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Current Status and Future Directions on Corneal Genetics

Editorial

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Introduction

The cornea, along with the sclera, serves as a protective shield for intraocular tissues. Moreover, the cornea accounts for two thirds of the eye's refractive power [1]. Corneal pathologies will disrupt the protective function and refractive status of the eye, leading to visual impairment and even subsequent intraocular complications such as endophthalmitis. In this editorial, we will highlight the current status of corneal research on gene mapping in the recent two decades and the possible future directions.

Corneal gene mapping grossly targets two categories of phenotypes: A) quantitative traits of the cornea, such as corneal thickness and corneal curvature, and B) corneal disorders such as astigmatism, keratoconus and dystrophies. Many of the phenotypes can present in Mendelian or multifactorial forms. The former usually occurs in families and is usually caused by mutations in specific genes, whereas the latter mostly presents as sporadic cases and is resulted from the interactions of multiple genetic and environmental factors.

Genetics of Mendelian Corneal Diseases

In the earliest stage of its development, corneal genetic research was mainly conducted through observation and analysis of the distributions of corneal phenotypes amongst families [2] or twins [3], leading to the understanding of their inheritance patterns. Not until the late 1980s, linkage analysis was then adopted for gene mapping for corneal diseases of Mendelian inheritance. For example, in 1989, a disease locus of X-linked megalocornea was found to be located in the chromosomal region Xq21.3-q22 [4]. A decade on in the 1990s, linkage analysis became the predominant method for gene mapping and a number of genetic loci had since been discovered. For example, a linkage locus of posterior polymorphous corneal dystrophy was mapped to 20q11 [5], and three autosomal dominant corneal dystrophies (viz. lattice dystrophy, granular dystrophy and Avellino dystrophy) were mapped to chromosome 5q [6].

The identification of the linkage loci had laid down the foundation for further identification of disease-causing genes and mutations for both dominant and recessive corneal disorders. For example, by generating a YAC contig of the 5q31 linkage region of autosomal dominant corneal dystrophies followed by cDNA selection, missense mutations were discovered in the beta ig-h3 gene in 6 families with granular dystrophy Groenouw type I, Reis-Bücklers corneal dystrophy, lattice corneal dystrophy type I, or Avellino corneal dystrophy, respectively [7]. Another example is the identification of disease-causing mutations in the *KERA* gene for the recessively-inherited form of cornea plana [8] through candidate gene analysis in a previously-identified linkage locus on 12q [9]. Similarly, after identifying a linkage locus on chromosome 1p34.3-p32 in a family with Fuchs' endothelial corneal dystrophy (FECD), Biswas et al. analysed the coding sequence of the *COL8A2* gene, which encodes the alpha2 chain of type VIII collagen (a component of endothelial basement membranes), and defined a missense mutation p.Gln455Lys in the family, suggesting that *COL8A2* is a disease-causing gene for FECD and that the underlying pathogenesis of FECD may be related to disturbance of type VIII collagen [10]. The identification of disease genes and mutations provides an important platform for understanding the molecular pathogenesis of corneal diseases.

The identification of *COL8A2* on the 12q linkage locus represents a good example illustrating the traditional gene mapping strategy for Mendelian corneal diseases. However, not all linkage loci contain well-defined candidate genes for follow-up of the linkage signals, rendering the recognition of the disease-causing genes and mutations difficult. For example, a novel linkage locus for keratoconus was mapped to a 5.6-Mb interval on 13q32 [11]. This locus contains 25 known transcripts, but none of the genes demonstrated any definite functional link to keratoconus; hence there is no excellent candidate gene in the locus. In view of this, Czugala et al. selected 8 positional candidate genes in the 13q32 region and sequenced them in the 13q32-linked keratoconus families. The mutation screening identified 4 sequence variants in three genes showing complete segregation with autosomal dominant keratoconus in a large family. By predicting the functional impact

of each variant, the authors suggested the p.Gln754His mutation in *DOCK9* may contribute to keratoconus [12]. As only 8 out of the 25 genes on 13q32 were sequenced and the p.Gln754His mutation was segregated with keratoconus in just one pedigree, the exact role of *DOCK9* as the disease-causing gene for keratoconus needs to be further elucidated.

With the advent of the next-generation sequencing platform, it is now possible to sequence a large number of genes simultaneously in a targeted locus or even the whole genome. This makes the gene identification in a known linkage locus can nowadays be performed at an unprecedented pace. For example, a locus for late-onset FECD was mapped to 18q21.2-q21.32 [13]. Recently, next-generation sequencing of all coding exons in the critical interval in a multigenerational pedigree with autosomal dominant FECD was performed. The authors identified a missense change in *LOXHD1* as the sole variant contributing to the clinical phenotype. Subsequent screening in a cohort of over 200 sporadic FECD patients identified another 15 missense mutations of the gene that were absent from more than 400 controls, supporting *LOXHD1* as the causative gene for late-onset FECD on 18q [14]. In another study, targeted next-generation sequencing was performed following the identification of a linkage locus on 15q for late-onset FECD and a nonsense mutation in *AGBL1* was identified to be disease-causing [15]. These studies illustrated the usefulness of next-generation sequencing in the gene hunting for corneal diseases.

The next-generation sequencing is also a powerful platform for gene discovery in disease pedigrees without any prior linkage loci, especially when the size of a family is small making linkage analysis difficult. Recently, whole exome sequencing with subsequent pipeline analysis identified a *de novo* mutation p.Met77Thr in the *NLRP1* gene as disease-causing for corneal intraepithelial dyskeratosis [16]. To the best of our knowledge, this is the only study in which whole exome sequencing was used to map for corneal disease genes. On the other hand, exome sequencing had been widely adopted in gene mapping for other eye diseases, such as retinitis pigmentosa (RP) [17,18] and high myopia [19,20].

Apart from whole exome sequencing (which targets mainly on coding and splicing regions), whole genome sequencing, which also covers intronic regions, had also been applied to disease gene mapping. Whole genome sequencing has led to the identification of causative genes for systemic diseases such as Charcot-Marie-Tooth neuropathy [21] and chronic lymphocytic leukemia [22]. So far, there is one report on using whole genome sequencing to map for eye disease genes. In using whole genome sequencing in patients with retinitis pigmentosa, Nishiguchi et al. detected homozygous or compound heterozygous mutations in 7 genes known to be associated with autosomal recessive RP, and also identified a new RP gene, *NEK2* [23]. In view of the power of the next-generation sequencing platform in gene mapping in contrast to the limited genetic information identified previously for corneal diseases, it could be expected that the application of the next-generation sequencing in gene mapping for corneal diseases could represent a major direction in future corneal genetic research.

Genetics of Multifactorial Corneal Phenotypes

The genes illustrated above are mainly for the Mendelian form of corneal (or other ocular) diseases. Apart from these, there is another group of genes and variants that are associated with the multifactorial form of corneal traits and diseases. With the completion the HapMap project and the advent of the genome-wide association analysis platform, genome-wide association study (GWAS) has become a predominant genetic methodology for mapping of susceptibility gene variants for eye diseases. In GWAS, tens of thousands gene variants across the human genome were analysed simultaneously for disease-association. So far, multiple gene loci for corneal phenotypes have been identified by GWAS, including central corneal thickness [24-27], corneal astigmatism [28], corneal curvature [29], keratoconus [27,30], and FECD [31]. The gene loci identified by GWAS usually revealed ethnic diversities; therefore replication in different populations other than the initial cohorts is warranted to confirm the GWAS signals. An excellent example is that a single-nucleotide polymorphism, rs613872, in the *TCF4* gene for FECD [31] was confirmed in a meta-analysis to be strongly associated with FECD in different populations [32].

Future Directions

So far, a large group of genes and variants have been identified for corneal diseases and traits, however, they can explain only a small proportion of the genetic contributions to the phenotypes.Therefore more genes are yet to be identified. Moreover, the functional roles of the identified genes in the disease pathogenesis are poorly understood. With the upcoming susceptibility genes identified by GWAS with larger sample sizes and disease-causing genes identified by the other methods as mentioned above, along with downstream functional characterization of the roles of the genes in the diseases, the elucidation of the genetic architecture and molecular mechanisms of corneal phenotypes will be taken to new heights.

In addition, with more genes identified, genetic diagnostic panels can be designed for clinical use to diagnose patients earlier who are at risk of developing specific corneal diseases. Such gene panels have been tested in retinal diseases [33,34]. Moreover, with the identification of disease genes and their biological roles confirmed, gene therapies would be possible for corneal diseases, the part of the eye that is most easily accessible.

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