Prevalence of MYOC mutations in a cohort of Juvenile Open-Angle Glaucoma (JOAG) patients from Sub-Saharan Africa

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INTRODUCTION

- Juvenile open angle glaucoma (JOAG), a subset of primary open angle glaucoma, affects younger people aged 3 to 40 years
- Patients with JOAG have a lifetime high risk of blindness, especially in sub-Saharan Africa, due to the challenges of glaucoma care.
- This study aimed to determine the overall prevalence of *MYOC* mutations in a sub-Saharan African population and the specific mutations which are most common in this population

DESIGN & METHODS

- DNA was tested for *MYOC* coding sequence mutations using Sanger sequencing.
- Identified mutations were evaluated for pathogenicity by1) ClinGen scoring 2) Assessing prevalence in large public databases of patients with African ancestry (gnomAD and 1000 Genomes), 3) Mutation analysis algorithms (PolyPhen, SIFT, Blosum62, MutationTaster, CADD, and AlphaMissense).
- The prevalence of variants was compared between JOAG patients and normal controls from Ibadan using a mutation burden analysis using SKAT-O.

SOCIODEMOGRAPHIC CHARACTERISTICS

	Controls (n=48)	JOAG n= 45	P-Value
Age	25.1 ± 15.2	25.1 ± 7.4	0.99
Sex	27 (56.3%)	16(35.6%)	0.05
Ethnicity	47 (97.9)%	44(97.7%)	0.99
Family History of glaucoma	0	8(17.8%)	NA

RESULTS

- 10 instances of 4 *MYOC* variants were detected.
- A p.Pro370Leu variant, which has been previously categorized by the ClinGen as Pathogenic, was detected in three (6.7%) of 45 JOAG probands.
- A p.470Cys *MYOC* variant, previously categorized a Variant of Unknown Significance, was identified in one (2.2%) of 45 JOAG probands.
- A p.Glu352Lys variant, previously categorized as Benign, was detected in 2 (4.4%) of JOAG probands.
- Both the p.Pro370Leu and p.Arg470Cys variants were absent from control subjects and large public databases while p.Glu352Lys was present at a frequency >1%, which is inconsistent with pathogenicity.
- Five of six mutation analysis algorithms supported the pathogenicity of the p.Pro370Leu and p.Arg470Cys variants, while slightly fewer (4 of 6) suggested that p.Glu352Lys is pathogenic

CONCLUSIONS

- *MYOC* mutations are the most common known cause of JOAG in populations of European ancestry.
- Our case-control study estimated the prevalence of pathogenic *MYOC* mutations to be 8.9% in an African population from Nigeria.
- *MYOC* mutations are the most common known cause of JOAG in sub-Saharan Africa, however, they account for a minority of cases.

NEXT STEPS

- Conduct additional genotyping analyses in a larger cohort to identify mutations in other known JOAG-causing genes, such as *EFEMP1*.
- Pedigree Analysis: Whole-exome sequencing
- (WES) will be initiated for the two largest JOAG pedigrees, each comprising at least 20 individuals.
- We will focus on identifying rare variants that segregate with disease

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