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Editorial

PAX6 gene and its role in ocular malformations

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PAX 6 gene is located on short arm of chromosome 11 on locus 11p13.[1] Human PAX6 protein consists of 422 amino acids residues containing two DNA binding domains, a paired domain (128 AA) and homeobox domain (61 AA). The transactivation domain is Proline-Serine-Threonine (PST) rich. This gene is expressed throughout embryogenesis in late gastrula stage in the region of anterior neural plate, forebrain, all eye structures, ventral part of spinal cord and pancreas.

It is one of regulator of regulators and multi-functional proteins. Regulation of PAX6 gene is a complex process. There are four identified transcription start sites corresponding to promoter P0, P1, P α and P4. From two promoter P0 and P1 two different variants of transcription factors are formed which encode same proteins. From promoter Pα and P4 same truncated isoform without the paired domain is expressed.[2] This complex pattern of expression of transcriptional variants of PAX6 gene is regulated by several tissue specific regulatory factors.[3]

Numerous regulatory microRNAs are able to regulate expression of PAX6 gene at transcriptional level. It is involved in corneal morphogenesis,[4] differentiation of various neurons, mesenchymal stem cells, tumor development as in retinoblastoma, glioblastoma etc. in which it acts as a tumor suppressor gene.[5] Activity of PAX6 gene or protein can be regulated by post translational modification mainly by phosphorylation through kinases.[6]

Regulated PAX6 gene expression provides necessary levels and ratio of expressed transcription variants which play key role in development of eye and central nervous system.[7] PAX6 gene has important role in organogenesis which control the specification and differentiation of cells of different origin. It also plays important role in maintaining multipotent state of several types of progenitor cells (neuronal retina, pigment epithelium of retina, iris and ciliary body, cortex and some structures of brain) and their proliferation. It was seen that the homeodomain regulates cell proliferation while paired domain regulate cell differentiation. It regulates expression of specific transcription factors, cell line differentiation regulators and act as both activator and suppressor of transcription and control terminal differentiation of certain ocular tissues like secondary lens fibers, smooth muscle of sphincter in iris, etc.[8] PAX6 also helps in maintaining stem cell pool in lens epithelium, corneal limb, pigment epithelium, ciliary body and iris.[9]

These mutations are generally iatrogenic (96%) with some variants (4%) having whole gene deletions. Most common iatrogenic mutations have variable penetrance and expressivity. Mutations are either nonsense, frame shift, missense or located at splice sites and C- terminal extension.[10] Introduction of a premature termination codon is most common mutation which lead to termination of translation. These patients tend to present classical aniridia

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phenotype.[11] In missense variants, it is seen that they present with milder atypical phenotypes sometimes without iris defects but with defects like microphthalmia, optic nerve anomalies, coloboma, isolated foveal hypoplasia and anterior segment dysgenesis.[12,13] Chromosomal rearrangements like deletions, duplications, translocation, inversion and large deletions that included PAX6 and other neighboring genes like WT1 result in multisystem disease such as WAGR syndrome characterized by Wilms tumor, aniridia, genitourinary anomalies and mental retardation.[14] Most PAX6 genes causing aniridia are heterozygous, sporadic (two- third) or familial (one- third) in an autosomal dominant pattern.[15]

Aniridia is a pan ocular disorder which involves defect in formation of iris, cornea, lens, fovea and optic nerve bilaterally.[13,16] It comprises incomplete or partial iris hypoplasia with nystagmus and foveal hypoplasia with latter being main cause of diminution of vision since birth. MAC (microphthalmia, anophthalmia and coloboma) is a group of developmental eye disorder which is characterized by decrease or absence of ocular globe due to mutation of more than 90 genes. Anophthalmia is associated with homozygous PAX6 variant associated with biallelic loss of function of gene. Gillespie syndrome and Peter's anomaly (anterior segment dysgenesis) are also associated with PAX6 mutation.

1. Conflict of Interest

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None.

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