GLAUCOMA

Prevalence of Myocilin Gene Mutation in Adult-Onset Primary Open Angle Glaucoma and Non-Glaucoma Subjects who are Indigenes of Rivers State

Onua, A. A.[1], Pedro-Egbe, C.N.[1], Awoyesuku, E.A.[1], Agaviezor, B.O.[2] & Ordinioha, B.[3]

[1]Department of Ophthalmology, University of Port Harcourt, Nigeria
[2]Department of Animal Sciences/Genetics, University of Port Harcourt, Nigeria
[3]School of Public Health, University of Port Harcourt, Nigeria
Corresponding author: *Onua A. A.,*
E-mail: *azubuike.onua@uniport.edu.ng, +2348037206138*

Background: Glaucoma is the leading cause of irreversible blindness incapacitating over 80 million people worldwide[1-3]. Several pathogenetic mechanisms have been postulated to explain the optic nerve damage that occur in POAG among which genetic predisposition is prominent. Gene-Linkage-based studies have identified genes associated with POAG: Myocilin, Optineurin, WDR36, Tank-Binding Kinase (TBK1) and APbb2[4-10].
Objective: To investigate the prevalence of myocilin gene mutation in adult-onset POAG patients and non-glaucoma subjects who are indigenes of Rivers State.
Methods: This was a comparative cross-sectional study of the prevalence of mutations in myocilin gene among established adult-onset primary open angle glaucoma patients and their age and sex-matched non-glaucoma phenotypically normal subjects who are indigenes of Rivers State recruited from the 23 LGAs in Rivers State through a multi-stage random sampling technique.
Sample size was determined from the formula for comparing two proportions[11]:

$$n = \frac{(Z\alpha/2 + Z_{1-\beta})^2}{(P1-P2)^2}\ \{P1(1-P1) + P2(1-P2)\}$$

- Where: n = minimum sample size
- $Z_{\alpha/2}$ = standard normal deviate (5% level of significance = 1.96)
- $Z_{1-\beta}$ = standard normal deviate corresponding to a power of 80% = 0.84
- P1 = 4.4% = 0.044 (prevalence of myocilin mutation among patients with adult-onset glaucoma in Ghana was 4.4%[12]
- P2 = 1% = 0.01 (prevalence of myocilin mutation in the general non-glaucoma population was 1%[13]
- P1 – P2 = the smallest difference between two groups

Substituting the values of $Z_{\alpha/2,}$ $Z_{1-\beta}$, P1 and P2 in the formula;

$$n = 352.4 \approx 353$$

An adjustment for non-response rate of 10% =392.2≈393 persons in each group

Clinical assessment combined with findings from clinical records were used. Venous blood from the study participants were obtained for genomic analysis. DNA was extracted; amplified; with specific primers for myocilin using polymerase chain reaction. Bioinformatic analyses were done with Simple Modular Architecture Research Tool (SMART) software; for protein domain structure prediction and Molecular Evolutionary Genetics Analysis (MEGAX) for evolutionary genetic analyses. Statistical Package for Social Sciences (SPSS) Version 25 was employed for demographic and inferential statistics. A p-value of $\leq$ 0.05 was considered significant.
Results: Total of 786 participants participated in the study (Table 1). The mean age for each study group was 59.8 ± 11.8 years. The prevalence of myocilin gene mutation (MYOC) in the overall study population was 5.3%, in the POAG group was 8.4%, and 2.3% in the non-glaucoma group (Table 2). This observed difference was statistically significant (p=0.042). The mean intraocular pressure for

the non-glaucoma phenotypically subjects was 13.8mmHg and in the adult-onset Primary Open angle Glaucoma subjects-15.2mmHg. The difference in the mean IOP of the different groups was not statistically significant (p=0.076). Eighty-three percent of the subjects with adult-onset POAG and 4.6% of the respondents in the non-glaucoma group had positive family history of glaucoma (Table 3).

Table 1: Age-Gender characteristics of the study population

Variables	Distribution in Adult onset POAG cases n=393		Distribution in Normal subjects n=393		Total	(%) Value	Chi-Square	p-Value
	(n)	(%)	(n)	(%)				
Gender								
Male	197	(25.1)	196	(24.9)	393	(50)		
Female	196	(24.9)	197	(25.1)	393	(50)		
Total	**393**	**(50)**	**393**	**(50)**	**786**	**(100)**		
Age Group (Years)								
40-49	91	(11.6)	91	(11.6)				
50-59	108	(13.7)	108	(13.7)				
60-69	117	(14.9)	117	(14.9)				
70-79	48	(6.1)	48	(6.1)				
80-89	29	(3.7)	29	(3,7)				
Total	**393**	**(50)**	**393**	**(50)**	**786**	**(100)**		
Mean age = 59.8±11.8			*Age Range 40 to 86 years*			*0.000*	*1.000*	

Table 2: Prevalence of mutation in the myocilin gene among in the two groups

	Mutation in Myocilin gene PRESENT	Mutation in Myocilin gene ABSENT	TOTAL	Prevalence
POAG patients Group	33	360	393	8.4%
Non-Glaucoma Group	9	384	393	2.3%
TOTAL	**42**	**744**	**786**	**p-value = 0.042**

Table 3: Family History of Glaucoma in the Study Population

Positive Family History of Glaucoma	N	(%)	N	(%)	Total	(%)	Chi-Square test	p-value
First Degree Relative	326	(83.0)	18	(4.6)	344	(43.8)	573.99	0.000
Second Degree Relative	120	(30.5)	12	(3.1)	132	(16.8)		
Unaware	67	(17.0)	375	(95.4)	442	(56.2)		
Total	**393**		**393**		**786**			

Discussion: The prevalence of mutation in myocilin gene in the overall study population was 5.3%, 8.4% among POAG group and 2.3% among the control group. This observed difference was statistically significant. Our findings compare well with the work of Challa et al., in Ghana[12] and Fingert et al., in the United States of America[13]. Variations in the degree of expressivity and penetrance of genetic trait could be the reason for the lack of glaucomatous damage in the non-glaucoma, phenotypically normal subjects who tested myocilin gene mutation positive.

Conclusion: Mutations in myocilin gene are associated with adult-onset POAG in Rivers State and its use as a biomarker for POAG needs further investigations.

Keywords: *Myocilin gene mutation, adult-onset primary open angle glaucoma, Rivers State indigenes, prevalence*

References

1. Quigley HA and Broman, A.T. The number of people with glaucoma worldwide in 2010 and 2020. Br J Ophthalmol; 2006. 90:262–267
2. Abduls MM, Sivasubramaniam S, Murthy GVS, Gilbert C, Abubakar T, & Ezelum CH. Causes of blindness and visual impairment in Nigeria: The Nigerian National Blindness and Visual Impairment Survey. Invest Ophthalmol 2009; Vis Sci., 50(9), 4114-4120.
3. Ashaye A. Glaucoma Blindness: Facts, Fancies and Fables. 12th Faculty Lecture, Faculty of Ophthalmology, National Postgraduate Medical College of Nigeria. Ibadan; 2010. Book Builders:1-48
4. Allingham RR, Liu Y & Rhee DJ. The genetics of primary open angle glaucoma: A Review. Exp Eye Res., 2009; 88: 837–844.
5. Bowling B. Kanski's Clinical Ophthalmology. A Systemic Approach. 8th Edition, Edinburgh. Elsevier Butterworth-Heinemann 2016; 306-366
6. Monemi S, Spaeth G & DaSilva A. Identification of a novel adult-onset primary open-angle glaucoma (POAG) gene on 5q22.1. Hum Mol Genet 2005; 14:725–733.
7. Nazir S, Mukhtar M, Shahnawaz M, Farooqi S, Fatima N, Mehmood R & Sheikh N A. Novel single nucleotide polymorphism in exon 3 of MYOC enhances the risk of glaucoma. PLoS One. 2018; 13: e01951572018.
8. Fan BJ & Wiggs JL. Glaucoma: Genes, Phenotypes, and New Directions for Therapy. J Clin Invest 2010; 120: 3064–3072.
9. Fingert JH. Primary Open-Angle Glaucoma Genes. Eye (Lond) 2011; 25: 587–595.
10. Stone EM, Aldave AJ and Drack AV. Recommendations for genetic testing of inherited eye diseases: report of the American Academy of Ophthalmology task force on genetic testing. Ophthalmology 2012; 119:2408–2410.
11. Lwanga SK, Lemeshow S & WHO. Sample Size Determination in Health Studies: A Practical Manual. Geneva: World Health Organization 1991; 10-28.
12. Challa P, Herndon LW, Hauser MA, Broomer BW, Pericak-Vance MA, Ababio-Danso B & Allingham RR. Prevalence of Myocilin Mutations in Adults with Primary Open-angle Glaucoma in Ghana, West Africa. *Journal of Glaucoma* 2002; 5: 416-420.
13. Fingert JH, Elise-Héon E, Liebmann J M, Yamamoto T, Craig JE, Rait J, Kazuhide Kawase K, Hoh S, Yvonne M, Buys Y M, Joanne-Dickinson J, Robin R, Hockey RR, Donna Williams-Lyn D, Trope G, Kitazawa Y, Robert Ritch R, Mackey DA, Wallace L, Alward M, Sheffield VC & Stone EM. Analysis of myocilin mutations in 1703 glaucoma patients from five different populations. Human Molecular Genetics 1999; 8: 899-905.