PERSPECTIVE

Molecular genetics of macular dystrophies

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Macular dystrophies represent a heterogeneous group of disorders spanning a broad spectrum of clinical, histopathological, and laboratory findings. Despite this variability, fundus changes involving the macula and retinal pigment epithelium (RPE) and clinically significant loss of central or functional vision are characteristic of these disorders. As a group of diseases with a strong genetic component, many macular dystrophies are excellent candidates for study using molecular biological techniques such as genetic linkage analysis, positional cloning, and the candidate gene approach. Such molecular investigations have been successful, and genes for several inherited maculopathies including Stargardt's macular dystrophy,¹⁻³ North Carolina macular dystrophy,^{4,5} Best's vitelliform macular dystrophy,⁶ and Sorsby's macular dystrophy^{7,8} have been mapped to specific chromosomal loci. In addition to elucidating the aetiology and pathogenesis of these rare heritable disorders, it is hoped that the identification of individual genes and molecular pathways involved in inherited macular dystrophies will give greater insight into the more complex aetiology of age-related macular degeneration (ARMD).

ARMD is the most common cause of blindness among the elderly in many Western countries including the UK and the USA.⁹⁻¹¹ By 1996, it is estimated that over two million people in the USA alone will have ARMD, and more than 100 000 will probably be blind from the disease.¹² Despite its prevalence, the aetiology and molecular pathogenesis of ARMD are poorly understood.¹³ This finding makes a rational approach to treatment difficult, and therapeutic options for ARMD limited. Direct application of molecular genetic techniques to ARMD is hindered by two major factors. Firstly, the late onset of ARMD makes genetic linkage experiments difficult because the parents of affected individuals are often deceased and the children of affected members are often too young to express the ARMD phenotype. Secondly, although genetic studies involving monozygotic twins suggest a major genetic component,¹⁴⁻¹⁷ ARMD in most patients is probably multifactorial including both genetic and environmental factors. For example, a high dietary intake of carotenoids has been associated with a lower risk of ARMD,¹⁸ whereas a high risk of ARMD has been associated with atherosclerosis in a study population in Rotterdam.¹⁹ Owing to these difficulties monogenic maculopathies sharing important clinical and histopathological findings with ARMD have been studied. Here, we review recent developments in this field and discuss the results with regard to the application of these techniques to the study of ARMD.

Classification of inherited macular dystrophies

The many forms of inherited macular dystrophy have previously been classified by mode of inheritance, age of onset, site of involvement, or chromosomal location (Table 1).^{13,20,21} The considerable number of diseases and the broad and overlapping range of phenotypes associated with

each disease makes it likely that some of these maculopathies may be identical and, in fact, caused by mutations in the same gene. For example, genealogical studies have recently established that central areolar pigment epithelial dystrophy, central pigment epithelial and choroidal degeneration, central retinal pigment epithelial dystrophy, and North Carolina macular dystrophy are genetically related disorders.²² Recent advances in molecular genetics will almost certainly alter the classification scheme of the various macular dystrophies. For example, it has recently been shown that mutations in several different genes, such as rhodopsin (chromosome 3q) and the RDS/peripherin gene (chromosome 6p) are associated with the same phenotype as seen in autosomal dominant retinitis pigmentosa.²³⁻²⁵ Conversely, a mutation in the same gene, RDS/peripherin, has been associated with different phenotypes such as retinitis pigmentosa, pattern dystrophy, and fundus flavimaculatus within the same family.²⁶ From these observations, it is apparent that in the future once the genes and mutations causing inherited macular dystrophies have been identified, a more rigorous molecular classification of these disorders will be possible.

Genetic linkage analysis, positional cloning, and the candidate gene approach

The process by which a gene is identified as being responsible for an ophthalmic disorder usually involves genetic linkage analysis followed by positional cloning and/or the candidate gene approach.²⁷

GENETIC LINKAGE ANALYSIS

Inherited human diseases have been difficult to study in the past for several reasons. Traditional genetic tests such as complementation and recombination are not applicable because it is not possible to control human reproduction.

Table 1 Chromosomal location of macular dystrophies*

Chromosome†	Name	Reference
1p21-p13	Stargardt's (R)	1
2p	Doyle's honeycomb dystrophy	74
2p16-21	Radial drusen (D)	75
6p12†	Macular dystrophy	72
6q11-q15	Stargardt's (D)	3
6q16	North Carolina macular dystrophy	4,5
6q25-q26	Cone dystrophy	43
7p15-p21	Cystoid macular dystrophy	76
8q24	Cystoid macular dystrophy	77
11q13	Best's vitelliform macular dystrophy	6
13q34	Stargardt's (D)	2
17q11	Cone-rod dystrophy	78
18q21	Cone-rod dystrophy	79
19q13.3-13.4	Cone-rod dystrophy	80
22q13-qter†	Sorsby's fundus dystrophy	46
Xp21.1-11.3	Cone dystrophy	81

*Modified from Bird²³; †indicates gene identified; D= dominant; R= recessive.

Further, the gene and mutations causing the disease are rarely known beforehand, and thus the standard tools of molecular biology, cloning, and sequencing cannot be used. One method of resolving these difficulties is through genetic linkage analysis. Using linkage analysis, one seeks to identify the chromosomal location of the disease-causing gene by searching for coinheritance between a specific DNA marker and the disease phenotype. Highly polymorphic microsatellite markers consisting of short tandem repeat sequences of DNA are found ubiquitously in the human genome. Using these genomic markers, an exhaustive search of the entire genome can be made to locate the chromosomal region of the disease gene.²⁸⁻³⁰ Once this region has been identified positional cloning or the candidate gene approach are usually used to identify the disease-causing gene.

POSITIONAL CLONING

Positional cloning frequently follows genetic linkage analysis as the second step in identifying the disease-causing gene. Once genetic linkage studies have localised the mutated gene to a narrow chromosomal region, overlapping DNA fragments called contigs spanning the candidate region are isolated.³¹ These gene fragments or contigs are then assayed for gene transcription and for mutations and the disease-causing gene is identified.

While genetic linkage analysis and positional cloning used in concert will definitively lead to the identification of the disease-causing gene, this approach is both laborious and time consuming. This approach, however, has been applied to the identification of the genes involved in Norrie's disease³² and choroideraemia.³³

THE CANDIDATE GENE APPROACH

The candidate gene approach, on the other hand, has the potential to reveal the correct disease gene without exhaustive cloning. Under this strategy, known genes at the chromosomal locus identified by genetic linkage analysis are surveyed for strict cosegregation with the disease phenotype. Genes that are linked to the disease allele with no recombination are then cloned, and mutations are sought. Though this approach has been successful, most notably in the case of retinitis pigmentosa,³⁴⁻³⁷ it is limited by the number of known genes in the candidate chromosomal region. The human genome project will undoubtedly increase the number of known genes and thereby facilitate both positional cloning and the candidate gene approach.

North Carolina macular dystrophy

DESCRIPTION AND CLINICAL FINDINGS

North Carolina macular dystrophy (NCMD) was first described in 1971 by Lefler *et al.*³⁸ Inherited as an autosomal dominant disease, the onset of NCMD occurs in infancy or even in utero.³⁹ Expression is broadly variable with funduscopic findings ranging from mild macular pigmentation to a large central macular excavation. The breadth of phenotypes associated with NCMD has caused confusion regarding its aetiology. Genealogical studies have recently demonstrated that central areolar pigment epithelial dystrophy (CAPED), central pigment epithelial and choroidal degeneration, and central retinal pigment epithelial dystrophy are genetically identical to NCMD.⁴⁰

DIAGNOSIS AND LABORATORY TESTS

Small and others have proposed a grading scale to span the spectrum of phenotypes of NCMD.⁵ Under this system, grade I NCMD is characterised by few, small, drusen-like specks at the level of the retinal pigment epithelium (RPE). Grade II NCMD is characterised by confluent yellow specks at the level of the RPE in the central macula, and

grade III is characterised by a single, discrete, large, well circumscribed central macular excavation with intact neurosensory retina. Though grades I and II NCMD resemble ARMD in phenotype, NCMD of any grade is quite stable. Visual acuity varies from 20/20 to 20/200 with the mean falling between 20/30 and 20/50.⁶ Patients with all grades of NCMD have normal electroretinogram (ERG), electro-oculogram (EOG), and colour vision tests.

GENETICS

A large family with NCMD inherited as an autosomal dominant, fully penetrant trait has been studied.²⁷ Linkage analysis of this kindred, now known to include more than 2000 individuals, localised the disease-causing gene to chromosome 6q14-q16.⁵ Currently, no retinal specific genes have been mapped to the NCMD locus. However, indirect evidence suggests that this region may contain a gene or genes essential to retinal and neural development. Gross cytogenetic changes involving chromosome 6q, such as unbalanced translocation and partial trisomy, have been associated with altered retinal development and mental retardation.⁴¹⁻⁴³ The identification of more genes in this region is an important area for future study.

The identification of a second kindred with autosomal dominant macular dystrophy similar to NCMD that does not map to the known genetic locus raises the possibility that NCMD is a genetically heterogeneous condition.⁴⁴ Because of the breadth of phenotypes associated with NCMD, though, this conclusion is uncertain. It is hoped that the identification of genes and mutations responsible for NCMD will elucidate the molecular mechanisms underlying the disease and enable greater diagnostic accuracy and refinement.

Sorsby's fundus dystrophy

DESCRIPTION AND CLINICAL FINDINGS

Sorsby's fundus dystrophy (SFD) is an autosomal dominant macular dystrophy first described in a 1949 study of five British families.⁴⁵ Patients with SFD typically present with decreased central vision and nyctalopia by the third or fourth decade of life. The prognosis is poor, and disciform scarring can extend towards the fundus periphery leading to a nearly complete loss of ambulatory or functional vision.⁴⁶ SFD is unique among the inherited retinal dystrophies as the only disorder in which haemorrhagic macular degeneration and choroidal neovascularisation commonly occur.⁴⁷ Because these changes are also observed in a clinically important subset of patients with ARMD, the study of SFD could provide insight into the pathogenesis of ARMD.

DIAGNOSIS AND LABORATORY TESTS

SFD is a progressive maculopathy with characteristic funduscopic findings and morphological changes at each stage.^{45,46} Early in the disease's course, funduscopic examination reveals an abnormal accumulation of confluent, drusen-like material at the level of Bruch's membrane. Later in the disease's course, neovascular membranes have been described along with atrophy of the choriocapillaris, RPE, and neuroretina. ERG studies reveal depressed b-waves consistent with decreased rod sensitivity.

GENETICS

Genetic linkage studies on a large Canadian family of Irish origin initially localised the SFD causing mutation to chromosome 22q13.1.^{7,46} Further study of the 49 genes that map to the candidate locus led to the discovery of mutations in the tissue inhibitor of metalloproteinase-3 (TIMP-3) gene.⁸ Mutations in exon 5 of the TIMP-3 gene were identified using the single stranded conformational

polymorphism (SSCP) method, and sequencing of the exon led to the identification of two missense mutations. In one mutation, a cysteine residue was substituted for a serine, and in another, a cysteine was substituted for a tyrosine. Though the detection of mutations in TIMP-3 in patients is not proof that these mutations are the cause of the SFD phenotype, the failure to detect these changes in normal individuals strongly suggests these mutations as the principal molecular defect in this disease.

Remodelling of the collagen, laminin, fibronectin, proteoglycans, and glycosaminoglycans in the extracellular matrix is an active process essential to normal development. This process is usually governed by a balance between proteinases, including serine, cysteine, and matrix metalloproteinases (MMPs), and the inhibitors of these proteinases including the family of tissue inhibitors of metalloproteinases (TIMPs). It is believed that mutations in TIMP-3 upset the balance between proteinases and their inhibitors in the RPE by reducing the activity of the gene product.⁸ It is probable that the additional cysteine residues participate in aberrant intramolecular or intermolecular bonding that leads to altered tertiary structure and diminished activity.

CLINICAL STUDIES

A recent development in the clinical treatment of SFD centres on the hypothesis that the thickened Bruch's membrane acts as a diffusive barrier between photoreceptors and their choroidal blood supply. Specifically, one study hypothesised that night blindness in SFD patients was caused by chronic photoreceptor deprivation of vitamin A.⁴⁸ The results of the study supported this mechanism, and vitamin A at a dosage of 50 000 IU per day was shown to reverse night blindness in SFD patients within 1 week. These positive clinical findings were confirmed by ERG studies showing increased b-wave amplitude reflecting normalised rod sensitivity. Although this finding appears promising, further study is necessary before these results can be translated into a treatment strategy, particularly because long term use of high dosage vitamin A is potentially toxic and may even be fatal.⁴⁹ In the study above, a reduction in vitamin A dosage to 5000 IU per day, led to the return of symptoms. Still, this study points to a new approach to the treatment of SFD, and it is hoped that these results and new insights into the role of the TIMP-3 gene will lead to a useful and safe treatment in patients with this condition.

Stargardt's macular dystrophy (fundus flavimaculatus)

DESCRIPTION AND CLINICAL FINDINGS

Stargardt's macular dystrophy, originally described by Stargardt in 1909, is the most common hereditary macular dystrophy and accounts for 7% of all retinal dystrophies.⁵⁰ Typically, patients present with decreased central vision, usually in the first or second decade of life. Funduscopically, it is characterised by bilateral atrophic changes in the macula, degeneration of the underlying RPE, and the presence of prominent yellow-white flecks in the posterior pole. Abnormally high levels of lipofuscin have been reported in these patients.⁵¹ The disease carries a very poor prognosis with final visual acuity in the 20/200 to 20/400 range. The existence of flecks was described later as fundus flavimaculatus by Franceschetti.⁵²⁻⁵³ It is now generally accepted that Stargardt's macular dystrophy and fundus flavimaculatus represent different presentations of the same disease entity. Although Stargardt's macular dystrophy was originally described as an autosomal recessive trait, several large families have recently been reported with an autosomal dominant mode of inheritance.^{2,3,54-58}

DIAGNOSIS AND LABORATORY TESTS

In recessive Stargardt's macular dystrophy, fluorescein angiography typically reveals hyperfluorescent spots which do not precisely correspond with the flecks. Silent or dark choroid is present in 85% of all cases, and a 'bull's eye' window defect appears in some advanced cases. ERG and EOG are usually normal in the early stages of the disease but may become abnormal in the advanced stages. In dominant Stargardt's macular dystrophy, the result of fluorescein angiography is variable. In one report, fluorescein angiography showed a classic dark choroid and 'bull's eye' window defect (K Zhang, P P Bither, L A Donoso, unpublished results) whereas another case failed to demonstrate these findings.³ ERG and EOG are usually normal as they are in the recessive disease.

CLINICAL AND GENETIC STUDIES

Most cases of Stargardt's macular dystrophy have presented as an autosomal recessive trait. Recently, a gene for recessive Stargardt's macular dystrophy was mapped to the short arm of chromosome 1 in eight families.¹ This result is consistent with genetic homogeneity and suggests that possibly only one gene is involved in this form of the disorder. In contrast, several different genes have been implicated in the autosomal dominant form of the disease. Of families studied so far, two disease genes have been localised to the long arm of chromosome 13 and the long arm of chromosome 6, respectively.^{2,3} As more families are studied through genetic linkage analysis, more genes may be discovered. The genetic heterogeneity is further complicated by the fact that mutations in the RDS gene and mitochondria genome can also cause fundus flavimaculatus-like findings on fundus examination.²⁶

Best's (vitelliform) macular dystrophy

DESCRIPTION AND CLINICAL FINDINGS

This disease is an autosomal dominant inherited disorder, first described by Best in 1905.⁵⁹⁻⁶⁰ Patients are found to have bilateral macular lesions at a very young age. Typical fundus findings include a yellow, egg yolk-like appearance of the macula. Visual acuity usually remains fairly good for the first five decades of life but eventually deteriorates in the sixth or seventh decades to legal blindness.

DIAGNOSIS AND LABORATORY TESTS

Fluorescein angiographic studies of patients with Best's vitelliform dystrophy generally reveal complete blockage of background choroidal fluorescence by the lesion itself. Choroidal fluorescence elsewhere appears normal. The ERG is usually normal. However, the EOG is characteristically abnormal in almost all cases of Best's disease. The light to dark ratio is below 1.5.⁶ This electrophysiological abnormality can be detected even in patients who lack ophthalmoscopic signs of macular lesions.

GENETIC STUDIES

A five generation family with 29 affected members has been studied. Linkage analysis mapped the disease-causing gene to chromosome 11q13.⁶ Subsequent studies of additional families indicate the gene in 11q13 is the major, if not single, gene responsible for Best's disease.⁶¹ ROM-1, which is specifically expressed in the outer segment of photoreceptor cells, appears to be a promising candidate gene for this disorder.⁶²⁻⁶³ However, linkage analysis with an STR marker within this gene has excluded it as the disease-causing gene.

Butterfly-shaped pattern dystrophy

DESCRIPTION AND CLINICAL FINDINGS

This relatively rare macular dystrophy belongs to a group of autosomal dominant dystrophies of the RPE.⁶⁴⁻⁶⁷ It is

characterised by bilateral, symmetric pigmentary lesions that tend to have the geometric shape of a butterfly. Visual acuity is initially either normal or only slightly reduced. A slow decrease in visual acuity is often associated with progressive atrophic changes in the fovea.

DIAGNOSTIC AND LABORATORY TESTS

Fluorescein angiography may reveal a window defect. The ERG is normal, but an abnormal EOG has been noted in some patients whereas in others it was normal.

GENETIC STUDIES

A homozygous mutation in the peripherin gene was initially found to cause the 'retinal degeneration slow' (rds) phenotype in the mouse.⁶⁸ Subsequently, several mutations in the human RDS/peripherin gene have been found to be associated with butterfly-shaped pattern dystrophy.⁶⁹⁻⁷³ The protein product of the RDS/peripherin gene is thought to play a role in the structural integrity of the photoreceptor outer segment discs. A mutation in this gene could cause a structural defect resulting in the disease phenotype.

Clinical applications

A compilation of the genes involved in macular dystrophies and ARMD may provide a new basis for classification of the various forms of disorders affecting the macula. It will be possible to divide families and individual patients into groups with diseases of similar or identical mutated genes. The natural history and clinical features of each disease type can then be investigated for diagnostic and prognostic information. This should also permit preclinical identification of family members at risk for the disease and foster longitudinal evaluation of therapy. Such an approach will be significant if an alteration in lifestyle or surveillance and treatment may decrease that individual's risk of manifesting the disease. Genetic mapping and investigation will eventually lead to the identification of disease-causing genes themselves. With a disease-causing gene in hand, gene therapy can be explored. One of the advantages of gene therapy is that it does not require a detailed understanding of the function of a gene product, only the ability to deliver the normal gene or its product to the appropriate ocular tissue. Ophthalmic gene therapy offers the advantage of easy accessibility of ocular tissues and direct visualisation of disease processes in comparison with other tissue or organs in the human body. For many autosomal dominant diseases, however, the benefit of the above gene replacement approach is rather limited. In these cases, the understanding of the function of the gene product holds the key to developing specific therapies. Isolation of the disease gene should make possible the identification of the protein product and its function, thus elucidating the biochemical mechanisms of disease. Such a study may direct the development of novel, effective therapies, which may interfere or block pathways leading to the clinical disease phenotype.

The genetic basis of macular dystrophies and certain subsets of ARMD may be related, given the similarities between these diseases. It is possible that different or less severe mutations in the same genes that cause early onset diseases could be involved in a substantial number of cases of ARMD. Thus, a better understanding of macular dystrophies may yield a genetic model for the pathogenesis of ARMD.

If specific mutations are found in macular dystrophies that also are associated with a subset of ARMD, the mechanism of pathogenesis may then be studied using cell culture or transgenic animals. For example, mice could be genetically engineered to carry a mutant gene causing

ARMD. Such systems are more practical to study than the human population. One must be aware, however, that not all of the features of the human macula are represented in lower vertebrates, such as mice. Nevertheless, if new therapeutic treatments were developed with these models, they could be applied to patients with ARMD or other hereditary degenerations.

Much progress has been made in the genetics and molecular biology of macular dystrophies. The mapping of the genes involved in macular dystrophies may offer significant insight into the mechanism of the pathogenesis of macular degeneration and therefore insight into ARMD. It is hoped that such genetic and molecular studies will contribute increasingly to the clinical diagnosis, management, and treatment of patients with macular degeneration in the years to come.

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