Novel Mutation in CTNNA1 causes Autosomal Dominant Pattern

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Supported by the Vision Science Research Program Scholarship

INTRODUCTION

Pattern dystrophy (PD) - A rare autosomal dominant disease of the macula1 - Pigment or lipofuscin deposits within the retinal pigment epithelium causing its erosion2,3 - Leads to impairment of central vision with progressive visual loss2,3 - PRPH2 and OTX2 are the most common genes implicated in PD2,3

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)

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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 nonsense 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 nonsense 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

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.

AIMS

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

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.
- 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, OTX2, PRPF31
- 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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Figure 9. Variant Validation

A. Unaffected
B. Affected

Table 1. Pathogenetic scores of CTNNA1 variant

<table>
<thead>
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<th>Score Type</th>
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<th>Scores considered significant</th>
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<tr>
<td>spo_dsp</td>
<td>-2.3</td>
<td>&lt;= -4</td>
</tr>
<tr>
<td>sift</td>
<td>0.041</td>
<td>&lt;= 0.05</td>
</tr>
<tr>
<td>PROVEAN</td>
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<td>&lt;= -2.5</td>
</tr>
<tr>
<td>polyphen</td>
<td>0.974</td>
<td>&gt;= 0.95</td>
</tr>
<tr>
<td>ma_score</td>
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