Autosomal dominant PRPF31 disease: A mimicker of autosomal recessive/X-linked inherited retinal degenerations illustrated through a four generation Northern Irish family

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Introduction

- Retinitis pigmentosa (RP) is the most common form of inherited retinal dystrophy characterised by progressive rod and cone degeneration.
- Syndromic (20-30% of RP cases) and non-syndromic forms have been reported.
- Clinically and genetically heterogenous with multiple modes of Mendelian (autosomal dominant, autosomal recessive and X-linked) and very rarely non-Mendelian inheritance (digenic) described.
- Heterozygous variants in *PRPF31* is a significant cause of autosomal dominant non-syndromic RP, typically characterised by non-penetrance in affected families which can lead to difficulties in genetic counselling without genetic testing.
- The *PRPF31* protein is a ubiquitously-expressed splicing factor that is involved in the assembly and stability of the U4/U6•U5 tri-snRNP complex through interaction with other splicing factors (*PRPF3, PRPF4, PRPF6, PRPF8* and *SNRNP200*).[1]
- Although most disease-causing *PRPF31* variants are null alleles, variant haploinsufficiency has been proposed to explain disease non-penetrance (ie disease severity is influenced by the expression level of wild-type *PRPF31*).[2]

Case

- Proband: Presented with nyctalopia since aged 5 years; diagnosed with RP aged 7 years **(Table 1)**.
- Paternal grandmother and grandaunt were also affected **(Figure 1)**.
- Both parents (III: 1 and III: 2) and older sister (IV:1) examined normally with normal electrophysiology **(Figure 2)**.
- They remain asymptomatic till this date.
- Mode of inheritance unclear and initial small panel testing did not yield any results.
- Further large panel testing showed a heterozygous whole gene deletion of *PRPF31* (around 16kb) which was confirmed as the familial variant in other affected and asymptomatic family members **(Figure 1)**.

	Age of symptom onset	Fundal features	Electrophysiology
Proband, 37 (IV:2)	5 years old—nyctalopia	• Typical RP phenotype **(Figure 3A-C)**	• Rod-cone dystrophy on ffERG • PERG information not available
Younger sister of proband, 34 (IV:3)	4 years old— nyctalopia and appearing "clumsy"	• Typical RP phenotype **(Figure 3D)** • Left eye affected by cystoid macular oedema but responsive to oral acetazolamide treatment	• Severely delayed and reduced ffERG (rod and cone responses) • PERG information not available
Daughter of proband, 13 (V:3)	5 years old—struggling with changing light conditions	• Typical RP phenotype **(Figure 3E-G)**	• Tested aged 6 years old • Undetectable DA 0.01 responses on ffERG • Moderately preserved DA 3.0, LA 3.0 and 30Hz flicker responses
Nephew of proband, 11 (V:1)	6 years old—nyctalopia 10 years old— bumping into objects	• Absence of bony-spiculed hyperpigmentation in mid-periphery • Diffuse small multifocal white "dots" in periphery **(Figure 3H-J)** • Hyper-autofluorescent ring at macula on FAF typical of RP	• Tested aged 8 years old • Undetectable DA 0.01 and 3.0 responses • Residual b-wave amplitude on LA 3.0 but implicit time delayed • Undetectable 30Hz flicker
Younger brother of V:1, 6 (V:2)	6 years old— mild nyctalopia but subjectively denies any visual issues	• Similar fundal phenotype to older brother **(Figure 3K-M)**	• Tested aged 6 years old • Undetectable DA 0.01 and 30Hz flicker responses • Severely reduced DA 3.0 and LA 3.0 responses • Preserved PERG responses

Table 1: Age of symptom onset, fundal features and electrophysiology (full field ERG and pattern ERG where available) findings of each affected family member. DA: dark adapted, FAF: fundus autofluorescence, LA: light adapted.

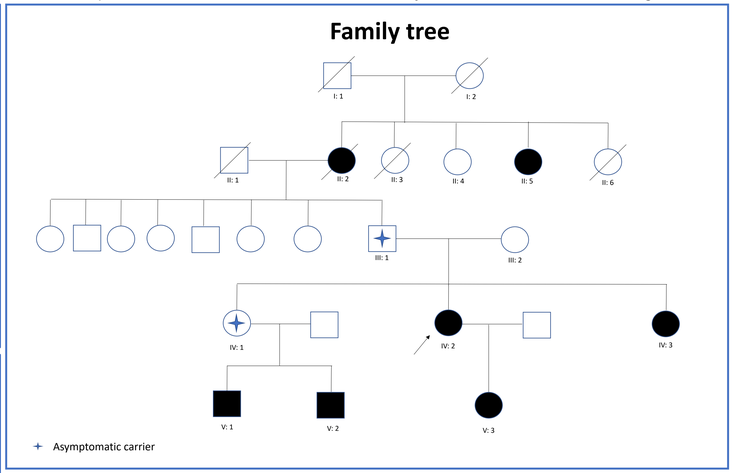


Figure 1: The family tree of this Northern Irish pedigree denoting autosomal dominant inheritance of the familial *PRPF31* variant. Filled symbols indicate affected members, open symbols are unaffected. Asymptomatic carriers are marked with an icon.

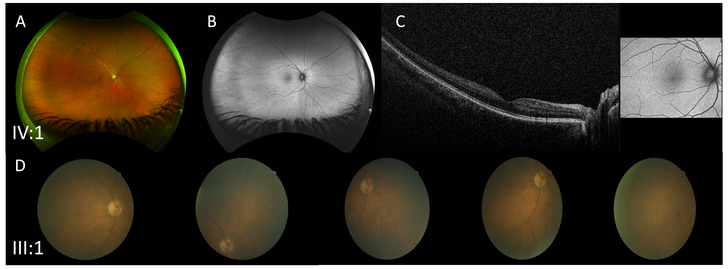


Figure 2: Colour fundus photograph, fundus autofluorescence and OCT images (where available) showing normal fundal examination of the asymptomatic carriers. Only the right eyes are shown here. Proband's older sister (IV:1; A-C) and proband's father (III:1; D).

Discussion and conclusion

- Disease non-penetrance characteristic of *PRPF31*-associated non-syndromic RP is clearly illustrated in this pedigree.
- Disease severity seems to be mild given the extent of gene deletion, which concurs with other previously reported families with large deletions of *PRPF31*.[3-5]
- Most affected patients with large *PRPF31* deletions reported in literature have typical RP phenotype, but two of the youngest members of our pedigree (V:1 and V:2) did not display any evidence of pigmentary retinopathy on colour fundal imaging.
- Genetic testing is key in non-penetrant conditions to aid diagnosis and counselling.
- Further research is needed to explain why pathogenic variants in *PRPF31* only display an isolated ocular phenotype despite being ubiquitously expressed.



Figure 3: Colour fundal photograph, fundus autofluorescence and OCT images (where available) of each affected family member. Only the right eyes are shown here. Proband (A-C), younger sister of proband (IV:3; D), daughter of proband (V:3; E-G), older nephew or proband (V:1; H-J) and younger nephew of proband (V:2; K-M).

References

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