Novel *C8ORF37* mutation causing cone rod dystrophy

El Matri L (1,2), Falfoul Y (1,2), Habibi I (3), Turki A (1), El Matri K (1,2), Chebil A (1,2), Schorderet D (3)
(1) Oculogenetic laboratory LR14SP01, Tunis, Tunisia; (2), Hedi Rais institute of Ophthalmology, Department B, Tunis, Tunisia; (3) Institute for Research in Ophthalmology (IRO), Sion, Switzerland

F120

Introduction:

Retinal dystrophies (RD) are a heterogeneous group of diseases in which the photoreceptor and retinal pigment epithelium (RPE) cells of the retina degenerate, leading to partial or complete blindness.

This group of rare genetic disorders shows substantial clinical and genetic overlaps with high genetic heterogeneity involving more than 220 genes identified so far.

Similar phenotypes may result from different gene mutations, and subtle differences in phenotypes may result from a similar mutation.

Our aim was to localize and identify the gene and mutations causing a special phenotype of cone rod dystrophy (CRD) in a consanguineous Tunisian family.

Methods:

We performed a clinical and molecular genetic study of a consanguineous Tunisian family with 3 individuals affected with CRD.

Patients underwent color fundus photography, fundus autofluorescence, SS-OCT and electrophysiology.

DNA sample from the index patient was subjected to whole exome sequencing (WES). Variants localized in homozygous regions were validated by Sanger sequencing. Familial segregation was performed.

Results:

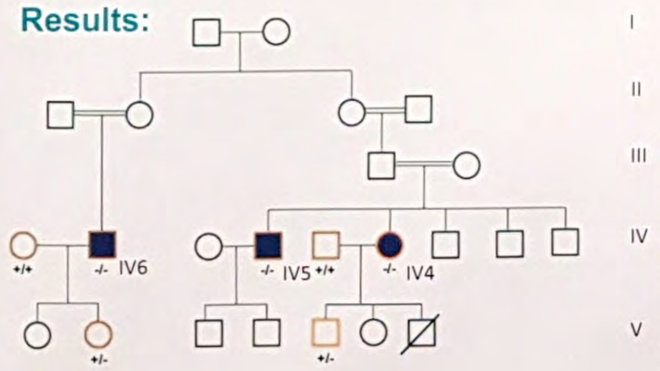


Figure 1: Patients IV.4 (A) and IV.5 (B): beaten-bronze aspect of the macula, peripheral RPE atrophy, mild optic atrophy, narrowing of the vessels with rare peripheral spicule deposits.
Patient IV.6 (C): gliosis of the posterior pole better visualized on OCT with diffuse retinal atrophy and rare peripheral spicule deposits.

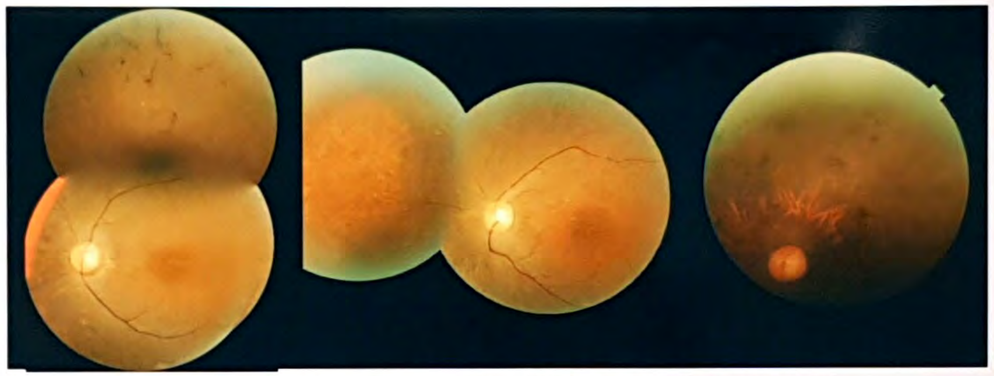


Figure 2: Left eye fundus autofluorescence of patients IV.4 (A); IV.5 (B); IV.6 (C)

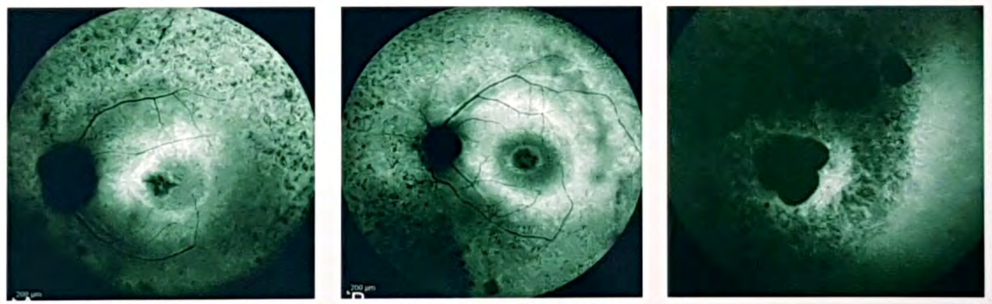
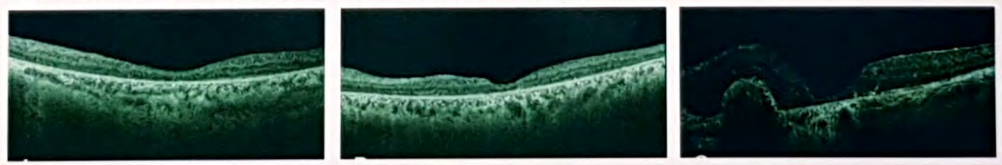
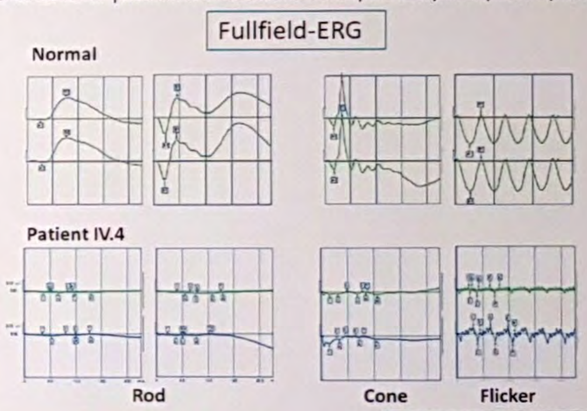


Figure 3: Left eye OCT of patients IV.4 (A); IV.5 (B); IV.6 (C)

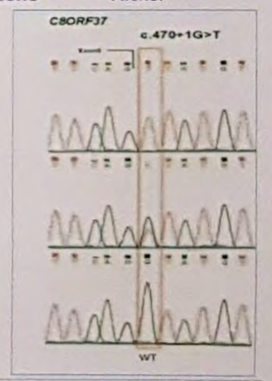


Patient	Gender	Age years	Age of onset	Visual acuity RE	LE
IV.4	F	32	8	Hand movement	
IV.5	M	30	10	1/10	1/20
IV.6	M	52	Infancy	Light perception	

Figure 4: ERG of patient IV.5 reduced scotopic and photopic responses



Novel homozygous splice-site mutation **(NM_177965: c.470+1G>T)** in ***C8ORF37***



References
•Rahner N, et al. Ophthalmic Genet. 2016; 37(3):294-300.
•Ravesh Z, et al. Mol Vis. 2015; 21:236-43.
•Van Huet RA et al. Invest Ophthalmol Vis Sci 2013; 54:4683-90.
•Heon E et al. Hum Mol Genet. 2016; 25(11):2283-2294.

Discussion and conclusions:

We describe a novel mutation in ***C8orf37***, coding to a ciliary cytoplasmic protein, observed in the index patient and in two-affected brothers. The **c.470+1G>T variant** is located in the donor splice side of intron 6 and was not detected in any databases, indicating that it is not a common polymorphism, and the strength of the splice donor site was predicted to be decreased by several splice site strength prediction programs. The localization of genetic abnormalities has been previously described by Rahner et al, as 56% of the mutations are located in exon 6 in the c-terminal region of *C8ORF37* and the majority of variant are splicing variant. Although mutated *C8ORF37* is a rare cause of RD (0,4% in Pakistani cohort), the phenotype of the patients shows broad variability ranging from CRD, RP with early macular involvement to syndromic conditions: Bardet-Biedl syndrome . Our patients showed phenotype variability depending on age; but with a constant early macular involvement

* No proprietary interest, no financial support