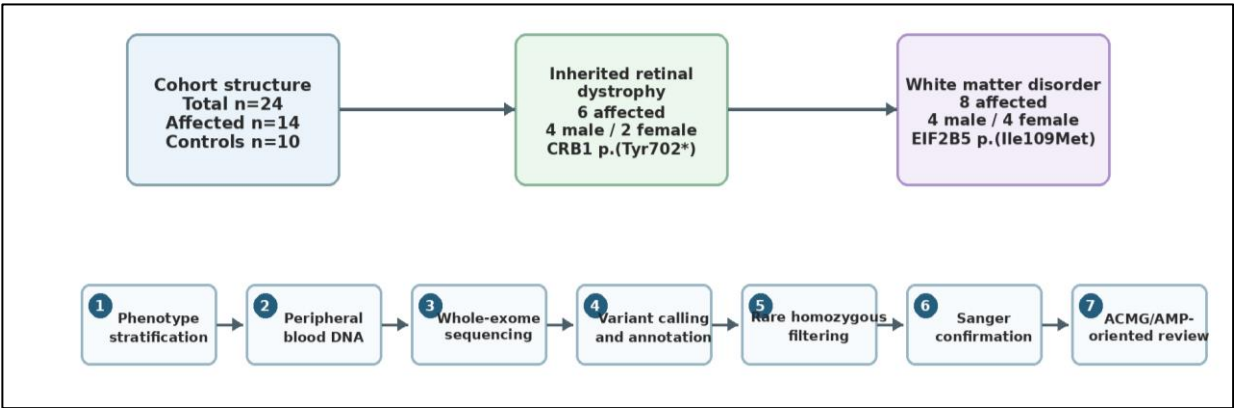


Figure 1. Study design and WES-based molecular interpretation workflow. The cohort includes 24 individuals: 10 controls, 6 inherited retinal dystrophy cases, and 8 white matter disease cases. The workflow links phenotype stratification to peripheral-blood DNA, WES, variant calling, rare homozygous filtering, Sanger confirmation, and ACMG/AMP-oriented interpretation.

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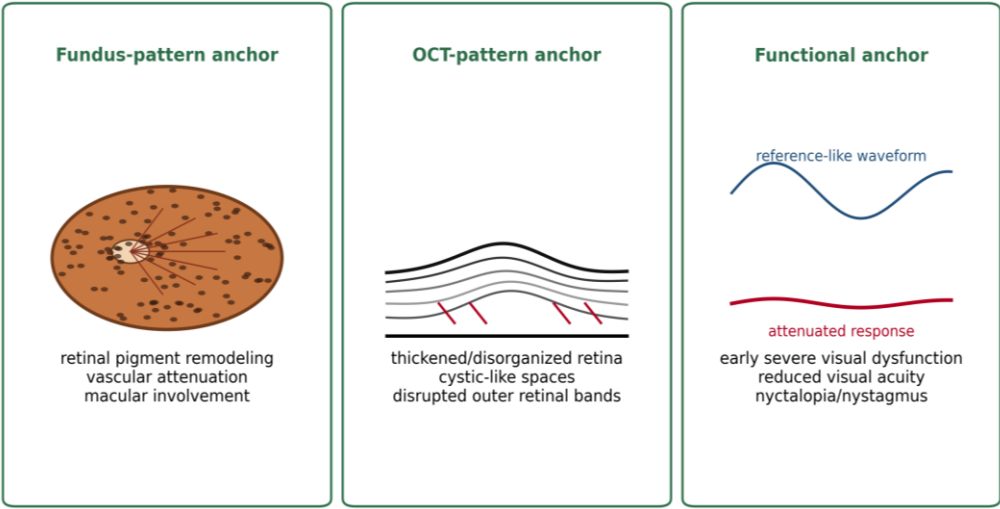


Figure 2. Retinal phenotype anchors for CRB1-associated disease. The schematic summarizes fundus-pattern, OCT-pattern, and functional features associated with CRB1-related retinal dystrophy.

ANONYMIZED SAMPLE STRUCTURE

The sample-level demographic and molecular characteristics of the analyzed cohort are presented in Table 2. Ages are reported as recorded for each participant, including the eight white matter disease cases (W01-W08).

Table 2. Anonymized sample-level structure used for molecular analysis.

ID	Group	Age	Sex	Consang.	Family/clinical status	Gene	Variant	Validation/result
C01	Control	20	Male	No	Unaffected control	Not applicable	Not applicable	Negative
C02	Control	21	Male	No	Unaffected control	Not applicable	Not applicable	Negative
C03	Control	28	Male	No	Unaffected control	Not applicable	Not applicable	Negative
C04	Control	17	Male	No	Unaffected control	Not applicable	Not applicable	Negative
C05	Control	14	Male	No	Unaffected control	Not applicable	Not applicable	Negative
C06	Control	19	Female	No	Unaffected control	Not applicable	Not applicable	Negative
C07	Control	11	Female	No	Unaffected control	Not applicable	Not applicable	Negative
C08	Control	10	Female	No	Unaffected control	Not applicable	Not applicable	Negative
C09	Control	30	Female	No	Unaffected control	Not applicable	Not applicable	Negative
C10	Control	18	Female	No	Unaffected control	Not applicable	Not applicable	Negative

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R01	Retinal dystrophy	8	Male	Yes	FAM01	CRB1	NM_201253.3:c.2106T>G; p.(Tyr702*)	Sanger confirmed
R02	Retinal dystrophy	10	Male	Yes	FAM01	CRB1	NM_201253.3:c.2106T>G; p.(Tyr702*)	Sanger confirmed
R03	Retinal dystrophy	13	Male	Yes	FAM01	CRB1	NM_201253.3:c.2106T>G; p.(Tyr702*)	Sanger confirmed
R04	Retinal dystrophy	15	Male	Yes	FAM01	CRB1	NM_201253.3:c.2106T>G; p.(Tyr702*)	Sanger confirmed
R05	Retinal dystrophy	18	Female	Yes	FAM02	CRB1	NM_201253.3:c.2106T>G; p.(Tyr702*)	Sanger confirmed
R06	Retinal dystrophy	8	Female	Yes	FAM02	CRB1	NM_201253.3:c.2106T>G; p.(Tyr702*)	Sanger confirmed
W01	White matter disease	1	Male	Yes	FAM09	EIF2B5	c.327A>G; p.(Ile109Met)	Sanger confirmed
W02	White matter disease	6	Male	Yes	FAM09	EIF2B5	c.327A>G; p.(Ile109Met)	Sanger confirmed
W03	White matter disease	22	Male	Yes	FAM10	EIF2B5	c.327A>G; p.(Ile109Met)	Sanger confirmed
W04	White matter disease	72	Male	Yes	FAM10	EIF2B5	c.327A>G; p.(Ile109Met)	Sanger confirmed
W05	White matter disease	8 mo.	Female	Yes	FAM11	EIF2B5	c.327A>G; p.(Ile109Met)	Sanger confirmed
W06	White matter disease	4	Female	Yes	FAM11	EIF2B5	c.327A>G; p.(Ile109Met)	Sanger confirmed
W07	White matter disease	16	Female	Yes	FAM12	EIF2B5	c.327A>G; p.(Ile109Met)	Sanger confirmed
W08	White matter disease	45	Female	Yes	FAM12	EIF2B5	c.327A>G; p.(Ile109Met)	Sanger confirmed

WHOLE-EXOME SEQUENCING AND VARIANT PRIORITIZATION

Genomic DNA from peripheral blood was analyzed by whole-exome sequencing. The analytic logic included sequence quality control, alignment to a human reference assembly, variant calling, annotation, and phenotype-driven prioritization. Filtering emphasized rare coding and splice-site variants compatible with autosomal recessive inheritance, especially homozygous variants recurrent within the same clinical category. Candidate prioritization considered gene-disease validity, molecular consequence, zygosity, phenotype fit, local-control status, and Sanger confirmation [14-16, 25].

SANGER SEQUENCING VALIDATION

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Candidate variants were validated by Sanger sequencing. Representative chromatographic evidence for targeted-region confirmation is shown in Figure 7.

ACMG/AMP-ORIENTED EVIDENCE ASSESSMENT

Variant interpretation followed ACMG/AMP-oriented logic and current HGVS nomenclature principles. Evidence was organized according to gene-disease validity, molecular consequence, phenotype specificity, case enrichment, Sanger confirmation, and local-control status [25-27].

STATISTICAL ANALYSIS

Descriptive statistics were used to summarize the cohort. Categorical variables were reported as counts and percentages, while age was summarized using the mean, median, and range. The age of 8 months was converted to 0.67 years for numerical analysis. Age distributions across the three groups were compared using the Kruskal-Wallis test. Fisher's exact test was used for phenotype-specific comparisons of variant-positive affected cases with controls because expected cell counts were small. Sex distribution across the three groups was assessed using the two-sided Fisher-Freeman-Halton exact test.

RESULTS

DEMOGRAPHIC AND CLINICAL COHORT STRUCTURE

The analyzed cohort included 24 individuals. Controls had a mean age of 18.8 years, a median age of 18.5 years, and an age range of 10-30 years. Retinal dystrophy cases had a mean age of 12.0 years, a median age of 11.5 years, and an age range of 8-18 years. White matter disease cases had a mean age of 20.8 years, a median age of 11.0 years, and an age range of 8 months to 72 years. Age distributions did not differ significantly across the three groups (Kruskal-Wallis $H = 3.14$, $p = 0.208$). Sex distribution also did not differ significantly among the groups (Fisher-Freeman-Halton exact test, two-sided $p = 0.769$). These demographic characteristics are summarized in Table 3.

Table 3. Demographic summary of the analyzed groups.

Group	n	Mean age, years	Median age, years	Age range	Male/Female
Controls	10	18.8	18.5	10-30	5/5
Retinal dystrophy	6	12.0	11.5	8-18	4/2
White matter disease	8	20.8	11.0	8 months-72 years	4/4

MOLECULAR FINDINGS

All 6 inherited retinal dystrophy cases carried a recurrent homozygous CRB1 variant, NM_201253.3:c.2106T>G; p.(Tyr702*), while all 10 controls were negative. This nonsense variant predicts premature termination of the CRB1 protein and is mechanistically coherent with loss of function in an established autosomal recessive retinal dystrophy gene [1, 2, 5, 6]. The predicted molecular consequence is illustrated in Figure 3.

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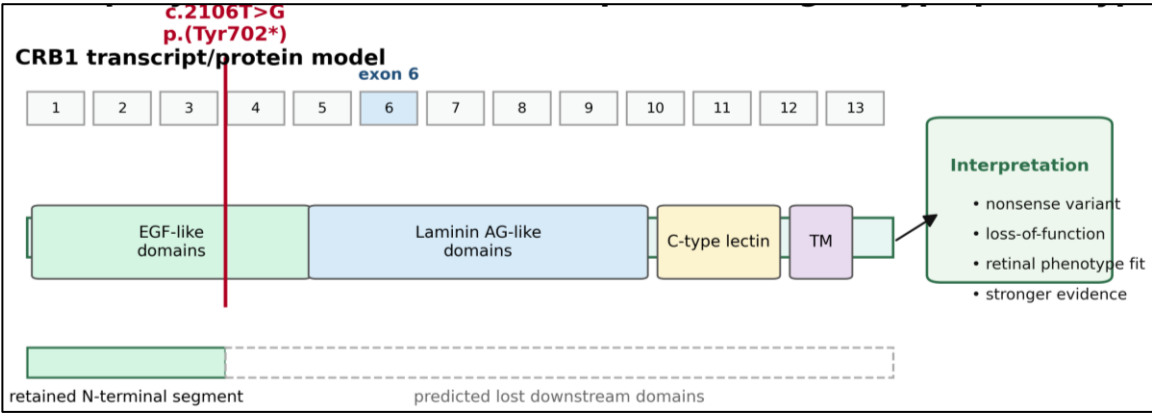


Figure 3. Molecular consequence model for CRB1 NM_201253.3:c.2106T>G; p.(Tyr702*). The schematic highlights premature termination, predicted truncation before downstream domains, and phenotype linkage to early-onset inherited retinal dystrophy.

All 8 white matter disease cases carried a recurrent homozygous EIF2B5 variant, c.327A>G; p.(Ile109Met), while all 10 controls were negative. EIF2B5 encodes the eIF2B epsilon subunit, and biallelic EIF2B variants are biologically coherent with vanishing white matter and related inherited white matter disease mechanisms [9-13]. The biological context of p.(Ile109Met) is summarized in Figure 4, while Figure 5 presents the MRI pattern framework relevant to EIF2B-related disease. The phenotype-specific molecular findings and exact-test results are summarized in Table 4.

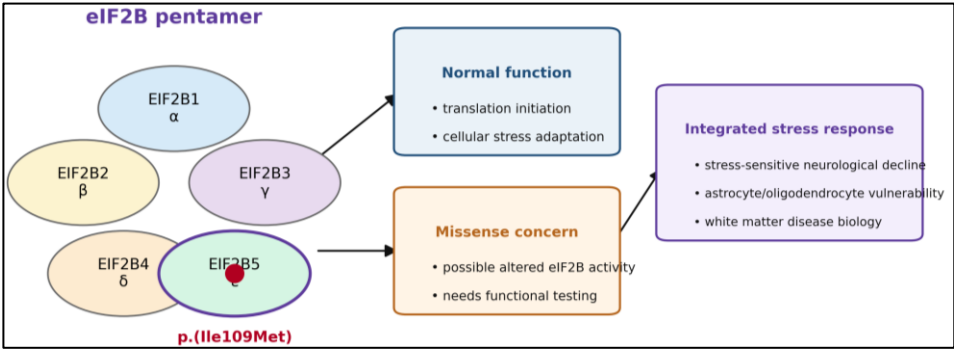


Figure 4. EIF2B5 p.(Ile109Met) biological context. The schematic places EIF2B5 within the eIF2B complex and summarizes how eIF2B-related dysfunction can impair translational control and integrated stress-response regulation in white matter disease.

Table 4. Phenotype-specific molecular findings and exact-test results.

Phenotype group	Positive affected	Gene	Variant	Zygosity	Sanger confirmed	Controls positive	Fisher exact p
Inherited retinal dystrophy	6/6	CRB1	NM_201253.3:c.2106T>G; p.(Tyr702*)	Homozygous	6/6	0/10	0.000125
White matter disease	8/8	EIF2B5	c.327A>G; p.(Ile109Met)	Homozygous	8/8	0/10	0.000023
Any affected patient	14/14	CRB1 or EIF2B5	Phenotype-specific recurrent variant	Homozygous	14/14	0/10	0.00000051

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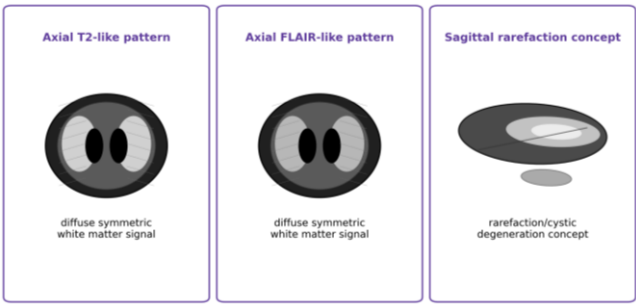


Figure 5. MRI pattern framework for EIF2B-related vanishing white matter disease. The schematic summarizes diffuse symmetric white matter signal abnormalities and rarefaction/cystic degeneration patterns used in radiological interpretation.

ACMG/AMP-ORIENTED EVIDENCE TABLES

Tables 5 and 6 summarize the ACMG/AMP-oriented evidence supporting the interpretation of CRB1 p.(Tyr702*) and EIF2B5 p.(Ile109Met), respectively. A visual comparison of the principal evidence components is provided in Figure 6.

Table 5. ACMG/AMP-oriented evidence map for CRB1 p.(Tyr702*).

ACMG code	Strength	Applied	Rationale
PVS1	Very strong	Yes	Nonsense variant p.(Tyr702*) in CRB1; loss-of-function mechanism is coherent with autosomal recessive CRB1 retinopathy.
PM2_supporting	Supporting	Cohort-level	The variant was absent from all 10 unrelated local controls.
PP4	Supporting	Yes	Phenotype is highly consistent with CRB1-associated inherited retinal dystrophy.
PS4_supporting	Supporting	Cohort-level	The variant was detected in 6/6 affected cases and 0/10 controls (Fisher exact p = 0.000125).
Overall interpretation	Overall	Likely pathogenic	Recurrent likely pathogenic CRB1 loss-of-function variant associated with inherited retinal dystrophy in the studied cohort.

Table 6. ACMG/AMP-oriented evidence map for EIF2B5 p.(Ile109Met).

ACMG code	Strength	Applied	Rationale
PM3_supporting	Supporting	Cohort-level	The variant occurred in the homozygous state in all eight affected cases across four recorded families.
PM2_supporting	Supporting	Cohort-level	The variant was absent from all 10 unrelated local controls.
PP4	Supporting	Yes	White matter disease phenotype is biologically coherent with EIF2B-related leukodystrophy/VWM spectrum.
PS4_supporting	Supporting	Cohort-level	The variant was detected in 8/8 affected cases and 0/10 controls (Fisher exact p = 0.0000229).
Overall interpretation	Overall	Disease-associated variant	Recurrent homozygous EIF2B5 variant associated with white matter disease in the studied cohort.

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	Gene-disease validity	Variant mechanism	Phenotype match	Cohort recurrence	Sanger validation	Controls positive
CRB1 p.(Tyr702*)	Established	Loss-of-function	Strong	6/6	Confirmed	0/10
EIF2B5 p.(Ile109Met)	Established	Missense	Consistent	8/8	Confirmed	0/10

Figure 6. ACMG/AMP-oriented molecular evidence map. The panel compares the principal evidence components supporting the interpretation of CRB1 p.(Tyr702*) and EIF2B5 p.(Ile109Met).

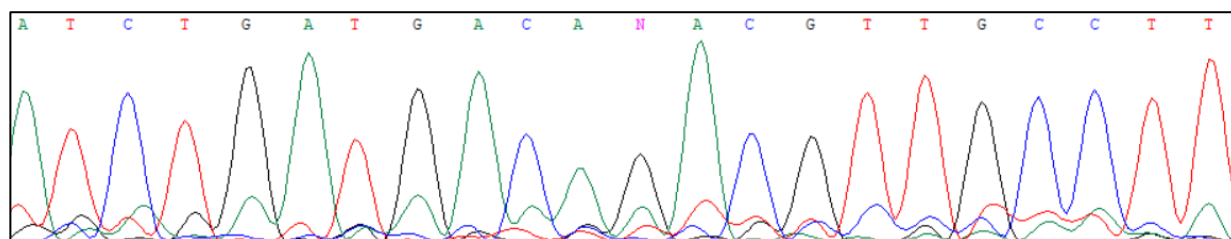


Figure 7. Representative Sanger sequencing chromatogram for targeted-region confirmation of the identified variant site.

DISCUSSION

These Iraqi molecular genetics cohort demonstrates a phenotype-specific recurrence pattern: CRB1 was detected in all retinal dystrophy cases and not in controls, whereas EIF2B5 was detected in all white matter disease cases and not in controls. This separation supports disease-group specificity within the studied cohort.

For the retinal dystrophy group, the CRB1 finding is the stronger molecular result. The p.(Tyr702*) nonsense change is consistent with a truncating loss-of-function mechanism in a validated retinal dystrophy gene. This interpretation agrees with recent CRB1 studies showing broad genotype-phenotype heterogeneity, severe early-onset presentations, OCT structural disruption, and clinically meaningful natural-history variation [1-8].

For the white matter disease group, the EIF2B5 finding is biologically coherent because EIF2B-related disorders are established causes of vanishing white matter and inherited white matter disease [9-13,28]. The p.(Ile109Met) variant occurred in the homozygous state in all eight affected cases, was confirmed by Sanger sequencing, showed concordance with the white matter phenotype, and was absent from all ten controls. Together, these findings support a recurrent cohort-level association between EIF2B5 p.(Ile109Met) and white matter disease.

The exact-test results demonstrate phenotype-specific separation within the studied cohort. Because the analysis is based on a family-based molecular cohort, the statistical findings describe the analyzed sample and are not estimates of national prevalence, founder effect, or population-level risk. The wide age range observed in the white matter disease group is consistent with the recognized clinical variability of EIF2B-related disorders, which may present from infancy through late adulthood.

Compared with broad diagnostic series in inherited retinal disease and rare Mendelian disorders, this study provides a focused analysis of two recurrent phenotype-specific variants supported by whole-exome sequencing and Sanger confirmation [14-24].

CONCLUSION

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These molecular genetics cohort identifies a phenotype-specific pattern of recurrent homozygous CRB1 and EIF2B5 variants in Iraqi consanguineous families. The CRB1 NM_201253.3:c.2106T>G; p.(Tyr702*) variant is interpreted as a recurrent likely pathogenic loss-of-function variant associated with inherited retinal dystrophy. The EIF2B5 c.327A>G; p.(Ile109Met) variant is interpreted as a recurrent homozygous variant associated with white matter disease in the studied cohort. Overall, the findings define a focused molecular pattern linking CRB1 to inherited retinal dystrophy and EIF2B5 to white matter disease.

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