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REVIEW ARTICLE

Understanding the Etiology of Astigmatism: A Literature Review

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ABSTRACT: Astigmatism is caused by the irregular curvature of the eye's cornea, affecting how light is refracted. Though astigmatism has been researched, and its effects are understood well, etiology is not fully characterized, and there are few effective treatment options. This review will characterize the current literature on the etiology and treatments of astigmatism and identify gaps for future research. Both genetic and environmental components contribute to the development of astigmatism. In our review, we found several genes with evidence of association with the development of astigmatism, including PDGFRA, FRAP1, SHH, and VAX-2. Additionally, we identified a few genes with mixed evidence of their connection to the development of astigmatism. We also identified evidence indicating that environmental factors, such as birth during periods of increased sunlight exposure and specific age-related variables, significantly influence the outcomes. In our review, we identified specific gaps in astigmatism etiology research. These gaps include the lack of clinical trials and limited additional research on these factors. Adding more GWAS studies that are wide in range can allow us to pinpoint a robust and evidence-backed cause of astigmatism. This review summarizes the current literature on astigmatism's genetic, environmental, and age-related factors and identifies gaps for future research.

KEYWORDS: Biomedical and Health Sciences, Genetics and Molecular Biology of Disease, Astigmatism, Corneal Curvature.

Introduction

Astigmatism is a common refractive abnormality that has affected millions of individuals worldwide. In the United States alone, it affects 1 in 3 people.[1] Astigmatism is caused by the irregular curvature of the eye's cornea, affecting how light is refracted and ultimately resulting in distorted vision.[2] While astigmatism can arise from irregularities in either the cornea or the lens, this review will focus specifically on corneal astigmatism. If left uncorrected, astigmatism can lead to blurred vision, eye strain, and, in severe cases, contribute to amblyopia, especially in children. Though astigmatism has been researched and its effects are understood well, the etiology is not fully characterized, and there are few effective treatment options. This review will characterize the current literature on the etiology of astigmatism and identify gaps for future research.

Discussion

Genetic Components of Astigmatism:

The genes PDGFRA, FRAP1, SHH, and VAX-2 have a relevant link to the development of astigmatism. Other instances of relevance are recorded but have little to no link to the development of astigmatism.[3]

Though little research has been conducted into its direct effect on astigmatism, the PDGFRA protein-coding gene plays a known role in corneal curvature. Genome-wide association studies (GWAS) are commonplace in genetic research that use large quantities of genomic data to identify associations between genotypes and phenotypes. One major GWAS meta-analysis involving five Asian cohorts (N = 8513) demonstrated that a cluster of single-nucleotide polymorphisms (SNPs) called rs7677751 located on PDGFRA was linked to the relevance of abnormal corneal curvature.[4] It is known that irregular corneal curvature causes astigmatism due to the distortion of the eye's focus and uneven light refraction, leading to blurred vision.[5] Another large GWAS study for corneal (n = 86,335) and refractive astigmatism (n = 88,005) was conducted on European populations that reported a significance of a cluster of SNPs on rs4864857, located on the 4q12 promoter region of PDGFRA.[6] Thus, future research is needed to investigate the impact of the PDGFRA-influenced abnormal corneal curvature on the development of astigmatism.

Several smaller studies investigated the link between PDGFRA and corneal curvature.[7–10] Most of these studies found a moderate link between the two,[11] though some reported no significance.[7,9] The scope of studies on the relationship between PDGFRA and corneal astigmatism demonstrates how further research is needed to establish a firm cause and effect between the two, due to the trend of some studies reporting significance and some reporting no significance.

In addition to PDGFRA, another gene has been implicated in the development of astigmatism, known as the FRAP1 gene, or mTOR. A GWAS study (n = 4289) conducted on Asian populations in Singapore found FRAP1 to be associated with corneal curvature development, and variations in FRAP1 can alter corneal curvature development.[12] The authors found this unsurprising as FRAP1 is known to influence metabolic pathways that affect epithelial growth, which is a main component of the cornea. At this time, little research has been performed to assess possible links between FRAP1-induced corneal curvature abnormality and astigmatism, and thus, more research is needed to establish a potential relationship.

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The sonic hedgehog (SHH) gene is generally associated with eye patterning in embryonic development. The evidence of a direct relationship between SHH and astigmatism is weak but largely unexplored. One analysis determined that a mutation of SHH caused an autosomal dominant syndrome in children, resulting in cataracts, vitreoretinopathy, primary open-angle glaucoma, and asymmetric myopia with astigmatism.[13] SHH and other genes in the hedgehog (HH) family are known to influence the regeneration of the corneal epithelium.[14] As astigmatism can have onset during any age, it is possible that variants in SHH that affect the regeneration of the corneal epithelium may contribute to astigmatism and its age of onset.[14] Future research should explore this potential connection. Additionally, there is evidence that the PAX6 gene interacts with SHH and influences the regeneration of corneal epithelium.[14–16] The current literature does not describe a relationship between SHH and astigmatism; thus, future research should aim to better characterize the link between the two.

Another gene that is potentially implicated in astigmatism onset is the VAX2 gene. The VAX2 gene is a protein-coding gene that forms the retina and the dorsoventral axis during eye development. According to a meta-analysis involving seven studies and (n = 22100) individuals, a susceptibility locus with SNP rs3771395 on Chromosome 2p13.3 was identified in the VAX2 gene. A susceptibility locus occurs when an allele is detected to increase the risk, but does not fully indicate disease expression.[17] This study suggests a connection between VAX2 and astigmatism, but the details of this connection are yet to be understood.3 Another study explored VAX2 overexpression and its role as a transcription factor, suggesting a particular link to VAX2 and neural retina development. When overexpressed, the VAX2 gene tends to alter other parts of the eye.[18] This could unveil a potential link between VAX2 overexpression and its effect on the cornea and the development of astigmatism, but more research is needed to confirm this.

In a large GWAS study with 14 European (n = 22250) cohorts and 9 Asian (n = 9120) cohorts, three new genes, CLDN7, ACP2, and TNFAIP8L3, were identified to have a possible contribution towards astigmatism. These genes have not been identified in any other study and represent areas that should be further investigated in future research.[19]

Environmental Components of Astigmatism:

Genetics alone may not explain astigmatism onset. Environmental factors could also play a role, as exposure to different conditions during development may affect corneal curvature at/before birth. A large study conducted in Israel (n = 67899) suggests multiple environmental factors are associated with astigmatism development.[20] An interesting finding shows that people born in longer perinatal photoperiods, which refer to people born in the summer months, are more likely to be diagnosed with the rule (WTR) astigmatism,[20] which is a subset of astigmatism where the vertical meridian of the eye is steeper.[21]

Additionally, some studies did not find evidence for a link between astigmatism and genetic factors. Namely, the Tehran Eye Study did not link the two, suggesting that astigmatism is not inherited and may result from environmental factors.[22] The development of astigmatism is complex and does not seem to be tied to one factor alone. However, evidence establishes a possible link for and against the environmental component of astigmatism development. There is insufficient research for definitive conclusions, emphasizing the need for future research.

Another potential factor that may lead to the development of astigmatism is age-related determinants. Many studies suggest that with age, the prevalence of astigmatism increases due to changes in the shape of the corneal curvature. This is because of a shift in the axis of the eye, which simultaneously encourages a shift from WTR to against-the-rule (ATR) astigmatism, the other subset of astigmatism where the horizontal meridian of the eye is steeper than the vertical meridian.[21,23,24] Increased astigmatism with age was also found in a population of myopic patients, suggesting this trend may occur independently of refractive error.

Limitations of Review

This review acknowledges several limitations inherent in both the extant literature and the present analysis. A considerable proportion of studies addressing the etiology of astigmatism focus on specific populations or age cohorts, thereby limiting the external validity of their findings. Moreover, genetic association studies often exhibit variability in outcomes. Environmental and behavioral factors remain underrepresented in literature, and their contributions to astigmatism development are not yet fully elucidated. Recognizing these limitations is essential to contextualize the findings and to inform future research directions aimed at elucidating the multifactorial etiology of astigmatism.

Conclusion

This review summarizes the current literature on astigmatism's genetic, environmental, and age-related factors and identifies gaps for future research. These gaps include the lack of clinical trials and limited research on these factors. Adding more GWAS studies that are wide in range can allow us to pinpoint a robust and evidence-backed cause of astigmatism. Current research that includes but is not limited to genes such as PDGFRA, SHH, FRAP1, VAX2, environmental factors such as perinatal photoperiod, and age-related causes opens pathways for these gaps in astigmatism research to be closed and identified. Future research should focus on conducting larger, diverse population-based GWAS, more clinical trials to validate findings, and investigations into how environmental and age-related factors interact with genetic predispositions.

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