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Myocilin and Glaucoma its Risk Factors

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ABSTRACT

Myocilin (OMIM601652) MYOC gene, first revealed as a protein isolated from cultured human Trabecular Meshwork (TM) cells after prolong dexamethasone treatment. Hence given the name TIGR (Trabecular Meshwork Inducible Glucocorticoid Response Protein). The human myocilin gene, a concealed acidic glycoprotein,contains 504 amino acids, positioned at chromosome 1(1q24.3 – 1q25.2), and filled with olfactomedin domain at its C terminus. Myocilin exists in various tissues throughout the eye and many other organs. Mutant myocilin cause endoplasmic reticulum pressure in eye angle tissues, including the trabecular meshwork, damaging the cells inside the meshwork, ultimately leading to structural changes in the outflow pathway, and high intraocular pressure.TM is vital in controlling pressure and mutations in MYOC.It has been recognized as the cause of juvenile and adult onset of primary open angle glaucoma.

Key words: *Myocilin gene, glaucoma, Trabecular Meshwork, mutation.*

INTRODUCTION

In 1997, Stone and other colleagues from laboratories testified the discovery of a genegiving it a nonspecific name GLAC1[1] being located on chromosome 1, it was named GLC1A."GLC" is the abbreviation for Glaucoma, "1" represents it as primary open angle glaucoma (POAG) and "A" stands for the first linkage for this disease [2]. Cultured human trabecular meshwork cells were treated with fairly high doses of dexamethasone in the laboratory. The changes in gene expression of the trabecular meshwork cells were found out by comparing corticosteroid-treated cells and compared with control cells. It revealed a protein that was noticeably increased when the trabecular meshwork cells were exposed to corticosteroids. Finally, the protein was coined as Trabecular Meshwork Inducible Glucocorticoid Receptor Protein (TIGR)[3]. MYOC is connected with the cytoskeleton in the retina because of the relationship of its products with cilium of the photoreceptors cells and its homology to non-muscle myocilin[4]. In 1998 the Human Genome Database Nomenclature Committee gave this gene the name myocilin, and currently it is well known as MYOC rather than TIGR [5].

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GENE STRUCTURE AND PROTEIN

Myocilin, a glycoprotein, is present in glycosylated[6-8] and non-glycosylated forms[5], comprising of three exon, two introns, and positioned atchromosome 1(1q24.3 – 1q25.2), with a length of about 17 kb [4,9,10]. It has three exons of length 604,126 and 782 base pairs respectively [11]. Exon 1 encodes for two coiled domains known as non-muscle myosin-like domain holding a signal peptide sequence targeting myocilin for secretion, and one leucine zipper motif that is associated in myocilin self-aggregation on the (N) terminal[11]. Exon 2 encodes for the central linker domain which is cleaved by calpain II and exon 3 encodes for the (C)-terminal olfactomedin (OLF)-like globular domain[12,13] (Figure 1). Certain copies, size ranging from 1.8 to 2.3 kilo base pairs are produced by the gene. The main characteristic in the size of the transcripts occurs due to differential use of three polyadenylation sites at the 3end[14,15].

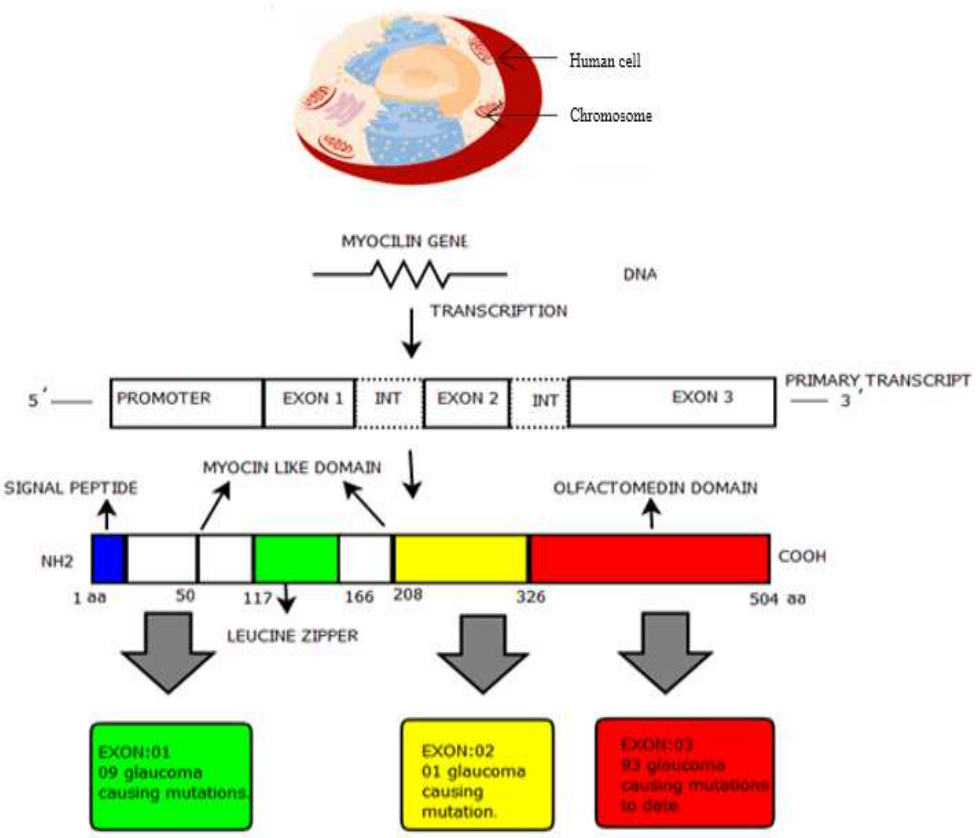

Fig. 1: Scematic diagram of Myocilin protein and its distribution of mutations

Human myocilin gene transcript acid glycoprotein of 504 amino acids with an isoelectric point of 5.2[4,9,15] and estimated molecular weight of 55.3-kilodalton (kDa), N-glycosylation at amino acids (aa) 57−59 (Asn-Glu-Ser)[12,16]. It has also been addressed that human wild-type myocilin was proteolytically cleaved between Arg226 and Ile227 in the aqueous humor and ocular tissues, resulting in a 35 kDa fragment consist of the C-terminal OLF domain and a 20 kDa fragment accommodate the N-terminal leucine zipper domain[17].

EXPRESSION SITE

Myocilin mRNA commonly exists in a various extraocular and intraocular tissues [5]. Inside the eye, it is found in trabecular meshwork, sclera, iris, retina, ciliary body, post laminar optic nerve head, choroid, cornea, lamina cribosa, vitrous and aqeous humor, uveal, corneoscleral and juxtacanicular regions[4,5,15,1823]. Remarkable levels of MYOC are expressed in trabecular meshwork and sclera[3,14,18,24] and majority of it is present outside the eye , such as heart, skeletal muscle, bone marrow, colon, thyroid, trachea, brain, schwann cells, sciatic nerve, stomach, renal podocytes and mesangial cells[4,9,15,18,25-27]. It is not found in urine, indicating that glomerular cells do not secrete large amount of myocilin[26].

PHYSIOLOGICAL FUNCTION

The actual physiologic function of myocilin in the cell is unidentified[28]. To some extent intracellularly, it may be linked tosome structural function within the cytoplasm, or it may associate with other molecules within the cells, probably as a molecular chaperone. Extracellularly, it may have been linked to creating resistance to aqueous outflow by binding to other extracellular molecules or to the cell membrane of trabecular cells.[5] Myocilin play a key role in myelination of sciatic nerve in peripheral nervous system[29,30]. In addition, it is expressed in bone marrow-derived mesenchymal stem cells (MSCs) for their differentiation into osteoblast *in vitro* and in osteogenesis *in vivo* and to increase cell proliferation and survival[28,31]. Overexpression of wild type myocilin in transgenic mouse skeletal muscle leads to increased muscle size proposingthat myocilin may regulate muscle hypertrophy[31]. In addition, it is believed that overexpression of myocilin can lead to accumulation of myocin protein in endoplasmic reticulum, inducing stress and subsequently trigger apoptosis[32]. In the tissues of eye angle,a large amount of myocilin may contribute in survival of trabecular meshwork cells[28]. Thiscellular component of trabecular meshwork can be altered and reduced with age, ultimately causing a risk of glaucoma by structural alteration in drainage passage way of aqueous humor[13,33]. Recent report supports that the myocilin gene is also involved in Wnt signaling, ERK signaling, RhoA signaling and laminin signaling for the regulation of cell proliferation and survival[28].

MUTATION AND MECHANISM OF DISEASE

To date, 93 disease causing mutations have been identified from 273 different variants of the myocilin (MYOC) gene, with preponderance (more than 90%) of these mutations located within third exon encoding olfactomedin domin (Figure 2 & Table 1)[1,12,34-40].

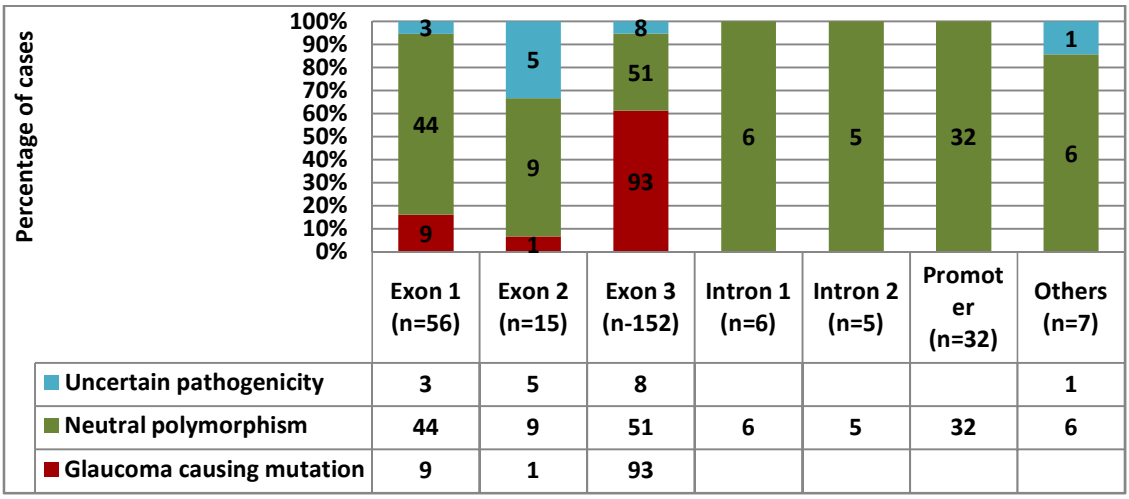

Fig. 2: Graphical representation of glaucoma causing mutation (9 in exon 1; 1 in exon 2; 93in exon 3) among the variants (273 in total) present in myocilin gene reported till 10–01–2016.

	Glaucoma causing mutation		Neutral polymorphism		Uncertain pathogenicity		Total	
Row Labels	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
Exon 1	9	16.07	44	78.57	3	5.36	56	100.00
Exon 2	1	6.67	9	60.00	5	33.33	15	100.00
Exon 3	93	61.18	51	33.55	8	5.26	152	100.00
Intron 1			6	100.00			6	100.00
Intron 2			5	100.00			5	100.00
Promoter			32	100.00			32	100.00
Others			6	85.71	1	14.29	7	100.00
Total	**103**	**37.87**	**153**	**55.88**	**17**	**6.25**	**273**	**100.00**

Table 1. Percentage of glaucoma causing mutation (16.07% in exon 1; 6.67% in exon 2; 61.18% in exon 3) among the variants (273 in total) present in myocilin gene reported till 10–01–2016.

Olfactomedins are a family of mucus proteins[5], and are major component of the extecellular matrix of the olfactory neuroepithelium[41]. Different missense mutations are linked with the different rangesin the ages of onset (Figure 3).

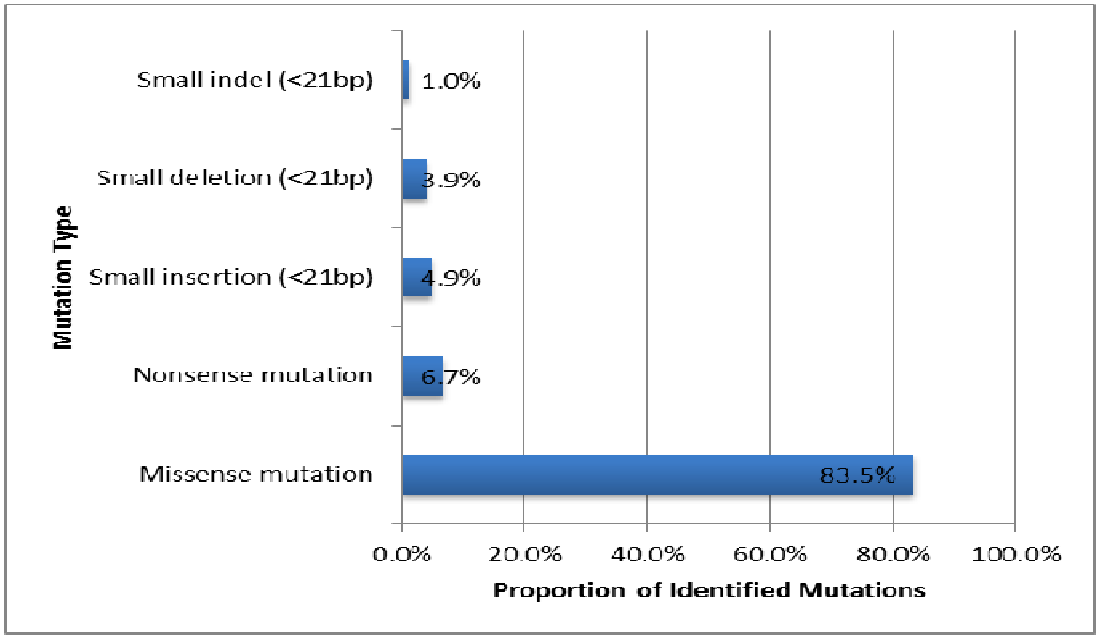

Fig. 3: Proportion of identified mutation in MYOC gene: missense 83.5%; nonsense 6.7%; 6 small insertion 4.9%; small deletion 3.9%; small indel;1.0%, reported till 05–01–2016.

POAG is differentiate into Juvenile onset Open Angle Glaucoma (JOAG) and adult onset POAG. JOAG onset,it may occur between the age of three to thirty while adult onset of POAG is diagnosed above the age of 40 years[42-44]. More or less 36% cases of the juvenile POAG have been reportedstarting from an early onset and with a more stern form of glaucoma. 2.4-4.6% of patients are found to be with adult-onset primary open glaucoma[1,11,13,45-47]. The distinct myocilin mutations, Pro370Leu (P370L), accounts for one of the most serious glaucoma phenotypes (Figure 4) and Gln368Stop (Q368X) is the utmost prevalent mutation expressed in POAG patients[2,17,37,45].

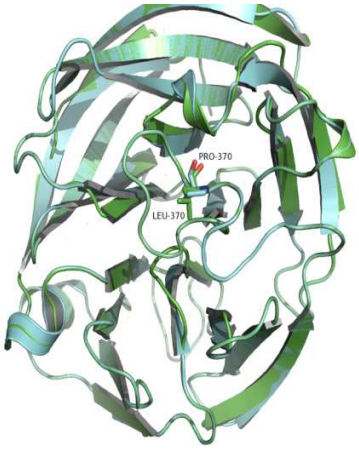

Fig. 4: Classical 3D structure of Myocilin Pro370Leu most serious Glaucoma causing mutation.

Numerous glaucoma-linked mutant myocilin, especially in the OLF domain,have been found to be misfolded and it forms detergent-resistant, secretion of incompetent aggregates[48-52]. However, one of the research reveals loss of one copy of myocilin gene does not cause early onset of glaucoma but it may interfere with remaining normal copy of protein causing a dominant negative effect[42].

Intracellularly, myocilin may have significance in mitochondrial functions. Overexpression of myocilin instigates apoptotic events by reduced mitochondrial respiration, potentially sensitizing cells in trabecular meshwork[53]. Therefore, mutation in third exon may get in the way with uptake or metabolism of the protein leading to its accumulation, obstruction of aqueous outflow and increase IOPs[54]. This atypical IOP alterations and limitations would ultimately consequence in deterioration of the sensitive optic nerve tissues, thus giving rise to glaucoma and probably blindness[54]. It is worth mentioning that not all patients with POAG who bear MYOC mutations have high intraocular pressure.Ayoung patient with POAG with normal ocular tension, who had MYOC Gln 368 Stop mutation in exon 3, which is usually associated with reasonable elevated intraocular pressure POAG, did not showed signs of high intraocular pressure[18].

Clinically and genetically glaucoma is heterogeneous[55]. More than 20 candidatechromosomal/genetic loci have been reported for POAG[56-58]. Glaucoma is one of the most important causes of irretrievable blindness worldwide and hypothesized to affect around 80 million people worldwide by 2020[59]. Itis known to causeprogressive loss of retinal ganglion cells and simultaneously the loss of axons, as well as cupping of the optic nerve head[60]. In general, glaucoma in humans can be classified into four major types: open-angle (chronic) glaucoma (also called primary open-angle glaucoma, POAG), angle-closure (acute) glaucoma (ACG), congenital glaucoma and secondary glaucoma with POAG being the most familiar type[61]. High-reaching intraocular pressure is typical in POAG and is a dominant risk factor for the disease[13]. It's not simple debate between the link of elevated intraocular pressure and retinal ganglion cell deterioration. A few individuals with no visible damage to optic nerve may have elevated IOP, while some others with normal IOP may have optic nerve damage (such as in low-tension or normal-pressure glaucoma (NTG) which is accepted as a subtype of POAG[13,62].

In the anterior chamber of eye, IOP is controlled by a balance between the production and outflow of the aqueous humor. Trabecular Meshwork, a specific tissue situated at the chamber angle next to the cornea, is believed to be the leading site for regulation of the bulk flow of the aqueous humor[63,64]. This tissue is divided into the uveal meshwork, corneoscleral meshwork, and juxtacanalicular (JCT) regions. In the uveal and corneoscleral meshwork, layers of trabecular beams made up of connective tissue or extracellular matrix (ECM) elements are lined by TM cells. In the JCT region, the TM cells reside relatively freely and embedded in the connective tissue. The outflow resistance is supposed to trace largely in the JCT/SC area. The pressure gradients and resistance to aqueous outflow are likely altered in the various types of glaucoma[65,66].

It is believed that impairment in the trabecular meshwork (TM) cell activities, cytoskeletal structure, cell-matrix and cell-cell adhesion, and/or the quantity and accumulation of the extracellular matrix (ECM) in trabecular meshwork tissues may all produce unfavorable effects on the outflow pathway, leading to intraocular pressure elevation and ultimately in the development of glaucoma[63,67-69].

RISK FACTORS

Primary open angle glaucoma (POAG)is proved to be highly variable and complicated disease. To obtain maximum protection against it and to find the best possible cure it is a mandatory fact to know in detail about the risks associated with POAG. The information about the possible causative agent behind POAG is vague, however, certain factors are found suspicious of having an etiological role. There are two prominent risk factors of glaucoma are; IOP and non-IOP factors. The major risk factor of POAG is IOP. Non-IOP risk factors come from age, sex, skin pigmentation, central corneal thickness (CCT), Corneal hysteresis, duration of optic disc hemorrhage, the degree of severity of glaucoma ,glaucoma in both eyes, myopia, cataract, family history of glaucoma, low ocular perfusion pressure, systemic hypotension, cardiovascular disease, diabetes, obesity, cerebrovascular disease and high blood cholesterol[40,70,71]. Few environmental factors known to modify IOP include; caffeine, smoking, alcohol, yoga posture, tight neck ties, weight lift and dietary fat intake.[40,71].

CONCLUSION

With the passage of time, much advancement occurred in glaucoma. However, only half of the total population is ever diagnosed of glaucoma due to irregular eye examination. The situation is even worst in the developing world.

Ever since the identification of myocilin gene and an immense research that has been conducted by many scientists, till date there is almost no findings about the pathology of myocilin gene expression in other tissue besides eyes. So, in near future there should be a concrete focus on this field, mainly focusing on the cancer cells. This elucidation may excavate information about differentiation and progression of cancer and correlation of myocilin gene with other diseases. Ultimately, it may curb clue for the treatment of glaucoma, cancer and other diseases. It is also important to further extend the knowledge in the olfactomedin protein including its actual function and receptors in different tissues.

Furthermore, future endeavors should be to undergo more detailed investigation to find out unknown factors why this mutation has high frequency in exon 3 rather than exon 1 and exon 2. We should have a keen look on gene to gene and gene to environment interactions in order to diagnose glaucoma. Also we can use different cost effective Bio-informatics tools and molecular techniques in order to narrow down the research. This will help us to identify new genetic variations and it will also help us find new preventive measures and cures.

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