Novel Mutation in *CTNNA1* causes Autosomal Dominant Pattern

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INTRODUCTION

Pattern dystrophy (PD)

- A rare autosomal dominant disease of the macula[1]
- Pigment or lipofuscin deposits within the retinal pigment epithelium causing its erosion[1,2]
- Leads to impairment of central vision with progressive visual loss[1,2]
- *PRPH2* and *OTX2* are the most common genes implicated in PD[2,3]

-The proband, a 25 year old female presented with PD. Panel based gene testing (n = 28) candidate genes for macular dystrophy was negative. Additional family members (n = 6) were recruited and examined.
-Three additional members were diagnosed to have PD (Figure 1)
-Best corrected visual acuity was 20/50 or better in all affected. II-1 had no symptoms
-Photophobia was present in the proband,
-Fundus photo and Optical Coherence Tomography (OCT) in two members of the pedigree are shown (Figures 2 – 5)

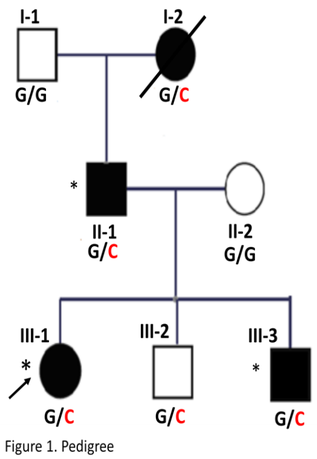

Figure 1. Pedigree

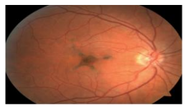

Figure 2. Fundus photo in Proband

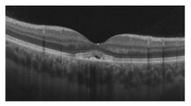

Figure 3. Proband's (III-1) OCT

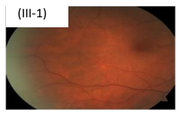

Figure 4. Fundus photo of unaffected (II-2)

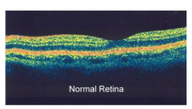

Figure 5. Normal OCT [4]

Figure 6. Fundus photo of (III-2)

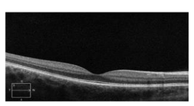

Figure 7. (III-2) 's OCT

-**Ethnicity**: European (Lithuanian/British)
-**Mode of Inheritance**: Dominant inheritance
Legend:
*= Three underwent WGS
Red= mutant allele in *CTNNA1*
(NM_001903: exon6:c.835G>C:p.A279P)

AIMS

To identify the genetic cause underlying PD in a three generation pedigree by doing WGS analysis

METHODS

Figure 8. WGS Filtering protocol

Genes from candidate gene panel (n = 11) were prioritized first during the filtering process. The same steps that were applied for whole genome filtering were used to do a target gene panel filtering approach.

PRELIMINARY RESULTS

- WGS filtering analysis using 3 affected family members indicated a novel missense variant in *CTNNA1* (NM_001903: exon6:c.835G>C:p.A279P) (Figure 8)
- A segregation analysis on all 7 family members was performed ; all affected family members were heterozygous for presumed disease-causing missense variant in *CTNNA1*. (Figure 9); However the variant was found in III-2 deemed to be clinically unaffected (Figure 6 & 7)
- The identified variant had strong predictive scores (Table 1) and was not found in GnomAD

Score Type	Pathogenicity Scores for CTNNA1 variant	Scores considered significant
spx_dsp	-2.3	<= -4
sift	0.041	<= 0.05
PROVEAN	-3.12	< -2.5
polyphen	0.974	>= 0.95
ma_score	2.42	>= 2
CADD_Phred	28.3	>= 15
PhylopPMam	2.52	>=2.5

Table 1. Pathogenetic scores of CTNNA1 variant

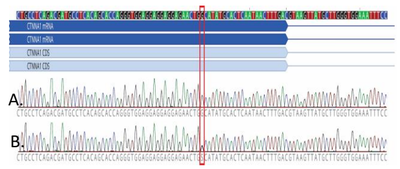

Figure 9. Variant Validation
A. Unaffected
B. Affected

Future Directions

- Compare allele expression levels of the wild type allele versus mutant allele via allele specific quantitative PCR or allele specific mass spectrometry , using patient derived cell lines from affected family members (including the seemingly unaffected person) and unaffected members in order to explore if incomplete penetrance plays a role in this PD case

-Explore other possible candidate variants in WGS that may be responsible for the phenotype.

Discussion & Conclusions

- We have identified a novel likely disease causing mutation in *CTNNA1* in a pedigree with PD.
- We postulate that incomplete penetrance may explain why the "unaffected" is a carrier of the disease causing variant
- Existing literature supports this conclusion :

→ There is one previous report in the literature where *CTNNA1* has been implicated with PD[2].
→Although there is no known incomplete penetrance in *CTNNA1*-related PD, there is literature showing incomplete penetrance cases for autosomal dominant eye diseases in the following genes: PRPH2[6], *OTX2*[7] , PRPF31[5]

- We also consider that late age of onset may be an alternative explanation
- Our discovery further supports the theory that *CTNNA1* is implicated in PD

References & Funding

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