Review article

The genetics of childhood cataract

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Abstract

Human congenital cataract has a diverse aetiology. In the proportion of cases where the cause is genetic, the disease shows wide phenotypic and genetic heterogeneity. Over the past few years, much research has been devoted to mapping the genes that underlie the disorder. This has been helped by the extensive array of naturally occurring and genetically engineered mouse cataract models and the abundance of human candidate genes. Most progress to date has been in the identification of genetic mutations causing autosomal dominant congenital cataract where eight genes have been implicated in cataractogenesis. Overall there is good correlation between the genetic mutations so far identified and the resulting lens phenotype but it is clear that mutations at more than one locus may give rise to similar forms of cataract.

The identification of genes causing inherited forms of cataract will improve our understanding of the mechanisms underlying cataractogenesis in childhood and provide further insights into normal lens development and physiology. Perhaps more importantly, it is likely that some of the genes causing early onset cataract will be implicated in age related cataract which remains the commonest cause of blindness in the world.

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Cataract is the term used to describe opacification of the crystalline lens of the eye. Opacities

vary in morphology, are often confined to a portion of the lens, and may be static or progressive. In general, the more posteriorly located and dense an opacity, the greater the impact on visual function.¹

Cataract is the commonest treatable cause of visual disability in childhood,^{2,3} with an incidence of 1-6 per 10 000 live births. There are many different causes including intrauterine infections, metabolic disorders, and chromosomal abnormalities.³ Cataract may also be inherited either as an isolated ocular abnormality or as part of a syndrome. The syndromic forms of cataract, which have recently been reviewed,⁴ will not be covered in this paper. In non-consanguineous populations, the majority of inherited non-syndromic cataract shows autosomal dominant (AD) inheritance, but X linked and autosomal recessive forms are also seen.⁴

Inherited non-syndromic cataract phenotypes

Classification of human inherited cataract is difficult because of the wide variation in morphologies observed.⁵ The lens develops by the formation of an embryonic nucleus during morphogenesis, around which lens fibres are deposited throughout life, initially forming the fetal nuclear region and thereafter the cortex (fig 1). Animal models suggest that the genes so far implicated in cataractogenesis are expressed in a time ordered, sequential fashion.⁶ Categorisation, therefore, more weighted towards the location of opacification rather than appearance, will accommodate these developmental considerations and best reflect the underlying genotype. Such a system is also clinically convenient.

Figure 1 The human crystalline lens.

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Figure 2 Examples of inherited cataract phenotypes. (A) Discrete non-progressive central anterior polar cataract (24 year old female). (B) Non-progressive posterior polar cataract (9 year old male). (C) Nuclear opacification (15 year old male). (D) Fine, dust-like (pulverised) opacities in lens with pulverulent cataract (32 year old male). (E) Discrete progressive blue-white pinhead and wedge shaped opacities typical of the blue dot or cerulean cataract (45 year old female).

Cataract affecting the nucleus (fig 2C) is common and suggests an abnormality of gene expression in early development. Opacities may be confluent or discrete. Affected subjects show bilateral symmetrical involvement with variable expressivity. An exception is the pulverulent cataract where the type and distri-

bution of the nuclear opacities can vary not only between family members but also between eyes of the same patient.⁵

Pulverulent cataract (fig 2D) derives its name from the dust-like “pulverised” appearance of the opacities which can be found in any part of the lens. The first detailed description

Table 1 Mapped loci for human congenital non-syndromic cataract with no candidate gene. Evidence for linkage to each locus is based upon the publication of single family data

Phenotype	Locus	Inheritance	OMIM No	Reference
Volkman (pulverulent)	1p36	Autosomal dominant	115665	67
Posterior polar	1p36	Autosomal dominant	116600	25
Anterior polar	14q24	Translocation	115650	24
Unknown	16p13.3	Translocation	156850	60
Marnier	16q22.1	Autosomal dominant	116800	57
Posterior polar	16q22.1	Autosomal dominant	116800	57
Anterior polar	17p13	Autosomal dominant	601202	26
Zonular-sutural (lamellar)	17q11-12	Autosomal dominant	600881	55
Cerulean	17q24	Autosomal dominant	115660	58
Unknown	I blood group locus	Autosomal recessive	212500	68
Sutural (lamellar)	Xpter-Xqter	X linked recessive	302200	69
(possibly synonymous with Nance-Horan syndrome)	(the recognition of various deletions probably refine the region to Xp22.3-21.1 ^{38 70})			

OMIM refers to *Online Mendelian Inheritance in Man* (<http://www3.ncbi.nih.gov/Omim/searchomain.html>)

of an affected family was published by Nettleship and Ogilvie⁷ in 1906. In this, the Coppock family, the cataract was confined to the embryonic nucleus and has been termed central pulverulent,⁸ in all probability the phenotype previously described as Doyme's discoid cataract.^{9 10} The Coppock family has not been the subject of a published linkage study, unlike the genealogically unrelated pedigree with cataract described as Coppock-like,^{9 11 12} which has been linked to the crystallin gene cluster region on 2q. It is of note that the Coppock phenotype and the cataract investigated by Renwick and Lawler in the "Ev family from southern England"^{13 14} have become synonymous. However, the latter involves the larger fetal nucleus with opacification increasing in density towards the periphery and is therefore identical to the family with zonular pulverulent cataract described by Poos.^{15 16}

Many other families with pulverulent cataract have now been described.^{7 17-19} It is clear that significant intra- and interfamilial variation, both in the distribution of the cataract and the degree of opacification, distinguish this phenotype from all others.

The concentric deposition of secondary lens fibres that occurs during growth of the normal lens results in the formation of lamellae. Opacities confined to a specific lamella therefore reflect a short period of developmental disturbance (usually during the fetal period) resulting in symmetrical bilateral lens opacification. Lamellar cataracts have also been called zonular, perinuclear, polymorphic,²⁰ or Marnier's cataract.²¹ The degree of opacification is variable and visual acuity may be well preserved or reduced enough to require surgical intervention.²² Commonly, cataract occurs at the anterior and posterior Y sutures. In some cases, cortical opacities or "riders" are associated with lamellar cataract.

Cataract limited to the cortex is rare and differs from lamellar cataract since opacification is restricted to a sector of outer cortical, often superior, lens fibres, adjacent to the lens capsule. The nucleus is unaffected. The pathogenesis is unknown but its distribution and subsequent progression suggest an abnormality of the later stages of lens development.

The presence of families with cataract limited to either the anterior or posterior pole of the lens is less amenable to explanation in terms of lens development. Anterior polar

cataracts (fig 2A) are bilateral, usually symmetrical, well circumscribed lens opacities that are rarely progressive and can be inherited as dominant, recessive, or X linked traits.^{23 24} Larger opacities often have a pyramidal shape, the apex of which may extend into the anterior chamber.^{5 25 26} Associations with microphthalmia²⁷ and astigmatism²⁸ implicate a gene involved in anterior segment development. Visual function is usually well preserved.²⁹ Families with posterior polar cataracts (fig 2B) are reasonably common. Affected subjects have bilateral, symmetrical lens opacities which are usually inherited as a dominant trait. Since opacification is close to the optically crucial, nodal point of the eye, vision is commonly reduced.³⁰ In some families, progressive accumulation of further posterior cortical opacities can lead to total cataract formation.^{10 14 25 31}

The blue dot (cerulean) cataract (fig 2E), first described by Vogt,³² is not truly congenital, but develops in childhood and progresses through early life.³³ The discrete, pinhead shaped, blue-white opacities are distributed throughout the lens becoming more numerous in the cortex where they may form large cuneiform (wedge-like) shapes in the mid-periphery. Within a pedigree, this phenotype is consistent in its distribution but variable in its severity. Acuity is usually well preserved; cataract extraction is rarely necessary before adult life and is usually associated with a good outcome.^{8 34}

A peculiar and rare form of cataract, "coralliform" or "aculiform", originally described by Nettleship,³⁵ is characterised by finger-like protuberances extending from the nucleus that resemble sea coral.^{10 36} The visual impact is variable but cataract extraction is usually required in the early years of life.

"Total" cataract, that is, lens opacity apparently affecting both nuclear and cortical regions, has been reported in families both with autosomal dominant³⁷ as well as X linked recessive congenital cataract.³⁸ It has also been reported as the end result of the progression of the phenotypes outlined above. Other uncommon phenotypes have been described in isolated cases, but not documented in families.

The molecular genetics of inherited cataract

In 1963, Renwick and Lawler¹³ described in their seminal publication the cosegregation of inherited cataract with the Duffy blood group

Table 2 Identified human congenital cataract mutations

Locus	Gene	Protein	Mutation	No of mutations	Phenotype	OMIM No	Reference
1q21-q25	GJA8	Connexin 50	Missense	2	Pulverulent	600897 (11622)	41
2q33-q35	CRYGC	γ C-crystallin	Missense*	1	Coppock-like	604307 (123660)	49, 50
2q33-q35	CRYGC	γ C-crystallin	Missense	1	Aceuliform	604307	50
2q33-q35	CRYGD	γ D-crystallin	Missense	1	Nuclear	123690	51
10q24-25	PITX3	Pitx3	Missense	1	Total	602669	37
13q11-q13	GJA3	Connexin 46	Missense	2	Pulverulent	121015 (601885)	43
17q11.1-q12	CRYBA1	β A3 crystallin	Splice site	1	Sutural	600881	54
21q22.3	CRYAA	α A-crystallin	Missense	1	Zonular central nuclear	123580	56
22q11.2	CRYBB2	β B2-crystallin	Chain termination	1	Cerulean	123620 (601547)	52
22q11.2	CRYBB2	β B2-crystallin	Missense	1	Coppock-like	604307	53

OMIM refers to *Online Mendelian Inheritance in Man* (<http://www3.ncbi.nih.gov/Omim/searchomain.html>)

*Re-examination of the original data suggests that the sequence changes noted originally in the γ E-pseudogene may not be the cause of the cataract.⁵⁰

Table 3 Candidate genes for human congenital cataract

Location	Symbol	Name
1p31-22	CRYZ	Crystallin ζ
1q21-25	CAE1, CX50	Connexin 50
2q33-35	CRYGA	Crystallin γ A
2q33-35	CRYGB	Crystallin γ B
2q33-35	CRYGC	Crystallin γ C
2q33-35	CRYGD	Crystallin γ D
2q33-35	CRYGEP1	Crystallin, γ E pseudogene 1
2q33-35	CRYGFP1	Crystallin, γ F pseudogene 1
2q34-36	CRYGBA2	Crystallin β A2
3q21-25	CP49	Phakinin
3	CRYGS	Crystallin γ S
4q28-31	PITX2/ RIEG1	RIG/PITX homeobox gene
6p25	FREAC-7	Forkhead related activator
6q	CX43	Connexin 43
10q25	PITX3	RIEG/PITX homeobox gene
11p13	PAX-6	PAX homeobox gene
11q21.1-23.2	CRYA2	Crystallin α B
12q13-14	MIP	Major intrinsic protein, aquaporin
13q11-12	CX46, CZP	Connexin 46
16p13.11-12.3	CRYM	Crystallin μ
17q11.1-12	CRYBA1	Crystallin β A1
19q13.4	LIM2	Lens integral membrane protein 2
20	CP115, LIFL-H	Filensin
21q22.3	CRYA1	Crystallin α A
22q11.2-12.1	CRYBB1	Crystallin β B1
22q11.2-12.1	CRYBB2	Crystallin β B2
22q11.2-12.1	CRYBB2P	Crystallin β B2 pseudogene
22q11.2-12.1	CRYBB3	Crystallin β B3
22q11.2-12.1	CRYBA4	Crystallin β A4

locus (*Online Mendelian Inheritance in Man* OMIM reference number 110700). This became the first autosomal disease to be genetically linked in man when, in 1968, the Duffy locus was assigned to chromosome 1.³⁹ Subsequent development of advanced molecular biological techniques has facilitated the identification of 20 further independent cataract loci (table 1) including 10 mutations (table 2). In most cases a candidate gene approach has been used once linkage has been established (table 3). There are, however, several practical considerations when mapping human cataract genes. A significant proportion of cataract mutations appear de novo often making family size small. While penetrance in all phenotypes is high, expressivity, age of onset, and rate of progression are variable, making careful ophthalmic evaluation critical. In addition, surgical modification of the disease can make it difficult to describe the phenotype accurately.

GENES IMPLICATED IN CATARACTOGENESIS

Recently, the Duffy blood group locus has been refined to 1q22-23⁴⁰ and a mutation identified

in the gene coding for connexin50 in a family with autosomal dominant pulverulent cataract.⁴¹ The gene was considered an ideal candidate since it is abundantly expressed in the human lens, its protein product forming an integral part of the extensive gap junction network of lens fibre membranes. Connexins are a diverse family of molecules that associate into heterogeneous oligomeric transmembrane structures with a central voltage gated ion channel, known as connexons. Connexons bridge the extracellular space allowing the passage of small molecules between adjacent cells.⁴² A feature of the mature lens cell is its metabolic inactivity. It is likely therefore that the connexin50 mutation which occurs in the highly conserved second transmembrane domain results in altered function with subsequent disruption of cell homeostasis observed as a loss of clarity. Further evidence is provided by the identification of mutations in another gap junction protein, connexin46 on 13q, in two families with pulverulent cataract.⁴³ Mutations of other connexin genes have also been implicated in other inherited disorders, namely Charcot-Marie-Tooth disease, inherited deafness, and congenital cardiac disease.⁴⁴⁻⁴⁶

α -, β -, and γ -crystallins constitute the main cytoplasmic proteins of the human lens. By forming tight packing stable oligomers that interact with the surrounding cytoskeleton (characterised by the presence of a unique beaded filament structure), lens fibre transparency is maintained.⁴⁷ β - and γ -crystallin genes have also been shown in many species to encode ubiquitous enzymes. α -crystallin has been shown to be a member of the heat shock protein family. This dual use of a distinct protein encoded by a single gene, termed gene sharing, is probably common in the lens and other systems.⁴⁸ These are clearly strong candidate genes and to date three cataract causing mutations have been identified.

The γ -crystallin gene cluster (2q33-q35) consists of genes γ A, B, C, D, E, F, and a gene fragment γ G.⁴⁹ Only γ C and γ D encode abundant proteins while γ E and γ F are pseudogenes by virtue of in frame stop codons (the γ F lacks a promoter as well). The mutation underlying the (pulverulent) Coppock-like cataract was thought to result in the activation of the γ E pseudogene whose product is an N-terminal protein fragment, the deposition of which was likely to cause the cataract.⁴⁹ Re-evaluation of

the original data has recently questioned this view and it is now considered likely that the cataract arises from a missense mutation in a highly conserved segment of exon 2 of the γ C-crystallin gene.⁵⁰

Another missense mutation in the γ D-crystallin gene that results in the substitution of arginine for cysteine at codon 14 has been suggested to result in a progressive nuclear cataract.⁵¹ Protein modelling predicts that the substitution results in subtle changes in the surface properties of the crystallin, consistent with the mild but progressive nature of the phenotype observed.

Crystallin β B2 is the only member of the β -crystallin gene cluster on 22q to be highly transcribed in the lens. Missense mutations in this gene are now known to result in the development of blue dot (cerulean)⁵² and the Coppock-like cataract.⁵³

Mutations in α -crystallin are now known to be cataractogenic. A splice site mutation⁵⁴ is thought to be responsible for the sutural (lamellar) opacities observed in a family mapped to 17q⁵⁵ and a missense mutation in the crystallin α A gene has been identified⁵⁶ in a family with zonular nuclear cataract.

The report of a mutation within the homeobox gene, *PITX3*, is the first to implicate a developmental regulator gene in the pathogenesis of congenital cataract. The G to A transition identified results in the substitution of serine for asparagine at codon 13 which, although not within the crucial homeodomain of the protein, is predicted to affect either DNA binding or inhibit protein-protein complex formation. Interestingly, mutations in *PITX3* have also been shown to result in anterior segment mesodermal dysgenesis (ASMD, OMIM 107250) in which cataract is encountered in combination with other complex anterior segment abnormalities.⁵⁷

GENETICALLY MAPPED CATARACT LOCI

It is of interest that many cataract families have been mapped to loci for which there is no known candidate gene (table 1). Two families with autosomal dominant cataract have shown linkage to the 1p36 locus, the first with a posterior polar phenotype²⁵ and the other a large Danish family with progressive zonular and nuclear opacities (probably pulverulent).⁵⁷ In the latter family, a mutation was sought in τ -crystallin, which is not expressed in the human lens but lies within this locus. Perhaps not surprisingly, no mutation was identified. Another Danish family, first reported by Marner, with primarily lamellar cataract, shows strong linkage to the haptoglobin locus on 16q22.1.

Another three families with dominantly inherited cataracts have been mapped to chromosome 17. The first, with anterior polar cataract, shows linkage to 17p13,²⁶ the second, with lamellar opacities, maps to 17q11-q12,⁵⁵ distinct from the third family with the blue dot (cerulean) phenotype, mapped to 17q24.⁵⁸

Anterior polar cataract has also been reported in association with an apparently balanced chromosomal translocation t(2;14)

(p25;q24).²⁴ Following the recognition of a female with multiple abnormalities, including congenital cataract in association with a terminal deletion of chromosome 14, it has been argued that a cataract locus must therefore reside in the region 14q24.⁵⁹

The recognition of another family with a reciprocal translocation has identified a further cataract locus on 16p.⁶⁰ In this family, a balanced translocation t(2;16)(p22.3;p13.3) was observed in four subjects; three had partial trisomy 2p derived from this translocation and two had a normal karyotype. All patients with translocations had cataracts and those with the normal karyotype had not, suggesting the cataract causing gene lay in the region 16p13.3. Autosomal recessive forms of inherited cataract have been reported in several genealogically distinct populations and seem particularly prevalent in the Japanese. Linkage to the I blood group has been suggested.⁶¹

The existence of X linked non-syndromic congenital cataract remains contentious. A number of pedigrees have been reported, though in many other modes of inheritance appear more likely. It has been suggested, however, that X linked cataract is either synonymous or closely related to the Nance-Horan syndrome, mapped to Xp. Furthermore, the recognition of chromosomal deletions of varying size in this region and the resulting phenotypes observed suggest that a cataract locus may reside within Xp22.3-21.1.³⁸

Significantly, exclusion data on other families with autosomal dominant cataract have been reported, strongly supporting the supposition that further genetic loci remain to be identified.⁵

Mouse models for human cataract

Opacification of the lens is relatively easily detected in mice and this has in part led to the recognition of a number of spontaneously occurring strains with heritable cataract traits. The use of teratogenic agents has also generated a number of mouse cataract models.

Mouse models have made considerable contributions to the field of cataract research. Firstly, they have confirmed the importance of several genes and proteins in the maintenance of lens clarity.⁶² Secondly, the extensive synteny between the mouse and human genomes has facilitated the identification of novel candidate genes for human cataract formation.⁶³ Thirdly, it is now clear that the lens plays an essential role in guiding normal eye development and the identification of certain mutations has enabled this process to be dissected.⁶⁴

Table 4 shows those mouse mutants for which there is a known human corollary. It is of note that the phenotypic appearances between the two species often differ. Possible explanations include difficulties in classification, differences in physiology, and alternative effects of different mutations within the same gene and the effects of different modifier genes.

Several other cataract causing mutations have been identified in mice⁶⁵ and it will be interesting if human homologues are soon identified. The exciting prospect is that mouse

Table 4 Mouse cataract models for which a human homologue is known

Mouse model	Mutated mouse gene (human gene, if different)	Mouse phenotype	Reference	Human phenotype
No2	<i>connexin50</i>	Nuclear	71	Pulverulent
<i>Cat2</i>	γ E-crystallin	Total opacity with microphthalmia	72	Coppock-like
<i>Cat2^{elo}</i>	γ -E crystallin	Eye lens obsolescence (microphakia)	73	
<i>ak</i>	<i>Pitx3</i>	Aphakia	74	Total
	<i>α3-connexin (connexin46)</i>	Nuclear	62	Pulverulent
<i>Po</i>	β A3 crystallin	Nuclear	75	Sutural
<i>lop18</i>	α A-crystallin	Nuclear	76	Zonular central nuclear
<i>Philly (Phil)</i>	β B2-crystallin	Nuclear	77	Cerulean/Coppock-like

cataract models will provide increasingly sophisticated experimental strategies for the study of the human disease.

Genotype-phenotype correlations

The presence of several clearly distinguishable human cataract phenotypes and a number of probable subtypes within each category parallel well the complex underlying genotype shown by human linkage studies. Furthermore, evidence that each phenotype maps to more than one locus suggests mutations in different genes may give rise to similar phenotypes.

In contrast, only γ C- and β B2-crystallin genes have to date been implicated in more than one phenotype. It is possible, however, that allelic heterogeneity will be shown to be more prevalent as different mutations within the same gene may affect the regulatory ability of the protein product or its ability to bind with other lens proteins. An example of this might be α -crystallin which is known to have both structural as well as chaperone-like functions. It remains to be seen whether the Volkmann and posterior polar cataract loci identified on 1p36 are indeed allelic.

Lens development and growth throughout life results from the temporal and sequential expression of a number of genes. There is some correlation between what is known about the distribution of proteins in the lens and the position of opacities seen in cataract. An example is the blue dot (cerulean) cataract resulting from a mutation in β -crystallin known to be found in the cortical region of the lens. Much remains to be elucidated in lens biology but the identification of further underlying genetic mutations in patients with cataract will be beneficial.

Genetic counselling

Genetic counselling in congenital cataract is usually straightforward when the abnormality is confined to the lens and there is a positive family history. Most families show autosomal dominant inheritance and the status of at risk subjects can readily be assigned by careful slit lamp examination after pupillary dilatation. Variability in disease expression is common and asymptomatic subjects should not be assumed to be unaffected. X linked and recessive forms of inherited cataract are rare and may be recognised when there is an appropriate family history.

Genetic counselling in isolated cases is more problematical. Most unilateral cataract is non-genetic but patients with bilateral cataract in whom there is no family history should

undergo further investigation to elucidate the cause.³⁰ Firstly, both parents and any sibs should undergo dilated slit lamp examination to exclude mild congenital opacities; the presence of such opacities will confirm the familial nature of the cataract and allow accurate counselling of recurrence risks. If other family members are normal, the child should be reviewed by a dysmorphologist or paediatrician to rule out any other clinical features that may suggest a multisystem disorder associated with cataract. Routine investigations include plasma urea and electrolytes, urinary amino acids (to exclude Lowe's syndrome in male infants), urinary reducing sugars (to exclude galactosaemia), and a screen for congenital infection, particularly rubella.³⁰ Other investigations may be required depending on other clinical findings. In the absence of a family history and where investigations prove normal, the risk of recurrence in subsequent pregnancies is extremely small.

When counselling adults with congenital cataract about the risk to their offspring, it is again important to review other relatives and where possible examine clinical records to exclude any syndromic forms of cataract or non-genetic aetiology. In adults without a family history, the risk of having an affected child is very small if the cataract is unilateral. The risk is higher in bilateral cases as some may represent new autosomal dominant mutations; the precise risk is difficult to quantify. Many of the adults seeking advice will have had multiple operations in childhood and still have severe visual impairment; they may have reservations about putting their own child through a similar experience. However, improvements in cataract surgery and optical management have resulted in greatly improved visual outcome and multiple operations are rarely necessary.⁶⁶ This improved prognosis should be discussed and it is important that the newborn child is examined by an ophthalmologist in the first few weeks of life to exclude cataract as the long term prognosis in infants that require early surgery is improved if surgery is performed promptly.

Note added in proof

Recently Berry *et al*⁷⁸ have reported that missense mutations in the gene encoding the major intrinsic protein of the lens (MIP) underlie an autosomal dominant form of polymorphic and lamellar cataract in man.

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- 1 Parks M, Johnson D, Reed G. Long term visual results and complications in children with aphakia: a function of cataract type. *Ophthalmology* 1993;100:826-41.
- 2 Evans J, Rooney C, Ashwood F, Dattani N, Wormald R. Blindness and partial sight in England and Wales: April 1990- March 1991. *Health Trends* 1996;28:5-12.
- 3 Lambert S, Drack A. Infantile cataracts. *Surv Ophthalmol* 1996;40:427-58.
- 4 Francois J. Genetics of cataract. *Ophthalmologica* 1982;184:61-71.
- 5 Ionides A, Francis P, Berry V, Mackay D, Bhattacharya S, Shiels A, et al. Clinical and genetic heterogeneity in autosomal dominant congenital cataract. *Br J Ophthalmol* 1999;83:802-8.
- 6 Graw J. Cataract mutations as a tool for developmental geneticists. *Ophthalmic Res* 1996;28(suppl 1):8-18.
- 7 Nettleship F, Ogilvie F. A peculiar form of congenital cataract. *Trans Ophthalm Soc UK* 1906;26:191-206.
- 8 Vogt A. Weitere Ergebnisse der Spaltlampenmikroskopie des vorderen Bulbusabschnittes. III. (Abschnitt-Fortsetzung.) Angeborene und früh aufgetretene Linsenveränderungen. *Graefes Arch Clin Exp Ophthalmol* 1922;108:182-91.
- 9 Smith P. A pedigree of Dooyne's discoid cataract. *Trans Ophthalm Soc UK* 1910;30:37-42.
- 10 Harman N. Ten pedigrees of congenital and infantile cataract; lamellar, coralliform, discoid and posterior polar with microphthalmia. *Trans Ophthalm Soc UK* 1910;30:251-74.
- 11 Harman N. Congenital cataract: a pedigree of five generations. *Trans Ophthalm Soc UK* 1909;29:101-8.
- 12 Duke-Elder S. The lens. In: Duke-Elder S, ed. *A system of ophthalmology*. London: Henry Kimpton, 1964:715-59.
- 13 Renwick J, Lawler S. Probable linkage between a congenital cataract locus and the Duffy blood group locus. *Ann Hum Genet* 1963;27:67-84.
- 14 Nettleship E. Seven new pedigrees of hereditary cataract. *Trans Ophthalm Soc UK* 1909;29:188-211.
- 15 Poos F. Ueber eine familiär aufgetretene besondere Schichtstarform: "Cataracta zonularis pulverulenta". *Klin Monatsbl Augenheilkd* 1926;76:502-7.
- 16 Waardenburg P, Franceschetti A, Klein D. *Genetics and ophthalmology*. Oxford: Blackwell Scientific Publications, 1961.
- 17 Girardet M. Une nouvelle famille de cataracte poussiéreuse centrale (cataracta centralis pulverulenta). *Ophthalmologica* 1943;105:24-36.
- 18 Marner E, Rosenberg T, Eiberg H. Autosomal dominant congenital cataract. Morphology and genetic mapping. *Acta Ophthalmol* 1989;67:151-8.
- 19 Scott M, Hejtmancik J, Wozencraft L, Reuter L, Marshall M, Parks M, et al. Autosomal dominant congenital cataract. Intercocular phenotypic variability. *Ophthalmol* 1994;101:866-71.
- 20 Rogae V, Rogae V, Korovaitseva G, Farrer L, Petrin A, Keryanov S, et al. Linkage of polymorphic congenital cataract to the gamma-crystallin locus on human chromosome 2q33-35. *Hum Mol Genet* 1996;5:699-703.
- 21 Marner E. A family with eight generations of cataract. *Acta Ophthalmol* 1949;27:537-51.
- 22 Cridland A. Three cases of hereditary cortical cataract, with a chart showing the pedigree of a family in which they occurred. *Trans Ophthalm Soc UK* 1918;38:375-6.
- 23 Merin S. *Congenital cataracts*. Boston: Little Brown, 1974.
- 24 Moross T, Vaithilingam S, Styles S, Gardner H. Autosomal dominant anterior polar cataracts associated with a familial 2;14 translocation. *J Med Genet* 1984;21:52-3.
- 25 Ionides A, Berry V, Mackay D, Moore A, Bhattacharya S, Shiels A. A locus for autosomal dominant posterior polar cataract on chromosome 1p. *Hum Mol Genet* 1997;6:47-51.
- 26 Berry V, Ionides A, Moore A, Plant C, Bhattacharya S, Shiels A. A locus for autosomal dominant anterior polar cataract on chromosome 17p. *Hum Mol Genet* 1996;5:415-19.
- 27 Clementi M, Rossetti A, Pesenti P, Tenconi R. Microphthalmia-congenital anterior polar cataract. *Ophthalmic Paediatr Genet* 1985;6:189-92.
- 28 Bouzas A. Anterior polar congenital cataract and corneal astigmatism. *Pediatr Ophthalmol Strab* 1992;29:210-12.
- 29 Helveston E, Ellis F. *Paediatric ophthalmology practice*. St Louis: Mosby; 1980.
- 30 Lambert S. Lens. In: Taylor D, ed. *Paediatric ophthalmology*. Oxford: Blackwell Scientific publications, 1997:461.
- 31 Nettleship E. A pedigree of presenile or juvenile cataract. *Trans Ophthalm Soc UK* 1912;32:337-52.
- 32 Vogt A. Die spezifität außer borener und erworbener starformen für die einzelnen linsezuene. *Albrecht Von Graefes Arch Clin Exp Ophthalmol* 1922;108:219-28.
- 33 Kivlin J, Lovrien E, George C, Cannon L, Maumenee I. Linkage between cerulean cataract and PGP. *Cytogenet Cell Genet* 1985;40:669.
- 34 Bodker F, Lavery M, Mitchell T, Lovrien E, Maumenee I. Microphthalmos in the presumed homozygous offspring of a first cousin marriage and linkage analysis of a locus in a family with autosomal dominant cerulean congenital cataracts. *Am J Med Genet* 1990;37:54-9.
- 35 Nettleship E. On heredity in the forms of cataract. *The Royal Lond Ophthalm Hosp Rep* 1906;17:218-22.
- 36 Gunn RM. Peculiar coralliform cataract with crystals in the lens. *Trans Ophthalm Soc UK* 1895;XV:119.
- 37 Semina E, Ferrell R, Mintz-Hittner H, Bitoun P, Alwar W, Reiter R, et al. A novel homeobox gene PITX3 is mutated in families with autosomal dominant cataracts and ASMD. *Nat Genet* 1998;19:167-70.
- 38 Warburg M. X-linked cataract and X-linked microphthalmos: how many deletion families? *Am J Med Genet* 1989;34:451-3.
- 39 Donahue R, Bias W, Renwick J, McKusick V. Probable assignment of the Duffy blood group locus to chromosome 1 in man. *Proc Natl Acad Sci USA* 1968;61:949-55.
- 40 Mathew S, Chaudhuri A, Murty V, Pogo A. Confirmation of Duffy blood group antigen locus (FY) at 1q22-q23 by fluorescence in situ hybridisation. *Cytogenet Cell Genet* 1994;67:68.
- 41 Shiels A, Mackay D, Ionides A, Berry V, Moore A, Bhattacharya S. A missense mutation in the human connexin 50 gene (GJA8) underlies autosomal dominant "zonular pulverulent" cataract, on chromosome 1q. *Am J Hum Genet* 1998;62:526-32.
- 42 Goodenough D, Goliger J, Paul D. Connexins, connexons and intercellular communication. *Annu Rev Biochem* 1996;65:475-502.
- 43 Mackay D, Ionides A, Kibar Z, Rouleau G, Berry V, Moore A, et al. Connexin46 mutations in autosomal dominant congenital cataract. *Am J Hum Genet* 1999;64:1357-64.
- 44 Janssen E, Kemp S, Hensels G, Sie O, Die-Mulders Cd, Hoogendijk J, et al. Connexin 32 gene mutations in X-linked dominant Charcot-Marie-Tooth disease (CMTX1). *Hum Genet* 1997;99:501-5.
- 45 Kelsell D, Dunlop J, Stevens H, Lench N, Liang J, Parry G, et al. Connexin 26 mutations in hereditary non-syndromic sensorineural deafness. *Nature* 1997;387:80-3.
- 46 Zelante L, Gasparini P, Estivill X, Melchionda S, D'Agruma L, Govea N, et al. Connexin 26 mutations associated with the most common form of non-syndromic neurosensory autosomal recessive deafness (DFNB1). *Hum Mol Genet* 1997;6:1605-9.
- 47 Lubsen N, Aarts H, Schoenmakers J. The evolution of lenticular proteins: the beta and gamma crystallin supergene family. *Prog Biophys Mol Biol* 1988;51:47-76.
- 48 Piatigorsky J. Gene sharing in lens and cornea: facts and implications. *Prog Retin Eye Res* 1998;17:145-74.
- 49 Brackenhoff R, Heskens H, Rossum MV, Lunsen N, Schoenmakers J. Activation of the gamma-E-crystallin pseudogene in the human hereditary Coppock-like cataract. *Hum Mol Genet* 1994;3:279-83.
- 50 Heon E, Priston M, Schorederet D, Billingsley G, Girard P, Lubsen N, et al. The gamma-crystallins and human cataracts: a puzzle made clearer. *Am J Hum Genet* 1999;65:1261-7.
- 51 Stephan D, Gillanders E, Vanderveen D, Freas-Lutz D, Wistow G, Baxevas A, et al. Progressive juvenile-onset punctate cataract characterised by mutation of the gamma-D-crystallin gene. *Proc Natl Acad Sci USA* 1999;96:1008-12.
- 52 Litt M, Carrero-Valenzuela R, LaMorticella D, Schultz D, Mitchell T, Kramer P, et al. Autosomal dominant congenital cataract is associated with a chain termination mutation in the human beta-crystallin gene CRYBB2. *Hum Mol Genet* 1997;6:665-8.
- 53 Gill D, Klose R, Munier F, McFadden M, Priston M, Billingsley G, et al. Genetic heterogeneity of the Coppock-like cataract: a mutation in CRYBB2 on chromosome 22q11.2. *Invest Ophthalmol Vis Sci* 2000;41:159-65.
- 54 Kannabiran C, Rogan P, Olmos L, Basti S, Rao G, Kaiser-Kupfer M, et al. Autosomal dominant zonal cataract with sutural opacities is associated with a splice mutation in the betaA3/A1-crystallin gene. *Mol Vis* 1998;4:21.
- 55 Padma T, Ayyagari R, Murty J, Basti S, Fletcher T, Rao G, et al. Autosomal dominant zonal cataract with sutural opacities localised to chromosome 17q11-12. *Am J Hum Genet* 1995;57:850-5.
- 56 Litt M, Kramer P, LaMorticella D, Murphey W, Lovrien E, Weleber R. Autosomal dominant congenital cataract associated with a missense mutation in the human alpha crystallin gene CRYAA. *Hum Mol Genet* 1998;7:471-4.
- 57 Eiberg E, Marner E, Rosenberg T, Mohr J. Marner's cataract (CAM) assigned to chromosome 16: linkage to haptoglobin. *Clin Genet* 1988;34:272-5.
- 58 Armitage M, Kivlin J, Ferrell R. A progressive early onset cataract gene maps to human chromosome 17q24. *Nat Genet* 1995;9:37-40.
- 59 Miller B, Jaafar M, Capo H. Chromosome 14-terminal deletion and cataracts. *Arch Ophthalmol* 1992;110:1053.
- 60 Yokoyama Y, Narahara K, Tsuji K, Ninomiya S, Seino Y. Autosomal dominant congenital cataract and microphthalmia associated with a familial t(2;16) translocation. *Hum Genet* 1992;90:177-8.
- 61 Yamaguchi H, Okubo Y, Tanaka M. A note on possible close linkage between the li blood locus and a congenital cataract locus. *Proc Jap Acad* 1972;48:625-8.
- 62 Gong X, Li E, Klier G, Huang Q, Wu Y, Lei H, et al. Disruption of alpha3 connexin gene leads to proteolysis and cataractogenesis in mice. *Cell* 1997;91:833-43.
- 63 Shiels A, Bassnett S. Mutations in the founder of the MIP gene family underlie cataract development in the mouse. *Nat Genet* 1996;12:212-15.
- 64 Graw J. Cataract mutations and lens development. *Prog Retin Eye Res* 1999;18:235-67.
- 65 Francis P, Berry V, Moore A, Bhattacharya S. Lens biology, development and human cataractogenesis. *Trends Genet* 1999;15:191-6.
- 66 Taylor D. The Dooyne lecture. Congenital cataract: the history, the nature and the practice. *Eye* 1998;12:9-36.
- 67 Eiberg H, Lund A, Warburg M, Rosenberg T. Assignment of congenital cataract Volkmann-type (CCV) to chromosome 1p36. *Hum Genet* 1995;96:33-8.

- 68 Ogata H, Okubo Y, Akabara T. Phenotype i associated with congenital cataract in Japanese. *Transfusion* 1979;19:166-8.
- 69 Krill A, Woodbury G, Bowman J. X-chromosomal-linked sutural cataracts. *Am J Ophthalmol* 1969;68:867-2.
- 70 Shambolian D, Lewis R, Buctow K, Bond A, Nussbaum R. Nance-Horan syndrome: localisation within the region Xp22.1-22.3 by linkage analysis. *Am J Hum Genet* 1990;47:13-19.
- 71 Steele E, Lyon M, Favor J, Guillot P, Boyd Y, Church R. A mutation in the connexin 50 (Cx50) gene is a candidate for the No2 mouse cataract. *Curr Eye Res* 1998;17:883-9.
- 72 Klopp N, Favor J, Loster J, Lutz R, Neuhauser-Klaus A, Prescott A, et al. Three murine cataract mutants (CAT2) are defective in different gamma-crystallin genes. *Genomics* 1998;52:152-8.
- 73 Cartier M, Breitman M, Tsui L. A frameshift mutation in the gammaE-crystallin gene of the ELO mouse. *Nat Genet* 1992;2:42-5.
- 74 Semina E, Reiter R, Murray J. Isolation of a new homeobox gene belonging to the Pitx/Rieg family: expression during lens development and mapping to the aphakia region on mouse chromosome 19. *Hum Mol Genet* 1997;6:2109-16.
- 75 Graw J, Jung M, Loster J, Klopp N, Soewarto D, Fella C, et al. Mutation in the betaA3/A1-crystallin encoding gene cryba1 causes a dominant cataract in the mouse. *Genomics* 1999;62:67-73.
- 76 Chang B, Hawes N, Roderick T, Smith R, Heckenlively J, Horwitz J, et al. Identification of a missense mutation in the alphaA-crystallin gene of the lop18 mouse. *Mol Vis* 1999;5:21.
- 77 Chambers C, Russell P. Deletion mutation in an eye lens beta-crystallin. *J Biol Chem* 1991;266:6742-6.
- 78 Berry V, Francis P, Kaushal S, Moore A, Bhattacharya S. Missense mutations in MIP underlie autosomal dominant 'polymorphic' and lamellar cataracts linked to 12q. *Nat Genet* 2000;25:15-17.