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Molecular Genetics of Pseudoexfoliation Syndrome (PXFS) and Glaucoma (PXFG)

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Pseudoexfoliation syndrome (PXFS) is an age-related, generalized disorder of the extracellular matrix characterized by the excessive production of elastic microfibrils and their aggregation into mature pseudoexfoliation fibrils [1]. It accounts for a majority of glaucoma cases in some countries and for approximately 25% of open-angle glaucoma cases worldwide [2]. Progressive obstruction of the aqueous humor outflow pathways by abnormal pseudoexfoliation material deposits cause chronic pressure elevation, optic nerve damage and subsequent development of open-angle glaucoma in eyes with PXFS, a condition known as pseudoexfoliation glaucoma (PXFG) [3]. Moreover, pseudoexfoliation deposits are found in a multitude of intra- and extraocular tissues, including conjunctiva, skin, and connective tissue compartments of visceral organs [1]. As shown by biochemical and immunohistochemical studies, pseudoexfoliation fibrils predominantly contain elastic fiber components, such as elastin, fibrillin-1, latent transforming growth factor binding proteins (LTBP-1/2), and fibulins (fibulin-2/4), as well as lysyl oxidase-like 1 (LOXL1) [4-7], a key cross-linking matrix enzyme normally required for proper elastic fiber formation and stabilization [8]. However, the exact composition of the abnormal extracellular material as well as the mechanisms responsible for its excessive production and accumulation still remain elusive.

PXFS is generally considered as a complex, multifactorial, late-onset disease involving a combination of genetic and non-genetic factors in its etiopathogenesis [9]. Several lines of evidence, including regional clustering, familial aggregation, and genetic analyses, have previously supported a genetic predisposition to pseudoexfoliation [10]. Since a simple inheritance model was not evident, a complex inheritance pattern caused by the contribution of multiple genetic factors and environmental conditions has been suggested [11]. To date, circumstantial evidence exists for the contribution of several genes with relatively small effect sizes, such as *CLU* (clusterin), *CNTNAP2* (contactin-associated protein-like 2), and *APOE* (apolipoprotein E) in some study populations indicating a modifying rather than a direct genetic effect [9,12-15]. In contrast, *LOXL1* has been identified as a major contributor and principal genetic risk factor for PXFS throughout all geographical populations examined [16,17]. Genetic studies in multiple geographical populations have provided conclusive evidence that two single nucleotide polymorphisms (SNPs) in exon 1 of the *LOXL1* gene represent the principal genetic risk factor for both PXFS and PXFG [16,17]. Although the pseudoexfoliation-associated *LOXL1* missense variants showed a different allele frequency within different geographical populations, a high-risk haplotype (G-G) formed by the two coding SNPs rs1048661 (R141L) and rs3825942 (G153D) appeared to be the strongest associated risk factor for pseudoexfoliation in Caucasian and European populations, whereas the T-G and G-A haplotypes were associated with lower risks [16,18]. However, approximately 50% of the normal population was also found to carry the high-risk haplotype, indicating that, in addition to *LOXL1* risk alleles, other pseudoexfoliation-specific genetic variants or environmental factors may contribute to the risk of developing the pseudoexfoliation phenotype. Recently, novel polymorphisms in the promoter region of *LOXL1* have been identified to be associated with PXFS/PXFG in a U.S. Caucasian population and were suggested to influence *LOXL1* gene expression by causing a reduction in *LOXL1* protein expression and activity [19]. This is consistent also with the fact that *LOXL1* is downregulated by age in ocular tissues and PXFS is a late-onset disease.

LOXL1 is a key enzyme involved in elastic fiber synthesis and homeostasis by catalyzing the covalent cross-linking of tropoelastin monomers into elastin polymers through oxidative deamination of lysine residues [20]. Recently, it was shown that *LOXL1* and elastic fiber components are transiently upregulated in ocular tissues during the early stages of the fibrotic pseudoexfoliation process, suggesting their participation in the formation and aggregation of abnormal pseudoexfoliation fibrils [5]. This observation is in agreement with published studies demonstrating that *LOXL1*, in conjunction with its putative extracellular substrates, becomes transiently upregulated and activated at early stages of fibrogenesis (e.g., in liver fibrosis) [21]. Profibrotic growth factors, particularly TGF-β1, increased cellular and oxidative stress, and low-grade inflammatory processes appear to contribute in the regulation of the expression of *LOXL1* and extracellular matrix molecules in various experimental settings and may therefore be considered candidate co-modulating factors in pseudoexfoliation pathophysiology [20]. Consistently, it may be hypothesized that the abnormal matrix process characteristic of PXFS can be activated by certain fibrogenic stimuli and, in the background of the high-risk *LOXL1* haplotype, participate in the formation and accumulation of pseudoexfoliation aggregates within intra- and extraocular tissues. In fact, dysregulated expression of *LOXL1* has been previously shown to be substantially involved in pseudoexfoliation pathophysiology. The available data indicate that *LOXL1* is transiently upregulated in anterior segment tissues at early stages of pseudoexfoliation fibrogenesis, together with elastic fiber constituents, to participate in the formation of the aberrant fibrillar aggregates [5,22]. Thus, LOXL1 and elastic fiber components, such as elastin, fibrillin-1, LTBP-1/2, and fibulin-2/4, were found to be prominent components of fibrillar pseudoexfoliation aggregates in the anterior segment. In the posterior segment, lamina cribrosa tissue of pseudoexfoliation eyes revealed a

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site-specific downregulation of *LOXL1* and elastic fiber constituents, which was associated with a pronounced elastosis of the laminar beams and which has been suggested to represent a major susceptibility factor for a pseudoexfoliation-associated risk of glaucoma development and progression. These differential expression patterns indicate that other pseudoexfoliation and tissue-specific factors may modulate local *LOXL1* expression levels in addition to genetic predisposition.

In view of these considerations, it is reasonable to assume that the combined effect of *LOXL1* genotype and external factors or stress conditions with fibrogenic potential, which are known to be present in the anterior segment of pseudoexfoliation eyes, might influence the manifestation of the disease (i.e., the accumulation of abnormal fibrillar aggregates). Candidate factors, which might stimulate the synthesis of abnormal pseudoexfoliation fibrils, include profibrotic growth factors (TGF-β1), cytokines (IL-6), and amino acids (homocysteine), as well as various stress conditions such as oxidative stress, UV radiation, and hypoxia. In response to these profibrotic triggering factors, *LOXL1* may become upregulated in pseudoexfoliation tissues together with elastic matrix components serving as putative substrates for an abnormal cross-linking action of the enzyme. It is likely that through such protein–protein interactions the effects of the pseudoexfoliation-associated *LOXL1* variants become more significant [22].

Methylenetetrahydrofolate reductase (*MTHFR*) and apolipoprotein E (*APOE*) genes have been investigated in relation to pseudoexfoliation and glaucoma [15, 23-26]. A common C677T polymorphism in the *MTHFR* gene causes reduced activity of this enzyme due to thermolability and is the most common genetic factor for moderate hyperhomocysteinemia and a higher prevalence of C677T has been found in primary open-angle glaucoma (POAG) [24]. Therefore, this polymorphism is debated as a potential genetic risk factor for PXFS, PXFG and POAG. Furthermore, homocysteine causes dysregulation of matrix metalloproteinases and their inhibitors [27], which has been implicated in the pathogenesis of PXFG [28].

The ApoE protein plays an important role in neural function as it is involved in neurite outgrowth and repair from injury [29]. It is upregulated in response to oxidative stress and appears to act as an antioxidant. Three common alleles exist; ε2, ε3, and ε4. The ε3 allele is considered to be the ancestral allele; and ε2 and ε4 are considered as variants, on the basis of single point mutations in two amino acid positions; 112 and 158. *APOE* alleles modulate the biological functions of ApoE in part by altering the binding of the different lipoprotein subclasses and affecting their catabolism [30].

The average worldwide prevalence of PXFS ranges from 10% to 20% of the general population over the age of 60 years. However, studies have shown much higher prevalence in Nordic and Greek populations [31]. In the Northwest region of Greece called Epirus, PXFS was diagnosed in 24.3% of the population over the age of 50 years [32]. The underlying causes of the differences in prevalence rates between age-matched geographical and ethnic populations remain unknown, but appear to be mainly related to variation in genetic background. Our investigation on the impact that specific gene polymorphisms have on the Greek population will further elucidate the mechanisms that are implicated in PXFS/PXFG.

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