Allelic Frequency and Distribution of M98k Variant in OPTN Gene Associated with Adult-Onset Primary Open Angle Glaucoma in Puerto Rico

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ABSTRACT

Glaucoma is a severe neurodegenerative, hereditary condition that is increasingly prevailing in native Puerto Rican citizens. The purpose of this study is to correlate the M98k (rs11258194) missense variant in the Optineurin (OPTN) protein with Adult-Onset Primary Open Angle Glaucoma (POAG) in Puerto Rico; in addition, determine the distributional mutated allelic frequency throughout the Island. Optineurin is an adaptive protein that interacts in various nervous cell processes such as vesicular transportation, signaling and autophagy. By selecting 625 patient samples that span a total of 30 municipalities as a guide of the general population, we were able to genotype the samples by RT-PCR with a TaqMan Assay for SNP rs11258194. The samples were further analyzed through geographic distribution via MapViewer, a map-rendering tool. The results showed a total of 60 mutated alleles (48 heterozygous, 6 homozygous) mainly distributed along the coastline of Puerto Rico. Therefore, heterozygous patients with M98k variant present are more prone than wildtype patients to develop a neurodegenerative condition. Further studying will confirm if homozygous patients present POAG or other nervous-related condition such as Amyotrophic Lateral Sclerosis.

INTRODUCTION

ADULT-ONSET PRIMARY OPEN ANGLE GLAUCOMA (POAG)

- Glaucoma is a progressive condition characterized by the neurodegeneration of the optic nerve fiber that can result in a particular pattern of loss of vision, and eventually blindness.
- High intraocular pressure (IOP) is one of the main risk factors but is not necessarily going to cause glaucomatous nerve damage.
- Adult-onset POAG ranges from 4o years and above.
- It affects approximately 3 million people in the United States and 42.6% in Puerto Rico.
- Symptoms include tunnel vision, peripheral vision loss, pain, redness, etc.

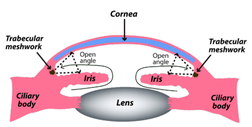


Fig. Open angle between the iris and the cornea, and identification of blocked trabecular meshwork.

Fig. Normal vision fields vs. Open angle glaucoma tunnel vision

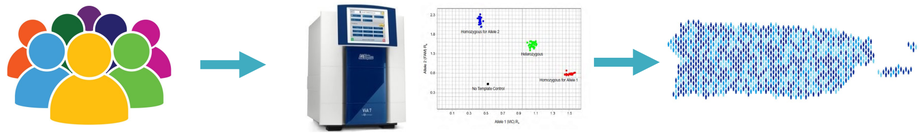
OPTN AND M98K

- OPTN is an adaptive protein that participates in cellular processes such as vesicle transportation, signaling and autophagy.
- It is in chromosome 10, at the genomic position 14. It has a total of 16. exons, where there are 3 noncoding exons at 5' UTR and 13 coding exons for a 577 amino acid protein.
- The single-nucleotide polymorphism rs11258194 (M98k) is a missense mutation where thymine is substituted with adenine resulting in an amino acid change from methionine to lysine.
- This autosomal dominant mutation is a risk-factor alteration for heterozygous individuals.

OBJECTIVES

- Determine the population's allelic frequency and distribution for the affected allele with the variant rs11258194 in Puerto Rico.
- Calculate the allele frequency with variant rs11258194 in different age groups.
- Correlate the variant rs11258194 and Adult-Onset Primary Open Angle Glaucoma in Puerto Rico.

METHODOLOGY



625 Samples
30 Municipalities

DNA repertoire
J. C. Martínez-Cruzado Lab

Genotyping by RT-PCR
Allelic Discrimination

TaqMan Assay for SNP rs11258194
Allele Frequencies

Distribution and Frequency in Puerto Rico

Distribution Maps
Map Viewer

RESULTS

THIS PROJECT

Heterozygous (TA): **48**

Homozygous (AA): **6**

Total samples**: 625**

1000GENOME

Heterozygous (TA): **6**

Homozygous (AA): **0**

Total samples: **108**

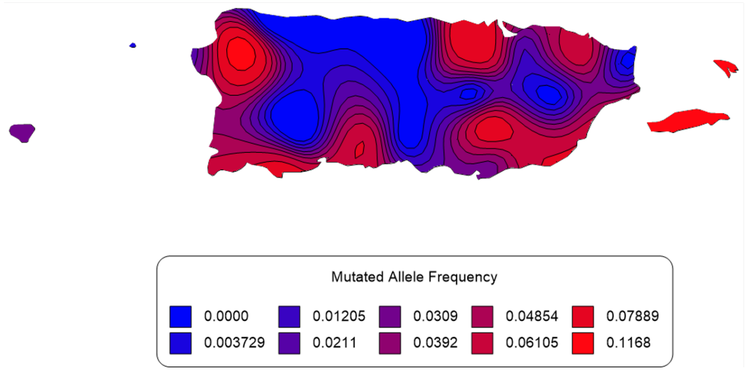


Table. Mutated allelic frequency per region and in total in Puerto Rico. Total frequency results are being compared with the frequency calculated by 1000Genome Project on 2015.

REGION	FREQUENCY	FREQUENCY (%)
North	0.04098	4.10%
East	0.1118	11.2%
South	0.03781	3.78%
West	0.06462	6.46%
Center	0.03191	3.19%
TOTAL	**0.04800**	**4.80%**
Total 1000Genome:	0.02900	2.9%

PRELIMINARY CONCLUSIONS

- The presence of the SNP rs11258194 in Optineurin protein is confirmed in Puerto Rico.
- Based on previous 1000Genome (2015), there is a higher frequency calculated of 4.8%, than expected frequency of 2.9% of the M98k in the Island.
- The distribution of individuals with the affected allele is presented along the coastline of Puerto Rico. The pattern is clustered but not regionalized.
- The East side has the highest frequency (11.19%), while the north and center have the lowest frequency yet (3.19 - 4.10%).

FUTURE PLANS

We will continue sampling patients that have been previously diagnosed with glaucoma or that present any related symptoms within Puerto Rico. The volunteers will fall under one of the five desired study groups:

- 21-40 Suspects
- 40-60 Diagnosed
- 40-60 Suspects
- 60+ Diagnosed
- 60+ Suspects

The last four categories are divided into two main conditions: Primary Open Angle Glaucoma and Amyotrophic Lateral Sclerosis (ALS). ALS has been previously identified to express in patients with the allele mutated for M98k. Therefore, we will only be recollecting samples of patients that present any of these conditions or related symptoms, since any alteration of this variant will be reflected in the nervous cell signaling.

ACKNOWLEDGEMENTS

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