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REVIEW ARTICLE

INFLUENCE OF POLYMORPHISMS OF GENES AND VARIABLE EXPRESSION ON CONNECTIVE TISSUE-RELATED OPHTHALMIC DISORDERS

Grzegorz ROTUSKI[1], Katarzyna KOMAR[2], Aleksandra PRZYBYSZ[3], Ewelina MACULEWICZ[2,3]
1 Department of Ophthalmology, Military Institute of Aviation Medicine, Warsaw, Poland
2 Department of Biomedical Research and Human Performance Optimization, Military Institute of Aviation Medicine, Warsaw, Poland
3 Department of Biomedical Sciences, Józef Piłsudski University of Physical Education in Warsaw, Poland

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Author's address: G. Rotuski, Military Institute of Aviation Medicine, Krasinskiego 54/56 Street, 01-755 Warsaw, Poland, e-mail: grotuski@wiml.waw.pl

Introduction: Connective tissue disorders are impacting ocular health – they can be either congenital in the case of genetic syndromes or acquired when it comes to autoimmune diseases. However, some gene polymorphisms and their variable expression in individuals can cause more discrete features leading to an increased risk of ophthalmic diseases developing progressively with aging. Collagen is the main component of the extracellular matrix, but various types with different biochemical properties are present within the eye and other constituents that interact with each other upon receiving gene-mediated signalling instructions.

Methods: A literature review was performed across online databases to synthesize current knowledge from the last 10 years on genetic mutations leading to connective tissue disorders that affect ophthalmic pathology. Various combinations of keywords and Medical Subject Headings were used.

Results: A total of 312 papers were collected using the above search criteria, among which 87 were judged relevant to the topic. The interest in ophthalmic genetics appears to be significantly increasing in recent years.

Discussion: The findings suggest that the relationships between genetics, ophthalmic diseases, and connective tissue disorders remain difficult to understand, despite the identification of multiple loci involved in the disease cascade, including variants of unknown significance. The growing evidence that our diet, lifestyle, and environment affect our genetic predispositions to diseases contradicts the idea that these factors are unmodifiable.

Conclusion: The review highlights that genetic and environmental interactions underpin many ophthalmic connective tissue disorders, underscoring the need for integrative genomic and clinical research.

Keywords: glaucoma, myopia, keratoconus, ophthalmic genetics, collagen, connective tissue, extracellular matrix, aviation pilots

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INTRODUCTION

Genetics plays a fundamental role in most known diseases, and this is equally true in the field of ophthalmology. Numerous genes have been identified to cause specific pathologies, and many more are currently being investigated. However, the presence of multiple factors decides on the effect of DNA expression in the organism, called the genotype-phenotype correlation [9]. Firstly, the DNA material can be divided into introns and exons – active and inactive regions, respectively. The inactivated segments vary from person to person, meaning different parts of the genetic material determine the anatomy and physiology of each person's tissues. Furthermore, the inactivation and reactivation of DNA are dynamic processes that occur throughout one's lifetime. One typical example of this phenomenon is the regional silencing of selected parts of the X chromosomes in human females [19]. Genetic autoregulation is achieved through diverse mechanisms, either:

- DNA methylation (selective silencing of genes),
- RNA interference (siRNA binds to mRNA to inhibit its translation; long non-coding RNA e.g. IncRNA can silence specific genes),
- genomic imprinting (only one allele of a gene is expressed),
- or chromatin remodelling by histone acetylation, phosphorylation, ubiquitination (to more compact heterochromatin or looser euchromatin, which influences gene accessibility) [10].

Furthermore, genes have polymorphisms, which derive from individual alterations in the pattern of nucleotide pairs: adenine-thymine (A-T) and cytosine-guanine (C-G) occurring in a DNA sequence. Additionally, the expression of genes varies between individuals based on the physiological demand. On top of that, intergenic interactions also differ based on the metabolic processes taking place, with environmental, lifestyle, and nutritional factors in play [55]. After DNA is translated into RNA and then transcribed into proteins, further molecular interactions determine the onset and severity of pathology. This demonstrates why comprehending the entire chain of events that causes ophthalmic pathology remains challenging and explains why developing genetic therapies that do not affect other physiological processes regulated by the targeted genes is so difficult.

This review article aims to identify studies on potential genetic factors behind ophthalmic disorders related to structural defects of the eye globe, resulting in refractive errors or neuronal loss with vision deterioration. The goal is to discuss the complexity of gene polymorphisms and their interactions and degrees of expression, as well as further individual diversity within proteomics and metabolomics. These factors prove challenging when identifying the exact pathomechanism of ocular diseases and developing a convenient therapeutic approach.

METHODS

This review was conducted using a systematic approach to identify and synthesize current evidence on the influence of gene polymorphism and expression on ocular health. A comprehensive literature search was performed across databases, including PubMed, Scopus, and Web of Science, for articles published in the last 10 years: between August 2015 and August 2025. Keywords and Medical Subject Headings terms such as "gene polymorphisms", "gene expression", "SNP", "glaucoma", "myopia", "connective tissue disorders," and "ECM" were used in various combinations. Peer-reviewed original research articles, clinical trials, case reports, and relevant review articles were included, provided they discussed the role of genetics in ophthalmic pathology. Articles not available in English, lacking full-text access, or focused solely on animal models were excluded. Reference lists of key articles were also reviewed to identify additional relevant studies.

RESULTS

The selected publications were critically appraised for methodological quality and relevance to the research question. 312 papers were analysed by the first three authors independently to discard duplicates and low-quality articles, leaving 114 papers for consideration, among which 87 were accepted by the last co-author. Publications showed a marked increase in the last 5 years, reflecting the rapid growth of research interest in the topic of ophthalmic genetics.

DISCUSSION

The importance of collagen in ophthalmology

Collagen is a natural protein and a major extracellular matrix (ECM) component. It is biocompatible, biodegradable, and characterized by low allergenicity. The eye is built of many

collagen types that are either present or absent in the remainder of the body. The most abundant type I is constituting the outer ocular parts: sclera, corneal stroma, and lamina cribrosa, while its defects are linked with Ehlers-Danlos syndrome or osteogenesis imperfecta [49]. Collagen type II is essential to the composition of the vitreous body, and anomalies are connected to Stickler syndrome, for example. Type IV collagen is found in the lens and glomeruli of the kidneys. Therefore, mutations can result in Alport syndrome, which is characterized by lenticonus and nephropathy, among other features. Other types of collagen are less prevalent, but are still present, especially in the cornea, and are associated with various general disorders, such as atopic dermatitis and epidermolysis bullosa. This suggests that slowly progressive pathologies may also be related to less significant genetic alterations, as they do not cause such an evident phenotype. Collagen type VIII is mostly represented in corneal endothelium, with mutations leading to posterior polymorphous or Fuchs endothelial corneal dystrophies [70].

Apart from collagens, other key components of the ECM provide structural support and facilitate intercellular signal transmission. These include laminins, elastins, proteoglycans, fibronectins, integrins, and hyaluronan. They are essential for tissue repair or development, but also adequate stretching and contracting that happens, for instance, in vessels to regulate blood flow [46]. This may be important in cases of glaucoma, where the cribriform plate is subjected to pressure from both the intraocular and intracranial spaces, which has the potential to squeeze the axons of retinal ganglion cells passing through the plate's pores [2]. In this case, ECM remodelling may also worsen the risk of tissue confinement. Myopia and glaucoma are interconnected disorders. Firstly, they are connected by the mechanical stress on the retina caused by axial elongation of the eye globe. They may also be induced by a similar set of genetic polymorphisms, though this has yet to be proven [6]. Connective tissue disorders can induce refractive changes, either from scleral/corneal/lenticular thinning or deformation, leading to refractive errors such as myopia, hyperopia, and astigmatism. Reduced mechanical resistance of ocular tissues can also result in a higher incidence of glaucoma and retinal detachments.

At present, collagen substitutes are fairly often used in ophthalmology. Corneal components from human donors or obtained through bioengineering are used in keratorefractive surgery as scaffolds. Bandages on the ocular surface can counteract local inflammation. Ologen, a biodegradable collagen matrix implant, is utilized as a patch graft in glaucoma surgeries to prevent excessive healing and fibrosis, thereby enabling filtrating surgeries to function over a longer duration [69]. Another medical device based on connective tissue transplantation is Alloplant, where biomaterial from deceased donors is being transplanted to patients with various ophthalmic ailments, although this technology is of limited viability due to low-quality evidence [20]. Drug-delivery systems with low immunogenicity are continually being developed to ensure consistent therapeutic outcomes independent of patient compliance.

Collagen dressings or gels can reduce scarring and improve healing after eyelid surgeries or trauma. Due to inflammation control, some diseases are mediated through collagen fibers, such as scleritis and episcleritis. Even lubricating eye drops contain biosimilar components of the ECM. Collagen-based eye drops or gels help in cases of dry eye syndrome by stabilizing the tear film and protecting the ocular surface. Some treatments (e.g., microneedling, laser therapy) use stimulating fibroblasts to produce more collagen, improving firmness and elasticity upon proper integration in target skin tissues. Dermal fillers are used for periorbital rejuvenation to reduce wrinkles, fine lines, and volume loss around the eyes due to tear trough deformities or crow's feet. Unfortunately, the effect is only temporary due to poorer repair mechanisms related to aging and mediated by genetic factors. This necessitates repeat treatments, sometimes as frequently as every few months [7].

Environmental factors and gene expression

Gene expression can be modulated by environmental factors, including lifestyle and diet habits, as well as sun exposure. Ultraviolet (UV) radiation affects both the DNA structure and the daily cycle regulation. Air pollution, the presence of pesticides, and microplastic consumption, which currently affect most people around the world, are also significant factors. Viruses and other microorganisms can also influence gene expression [58]. Essentially, constant modifications take place in response to what happens in the surroundings. One worldwide issue and a common example of this modulation is dry eye disease, which is often broadly renamed ocular surface disease. Problems include worsening vision, local discomfort, stinging, and pain. Many treatment methods have been developed since every patient

has a slightly different multifactorial background, but the effects are temporary, and the chronicity of this disease significantly burdens public health. Environmental and lifestyle factors strongly influence the onset of the disease, making some individuals more susceptible to symptoms or reluctant to treatment [65]. The immune response is directly triggered by these external elements and mediates many diseases that affect the eye. The age at which a disease becomes prevalent and the degree to which specific tissues undergo apoptosis are dependent on gene expression [74].

Genetic polymorphisms

Genetic polymorphisms affect the way individuals respond to ophthalmic medications when they affect, e.g., CYP450 enzymes, also present on the ocular surface [60], resulting in different efficacy or toxicity in each case treated [35]. Polymorphisms related to immune response genes can impact the severity of inflammatory or infectious conditions, such as uveitis or keratitis [1,40,67]. Based on a basic example, people exposed to the same airborne viruses transmitted through the droplet route are going to experience either strong debilitating symptoms with a runny nose and cough, potentially exacerbating to laryngitis or pneumonia; on the other hand, they may end up having a headache subsiding the next day or remain asymptomatic. Recently, study methods are often based on Mendelian randomisation, consisting of exploring a particular phenotype against genetic variants known to be associated with an exposure agent [43]. Therefore, genetic polymorphisms are implicated in the manifestation of autoimmune diseases such as thyroid eye disease (TED) [14, 26], myasthenia gravis [83], multiple sclerosis [4], and uveitis [27, 28]. Suspected causes underlying the autoimmune cascade of events remain microorganisms, with different susceptibility among individuals.

Ocular oncology

Gene mutations play an important role in the onset of oncological tumours. Exposure to external sources of radiation, such as UV or ionizing radiation, can damage DNA. The induced changes should be repaired through repair mechanisms. However, if these mechanisms fail, the proliferation of defective cells occurs, which can lead to the growth of melanoma, for example. However, UV was not proven to affect neoplasia of the choroid and ciliary body similarly to skin melanoma [50]. Retinoblastoma can be a spontaneous mutation inside retinal cells in infants or young children, but it can also be generalized in the whole body when occurring prenatally and then poses a high risk of transmission to the offspring [12,48]. The ambiguous process leading to the growth of tumours is still poorly understood. On the other hand, vitamin D is more frequently discussed regarding its beneficial effects on overall health, with researchers suggesting specific receptor polymorphism as a potential trigger factor for ocular surface squamous neoplasia (OSSN) [56]. Regulating the cell cycle, it induces the apoptosis of defective cells and downregulates proinflammatory cytokines in order to eventually prevent malignant proliferation.

Retinal diseases

Age-related macular degeneration (AMD) has a multifactorial genetic background. Variants in genes like CFH, ARMS2 can alter complement activation, leading to an inflammatory response resulting in photoreceptor loss [54,63]. Single-nucleotide polymorphisms (SNPs) contribute to the incidence of neovascular AMD and the clinical response to treatment [16]. This knowledge can help identify patient response to particular drug formulations. In this matter, optogenetic therapy consisting of activating bipolar retinal cells to act as photoreceptors, can be one of the ways to recover vision in those patients [66] after promising preliminary results. Optogenetics is a technique in which photosensitive proteins (e.g., ion channels, receptors) are genetically introduced into specific cells to enable their activation or deactivation by irradiation with light of a specific wavelength. Among gene therapies, the effect of the modification of MCO-010, a gene encoding a protein that sensitizes retinal bipolar cells to light through an AAV vector, has also been studied. This gives a chance to retain/regain useful vision in individuals affected by retinitis pigmentosa or Stargardt disease. In a preliminary report on 6 patients, a 3 dB improvement in the mean retinal sensitivity (MD) in the perimetric study was achieved, further studies are ongoing [24]. Leber hereditary optic neuropathy, which significantly impairs the visual acuity of adolescents, is on the verge of gaining genetic therapy for its most common missense mutation in mtDNA-ND4 (m.11778G>A), which will be marketed as Lumevoq (lenadogene nolparvovec). Currently, an approved genetic therapy exists for treating the altered RPE65 gene, called Luxturna (voretigene neparvovec). Both treatments rely on the use of adeno-associated viruses, helping to incorporate the correct gene in retinal cells. Thanks to its relatively

weak immunogenic response and the blood-retinal barrier, the therapy has minimal adverse effects.

Polymorphisms can concern more crucial genes or larger sections of the genome, leading to an evident phenotypic presentation, which is the case for inherited retinal diseases. Mutations in RHO or USH2 genes are related to severe visual incapacity, while the term inherited does not mean the parents obligatorily transmitted the mutation to their offspring, since mutations can happen spontaneously de novo [11]. Retinal dystrophies and some optic neuropathies are also mediated by genetic pathology [22,30]. A myriad of genes have been identified as the probable cause, though the treatment still poses a challenge up to this day due to probable complex intergenic interactions [62]. Diabetic retinopathy, a prevalent disease in ophthalmology related to the constantly increasing incidence of diabetes worldwide, is also presumed to have genetic influences [42]. For instance, epigenetic modifications such as methylation and histone modification can impact genes involved in angiogenesis and inflammation [18], explaining why ophthalmic manifestations of hyperglycemia are not always directly related to blood sugar levels. Sorbitol dehydrogenase and microRNA-320a were discovered to be downregulated in the diabetic retinopathy [5]. Bringing their levels back to normal would possibly attenuate retinal vascular leakage and inflammation mainly by inhibiting VEGF, IL-6, and TNF-α expression.

The impact of genes on the fibrous tunic of the eye globe

It has been observed that aviation professionals, especially operating jet aircrafts, are prone to developing specific ophthalmic complications, such as central serous chorioretinopathy [86]. It is yet unclear whether the cause lies in their stressful conditions of work or atmospheric changes related to unique gravitational forces, vascular perfusion alterations and hypoxia. Some military pilots develop ocular pathologies while their colleagues of the same rank do not. This leads us to suspect that genetic factors play a key role, and that we need to understand these complexities to avoid debilitating conditions that would restrict these highly trained and skilled individuals from further duty. Certainly, knowledge of these factors in candidates beforehand would greatly contribute to selecting the best-suited career pathway.

For instance, refractive error is impeding some career choices. Ophthalmic surgery, aiming to correct the visual acuity to emmetropia, disqualifies pilot candidates in some countries. Transmission of hyperopia, myopia, and astigmatism to offspring proves genetics contribute to these diseases, but oftentimes they occur in children of unaffected parents, confirming the theories of selective gene silencing and environmental factors in play. Keratoconus is an example of corneal degeneration causing advanced myopic shift with irregular astigmatism, with known causes in atopic and allergic diseases affecting the ocular surface, as well as eye rubbing, frequent in young individuals with Down syndrome [8]. Genome-wide studies identified over 300 mutations linked with keratoconus, most importantly in genes: COL5A1 (causing other connective tissue disorders as well), LOX (also linked to high myopia and glaucoma), TGFBI gene (responsible for other corneal dystrophies too). FOXO1 and FNDC3B genes have been found to be strongly related with central corneal thickness.

Plural DNA alterations and genetic polymorphisms have been associated with the onset of myopia [53]. One hypothesis states that with more abundant food available in an increasing number of countries due to their constant development, there is a higher stimulation of growth factors due to more energy sources, among which IGF1 is one of the main potential culprits [15] by binding to scleral fibroblasts, increasing transcription of collagen genes. Children are reaching greater heights at an earlier age. Presumably, their eyes are receiving more stimuli, just as their bone epiphyses are. The trouble is that after reaching the full height, the globe can continue growing or degeneration can occur much later in life, when matrix metalloproteinases cause degradation of collagen fibres. Other than certain SNPs, insufficient DNA methylation or the action of non-coding mRNAs, environmental factors are also important in myopic pathology, and they can dictate specific genetic alterations [28]. Excess near work in childhood with dim lighting conditions and limited outdoor activity can exacerbate the activation of unwanted genetic pathways that technically occur as a response to physiological demand. This way, rising access to education in developing countries and the focus on building a career through hard intellectual work are probably augmenting the prevalence of myopia. Clinical significance has been researched regarding the potential of slowing down myopia progression in children, where it was demonstrated that the effectiveness of orthokeratology depends on nonsynonymous variants in retinal disease-related gene sets

[78]. The same is probable for atropine, whose mechanism is not exactly understood, so this topic requires further investigations. Along with the defocus incorporated into the multiple-segment spectacles prescribed for children at high risk for myopia, the effects seem to persist as long as the treatment lasts. Then, changes progressively revert to the point where risk-matched individuals not subjected to treatment would be anyway. This indicates that still undiscovered genetic factors inducing myopia are only halted by the treatment, but upon discontinuation, they get expressed as they would be in the first place.

Pro- and anti-inflammatory factors are supposedly somewhat correlated to myopia [61,85,87]. For instance, conjunctival allergies may increase the risk of eye globe axial elongation this way [38,76]. There is also a potential role for altered signalling in cone-driven OFF pathways in myopia development [77,79]. Non-coding RNAs and enhancers for refractive error can impact myopia as well [72]. Despite the fact that it is common knowledge that most diseases result from unmodifiable genetics, studies show the importance of enriching diets with polyunsaturated fatty acids and minimizing saturated fatty acids [21, 32, 41, 80]. This may be due to lowering inflammation, improved intercellular signalling, and fewer metabolic disruptions. Gender also plays a role, which is understandable since biological differences result from different sex chromosomes. This demonstrates that multiple parts of the genome are implicated in the process. Protective factors are currently being investigated and could be an example for genetic modification of a pathological gene variant in the future [52].

Many genes have also been found to be implicated in the pathogenesis of glaucoma [45]. In children, iridocorneal dysgenesis is the main suspected cause [82], resulting from collagen defects with fibril disorganization and structural integrity loss. In the adult population, however, degeneration of the trabecular meshwork is due to ECM remodelling, causing obstructed aqueous outflow, resulting in gradual IOP increase, which can also occur in spikes, being more destructive to the ganglion cells of the retina. This again is regulated by a variety of genes, with more being identified with time [23]. Glaucoma is a multifactorial disease caused by intraocular fluid filtration impairment leading to retinal compression on one hand, and visual pathway degeneration linked to vascular shortage, optic nerve/radiations compression, and other neuropathies on the other hand – each with its own genetic background that should be discerned in the diagnostic process [17]. The last group includes pathologies known as normal tension glaucoma [57], where gene polymorphisms can affect the elasticity of blood vessels and the cribriform plate. These structures are directly implicated in neuronal health. An interesting study differentiates two sets of genes: IOP-dependent and IOP-independent [31]. Glaucoma is also related to the degree of myopia, since posterior pole extension stretches the retina along and the mechanical stress is harmful to the cells, which are losing their junctional integrity and become more prone to IOP-induced damage. Aside from genes, metabolism markers were identified to be either protective or causative of glaucoma [73]. Furthermore, due to previous discoveries of gut microbiome influencing neuropsychiatric health – such as Alzheimer or Parkinson disease onset, similar connections were looked for regarding ocular pathologies [33,44], since eyes are essentially extensions of the brain.

Both diseases are supposedly interlinked, since myopia is essentially the selective expansion of ECM tissues in the sclera, while glaucoma due to high IOP arises from ECM-lowered support [71]. For instance, pigment dispersion syndrome shows a strong correlation of myopia with glaucoma [68]. Also, the cornea is often thinner in glaucoma, which is considered a risk factor [34]. On the other hand, not all highly myopic patients have a thinned cornea – some of them have less glaucomatous damage than hyperopes; the latter may experience RGC axonal loss due to confinement of structures within a smaller crowded disc and subclinical changes occurring in time [25]. So far, there is no strong evidence regarding the correlation between corneal degeneration and glaucoma. A study has found pleiotropism of certain SNPs in inducing many pathologies (AMD, DR, glaucoma) [81]. Some researchers showed cataract is less due to external factors than previously thought, but rather part of an ocular disease spectrum [36,75]. Obviously, ocular trauma hastens cataract formation when the lens capsule loses its integrity. Disturbing the fragile electrolyte balance leads to opacification. Also, due to the eyes being part of the central nervous system, some studies focus on researching the connection between the brain and ocular proteomes, finding several suspected common genetic risk loci [51]. Nevertheless, one needs to be aware of intergenic interactions that can cause many illnesses, generalizing to the whole organism, so it is easy to get lost in the genetic complexity [25].

In the last few years, much progress has been made in understanding the genetic basis of diseases, which translates to new possibilities of developing adequate treatments. Advances in whole genome sequencing (WGS) will allow for better tailoring of preventive strategies and ultimately treatments based on genetic profiles [13]. One such possibility could be CRISPR technology which has already been FDA-approved to treat sickle cell disease and certain types of beta thalassemia and are promising in the ophthalmology field as well [29,37,59]. In case of mitochondrial DNA (mtDNA), CRISPR cannot cross the double membranes of mitochondria, but new methods are being studied to overcome this adversity. A base editor was used to fix single-letter mutations in mitochondrial DNA without cutting it [84]. The recent discoveries around CRISPR technology, making in utero or postpartum genetic modifications possible, can be ground-breaking in raising healthy persons able to function in society, also making parenting more bearable [39].

CONCLUSION

Ophthalmic genetics is one of the most promising fields, with the potential to deliver significant therapeutic breakthroughs. In light of present knowledge, expanded research regarding the influence of genetics on ocular pathology will be crucial for prophylaxis and treatment of progressive diseases that cause irreversible damage, such as myopia, glaucoma, and retinal dystrophies. Various associations have been identified so far between ophthalmic diseases and connective tissue disorders, but the complexity of factors leading to uncontrolled tissue growth or unwanted cellular apoptosis needs to be examined further to develop preventive strategies. Moreover, the constant improvement and refinement of artificial intelligence tools may accelerate advances in analysing large complex datasets, facilitating future scientific research.

AUTHORS' DECLARATION

Study Design: Grzegorz Rotuski, Katarzyna Komar, Aleksandra Przybysz, Ewelina Maculewicz. **Statistical analysis:** Grzegorz Rotuski, Katarzyna Komar, Aleksandra Przybysz, Ewelina Maculewicz. **Data Collection:** Grzegorz Rotuski, Katarzyna Komar, Aleksandra Przybysz, Ewelina Maculewicz. **Manuscript Preparation:** Grzegorz Rotuski, Katarzyna Komar, Aleksandra Przybysz, Ewelina Maculewicz. The Authors declare that there is no conflict of interest.

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