Review article

Recent advances in the gene map of inherited eye disorders: primary hereditary diseases of the retina, choroid, and vitreous

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The diagnosis and basic understanding of many genetic ocular disorders have been aided by the identification of the disease causing chromosomal loci. These chromosomal loci have been mapped using the candidate gene or the positional cloning approaches. This review will focus on genetic disorders that primarily affect ocular function with emphasis on the most recent advances in the chromosomal mapping of these disorders. In particular, we will concentrate on the genetic diseases affecting the posterior segment of the eye including the retina, choroid, and vitreous. The success of linkage analysis has relied heavily on previous clinical classifications and there are numerous reports of distinct ocular diseases mapping to specific chromosomal loci. However, there are also many examples in which a well defined disease maps to any of a number of chromosomal loci. This genetic phenomenon is known as non-allelic or locus heterogeneity and can be viewed as reflecting the eye's limited repertoire of responses to a variety of genetic lesions. Another emerging pattern is that of "gene sharing" in which different mutations within the same gene can cause clinically distinct ocular diseases. Mapping of mendelian genetic disorders has helped refine the clinical classifications and has led to examples of both "lumping" and "splitting".

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Ocular tumours

RETINOBLASTOMA

Retinoblastoma, an embryonic neoplasm of the retina, is the most common primary intraocular malignancy in infants and children. The average annual incidence of retinoblastoma in the US population younger than 10 years old is 10·9 per million.[1] The gene maps to chromosome 13q14, consists of 27 exons spanning 180 to 388 bp of genomic DNA, produces a 4·7 kb transcript, and encodes a nuclear phosphoprotein consisting of 928 amino acids. The complete gene sequence is available.[2] The retinoblastoma (Rb) gene is a model for a class of recessive cancer genes where wild type alleles have a tumour suppressor function. Retinoblastoma predisposition segregates as an autosomal dominant trait with 90% penetrance, but the mutations are actually recessive at the cellular level since tumours arise only if both copies of the retinoblastoma gene are inactivated in a sensitive cell. These tumour inducing null mutations can arise by intragenic deletion, insertion, or translocation, by single nucleotide changes that affect coding or splicing sequences, or by epigenetic abnormalities such as hypermethylation of the promoter region.[3-13] Some retinoblastoma families show evidence of reduced or incomplete penetrance. The molecular basis of reduced penetrance has been investigated in eight different families.[14-17] Two families with reduced penetrance have mutations in the promoter region of the retinoblastoma gene that decrease but do not eliminate the Rb gene product and three families have a mutation that produces a mutant protein with presumed diminished tumour suppressor activity. One of the families studied actually has "pseudo-low penetrance" owing to independently derived Rb mutations in distant relatives.[17] In another two families, no common intragenic haplotypes were identified in relatives with retinoblastoma and no mutations were identified in the Rb genes.[16] These two families could be other examples of "pseudo-low penetrance" with relatives having independently derived Rb mutations.

Colour blindness

PROTAN AND DEUTAN SERIES

The red and green visual pigment genes have been cloned, sequenced, and mapped.[18-20] Mutations in these genes are the molecular basis for X linked colour vision abnormalities.[21-23] Genes for the red and green opsins lie on the long arm of the X chromosome within Xq28. These genes are arranged in a tandem array with one copy of the red pigment gene at the 5′ end and from one to five green pigment genes located downstream in a head to tail configuration presumably arising from unequal homologous recombination events. Only a single green pigment gene is expressed from this locus, probably the most proximal copy.[24] More than 95% of cases of red-green colour blindness arise from mutant genotypes owing to unequal intra- and intergenic re-

combination events giving rise to deletions or hybrid genes within the tandem array of pigment genes.[21 25-28] These mutations are the genetic basis for protanopia (absence of red colour vision), protanomaly (anomalous red colour vision), deuteranopia (absence of green colour vision), and deuteranomaly (anomalous green colour vision). A missense mutation within the human green visual pigment gene is another cause of deuteranomaly.[29] There is a direct correlation between anomalous red/green vision as detected by psychophysical experiments and the shifts in the in vitro absorption maxima of hybrid pigments produced from cloned cDNAs when compared to normal cone pigments.[30-32] In normal trichromats who display person to person variability in red colour matching, two common alleles of the red pigment gene have been identified and the respective shifts in their absorption maxima can account for the differences in psychophysical testing.[32-34] In general, persons with abnormalities in red-green discrimination have no other signs of retinal disease.

The complete loss of red and green cone function results in blue cone monochromacy, also known as incomplete achromotopsia. Males with this X linked trait use blue cones exclusively under photopic conditions and generally have an acuity of only around 20/200. These persons are capable of limited hue discrimination but only at intermediate light levels.[35 36] Blue cone monochromats have rearrangements within the red and green visual pigment gene cluster that result in the functional loss of both classes of opsin genes.[37 38] These mutations fall into two classes. In one class, the loss of functional genes is mediated by unequal homologous recombination and point mutations. A second class involves the deletion of a locus control region upstream of the red and green pigment gene cluster. The affected upstream region can normally function as an activator of cone specific gene expression in transgenic mice.[39]

TRITANOPIA

Tritanopia, the absence of blue colour vision, differs from the other colour vision disorders because it is inherited as an autosomal dominant trait with variable penetrance. The gene encoding the cone blue sensitive pigment has been cloned, sequenced, and mapped to chromosome 7 at position 7q31.3-q32.[18 21 40] Point mutations within the blue pigment gene have been associated with tritanopia.[41 42]

ROD MONOCHROMACY

The absence of functional cones is known as total achromatopsia or rod monochromacy. This condition is inherited as an autosomal recessive trait. Rod monochromatism is characterised by nystagmus in infancy that diminishes with age. There is severe photophobia and poor vision in ordinary lighting. Vision is improved with dim light to 20/200 but there is a total absence of colour discrimination. The fundus examination is normal but histopathological studies of eyes from patients show abnormal or absent cones.[43] There is evidence that the genetic locus for rod monochromacy is on chromosome 14.[44] In this report, a 20 year old white woman with rod monochromacy was found to have a 14;14 Robertsonian translocation and shown to be isodisomic for the maternal chromosome 14. The responsible locus on chromosome 14 has not been identified.

Congenital stationary night blindness

Congenital stationary night blindness (CSNB) is a group of genetically heterogeneous retinal disorders characterised by non-progressive night blindness. The disease can be inherited as an autosomal dominant, autosomal recessive, or X linked trait, and there can be phenotypic heterogeneity even between families with the same inheritance pattern. Electroretinographic evidence indicates an intact cone system but the rod system can be variably affected. The complete type has no detectable rod function, while the incomplete type has reduced rod function. Reduced visual acuity and nystagmus are variable clinical features of this disease. Myopia is often associated with X linked and recessive forms. A dominant form of CSNB can be caused by certain missense mutations in the rhodopsin gene.[45-47] These mutations are distinct from those responsible for retinitis pigmentosa, a progressive degeneration of both rods and cones. Dryja *et al*[46] could not find a rhodopsin mutation in a subject with the Nougaret type of CSNB, perhaps the most thoroughly studied form of autosomal dominant CSNB. A type of CSNB usually associated with myopia, nystagmus, and decreased visual acuity has been designated CSNB1 and mapped to the short arm of the X chromosome at position Xp11.3.[48-51] The frequent occurrence of myopia in this disorder is believed to be a pleiotropic effect of the unidentified CSNB gene rather than the result of a closely linked second gene.[51] The gene for CSNB1 might be allelic with unidentified genes responsible for retinitis pigmentosa and ocular albinism which have been assigned to the same region by linkage studies.[52-56]

Ocular albinism

Nettleship-Falls type ocular albinism or ocular albinism type 1 (OA1) is inherited as an X linked recessive disorder. The fundamental abnormality is believed to be defective melanogenesis within all pigment-containing cells, but the pigmentation appears grossly abnormal only in the eye. Affected males present with decreased visual acuity, nystagmus, and head nodding. Examination shows hypopigmentation of the fundus, foveal hypoplasia, prominent choroidal vessels, iris translucency, posterior embryotoxon, and optic disc hypoplasia.[57] Visual evoked potentials show evidence of abnormal crossing of the optic nerves at the chiasm. Carrier females may show iris translucency, pigment mottling at the fundus periphery, and abnormal macromelanosomes

on histological inspection of skin biopsies. Multipoint linkage analysis and comparative deletion mapping have refined the location of the OA1 gene within Xp22.3.[58-61] This same region has been linked to a form of X linked recessive ocular albinism with late onset progressive sensorineural hearing loss.[62] Both forms of ocular albinism may be clinical manifestations of different genes or the result of allelic heterogeneity within the same gene. While the gene for OA1 has not yet been identified, it has been localised within a 200 kb region that is contained within a 2·6 Mb yeast artificial chromosome contig.[63]

Forsius-Eriksson type ocular albinism or ocular albinism type 2 (OA2) was originally described in a family from the Åland Islands in the Sea of Bothnia. This form of ocular albinism is referred to as Åland Island eye disease (AIED). OA2 or AIED is inherited as an X linked recessive disorder. This form of ocular albinism has the clinical characteristics described for OA1. In addition, affected males with OA2 often have progressive axial myopia, astigmatism, defective dark adaptation, and protanomalous colour blindness. In contrast to OA1, the pigment containing cells in OA2 appear normal and there is no evidence of optic nerve fibre misrouting at the chiasm. Based on electrophysiological techniques, OA2 has been considered by some to be a form of congenital stationary night blindness with myopia (CSNB1).[56 64] The gene for OA2 was mapped by multilocus linkage analysis to the proximal region of Xp (Xp11.3),[54-56] the same region implicated in typical X linked congenital stationary night blindness with myopia and a form of retinitis pigmentosa. The possibility exists that OA2, congenital stationary night blindness, and retinitis pigmentosa are allelic. There is a discrepancy between mapping of OA2 to Xp11.3 and the finding that a patient with the clinical characteristics of OA2 and Duchenne muscular dystrophy carries a deletion of Xp21.3-21.2.[65 66] This finding would support the presence of an additional locus on the X chromosome for ocular albinism that closely resembles OA2.

A third form of ocular albinism (OA3) is inherited as an autosomal recessive disorder. This may be the genetic type found in most isolated cases of females with ocular albinism. OA3 is phenotypically similar to OA2 except that males and females are equally affected. Deletion analysis of one patient with OA3 has permitted a tentative chromosomal assignment to the q13-q15 region of chromosome 6.[67]

Retinitis pigmentosa

Retinitis pigmentosa (RP) is a set of genetic diseases that feature progressive photoreceptor degeneration. Tunnel vision caused by the early loss of peripheral photoreceptors is one hallmark of this disease. As the disease progresses, central vision is lost as well. On examination, middle aged patients with RP classically have fundus changes that include peripheral intraretinal pigmentation known as bone spicules, retinal vessel attenuation, and optic nerve head pallor. Diagnosis often depends upon full field electroretinographic testing, dark adaptation threshold testing, and evaluation of visual fields. The disease is genetically heterogeneous and can be inherited as an autosomal dominant, autosomal recessive, or X linked trait. Affected subjects without a family history of RP are designated as isolate or simplex cases. Most isolate cases are probably recessive cases although some may be X linked cases or new dominant mutations. Populations differ in the prevalence of each genetic type, but the recessive and isolate types usually account for the majority of cases.[68] Autosomal recessive RP in association with hearing loss is known as Usher syndrome and will be discussed separately. At least 11 chromosomal regions have been implicated as containing genes causing RP, and four of the genes have been identified. The numerical designation for each locus (for example, RP-1, RP-2, etc) used by McKusick in *Mendelian inheritance in man* (11th edition, 1994) and its online version (OMIM) has only categorical significance and does not correlate with disease severity, chronological order of gene identification, or population prevalence.[69]

The first RP locus mapped was for an X linked form of the disease.[70] Subsequent linkage and heterogeneity analyses support the existence of at least two loci on the X chromosome that are associated with RP.[71] These unidentified loci have been designated RP-2 and RP-3. RP-2 was localised within Xp11.3-p11.22 by polymorphic microsatellite analysis,[52] with the most likely position at Xp11.23.[53] The RP-3 locus was localised to Xp21.1 by multipoint linkage analysis.[72 73] Linkage data from a single family was suggestive of a third locus at position Xp21.3-p21.2 and designated RP-6.[71] However, deletion mapping data do not support the location of this third locus.[74] Kaplan *et al*[75] propose that RP-2 and RP-3 can be distinguished clinically. Patients with RP-2 are reported to have early onset night blindness and severe myopia whereas RP-3 patients have later onset night blindness and little if any myopia.[76] Other groups believe that the wide clinical variation in X linked RP makes genetic locus identification on the basis of clinical features problematical.[53]

Using the candidate gene approach, Dryja *et al*[77 78] identified mutations in the rhodopsin gene as a cause of autosomal dominant RP. Since these first reports of rhodopsin mutations, at least 60 different rhodopsin mutations have been identified and rhodopsin mutations are now known to account for about 25% of autosomal dominant cases.[79-105] The rhodopsin locus maps to chromosome 3q21-q24 and is designated as RP-4.

Mutations within the peripherin/RDS gene were also reported as a cause of autosomal dominant RP.[82 106-111] The peripherin/RDS gene was selected for screening because mutations in the homologous mouse gene called *rds* causes a slow form of retinal degeneration in mice. To date, mutations in the peripherin/RDS gene are estimated to account for approximately 3 to 5% of the autosomal dominant cases.

Interestingly, different mutations within the peripherin/RDS gene can cause a variety of clinically distinct disorders including retinitis punctata albescens,[112] vitelliform macular dystrophy,[108] macular dystrophy,[108] and pattern pigment dystrophy of the fovea.[113 114] There is phenotypic variation even within a family segregating a peripherin/RDS mutation, with affected relatives in one pedigree having either retinitis pigmentosa, pattern dystrophy, or fundus flavimaculatus.[109] The peripherin/RDS gene maps to chromosome 6p21.1-cen[115 116] and is designated RP-7.

A third locus for autosomal dominant RP has been mapped to the pericentric region of chromosome 8 between 8p11 and 8q21.[117] This locus is designated RP-1 and the gene is not yet identified. Linkage analyses have implicated unidentified loci on 7p (RP-9) and 7q (RP-10), each assignment based on one autosomal dominant pedigree to date.[118 118A 119] A sixth dominant locus (RP-8) has been mapped to chromosome 19q13.4.[120] Linkage exclusion of all the previously identified loci in one family with autosomal dominant RP and hearing loss suggests the existence of at least one additional gene for autosomal dominant RP.[120 121]

There are at least three loci where mutations can cause autosomal recessive RP. The candidate gene approach was used to identify these mutations. Recessive RP can be caused by a null mutation in the rhodopsin gene and by mutations in the β subunit of the rod cGMP phosphodiesterase.[122–125] Additional recessive mutations have been identified in the gene for the rod cGMP activated channel protein.[126]

Retinitis pigmentosa and hearing loss

USHER SYNDROMES

The autosomal recessive forms of retinitis pigmentosa associated with hearing loss are known as the Usher syndrome. The Usher syndrome is phenotypically and genetically heterogeneous. It accounts for about 15% to 20% of patients with retinitis pigmentosa and 50% of patients with combined deafness and blindness. Patients with Usher syndrome type I have retinitis pigmentosa, profound congenital sensorineural deafness, and vestibular ataxia. The retinitis pigmentosa usually becomes symptomatic within the first two decades of life. Usher syndrome type II is characterised by retinitis pigmentosa, partial acquired hearing impairment, and no ataxia. The retinitis pigmentosa usually becomes symptomatic in early adulthood. Not only is there non-allelic heterogeneity between Usher syndrome types I and II, but there is non-allelic heterogeneity within each type of Usher syndrome. At least five different chromosomal loci have been inferred from linkage studies. One locus for Usher syndrome type I is chromosome 14q32.1-q32.3 based on a study of 10 French families.[127] This genetic form of Usher syndrome is designated USH1A. Two additional loci have been mapped to chromosome 11.[128–130] One locus is at position 11q13.5 (USH1B) and was found among British pedigrees. The other locus was found in French-Acadian families and localises to the interval 11p15.2-p14 (USH1C). Some but not all Usher syndrome type II families are linked to markers on chromosome 1 between 1q42-qter (USH2A).[131–134] A candidate gene for Usher syndrome type II was a choroideremia-like (CHML) gene that maps to chromosome 1q42-qter.[133] Single strand conformation polymorphism analysis and direct sequencing of the CHML gene in patients with USH2A did not identify any disease specific mutations. The gene responsible for any form of Usher syndrome has not as yet been identified.

Recently, the locus for another form of syndromic autosomal recessive RP, the Bardet-Biedl syndrome, was linked to the long arm of chromosome 16 between regions q13 and q22.[135 136] In addition to retinitis pigmentosa, this disorder is characterised by mental retardation, obesity, polydactyly, syndactyly, and hypogonadism. The chromosome 16q locus was excluded from two additional unrelated families with Bardet-Biedl syndrome. This syndrome provides yet another example of non-allelic heterogeneity in families with clinically indistinguishable diseases.

Retinal dystrophies

CONE DEGENERATIONS

Cone degenerations can be inherited as autosomal dominant, autosomal recessive, or X linked disorders. The disorders are phenotypically heterogeneous but usually present with decreased central visual acuity, fine nystagmus, defective colour vision, and photophobia. Unlike the retinitis pigmentosa syndromes, cone degenerations usually present with intact peripheral vision and night vision. Night blindness and peripheral field loss can develop, especially in the cone-rod dystrophies. On examination, these patients may have normal appearing fundi or they may have central retinal pigment epithelial changes and an associated macular lesion with the appearance of a bull's eye. The diagnosis usually depends on full field electroretinographic testing, colour testing, and dark adaptation threshold testing to evaluate cone function. Using the candidate gene approach, Reichel *et al*[137] identified the first genetic mutation responsible for a cone degeneration. In this X linked pedigree, affected males and carrier females were found to have a 6·5 kb deletion within the red pigment gene at position Xq28. Another locus for X linked cone dysfunction was reportedly mapped by linkage analysis to the region Xp21-p11.1.[138 138A] A possible locus for an autosomal dominant form of cone dystrophy was proposed to be on chromosome 6 in the region q25-q26 based on the identification of a translocation.[139] Another photoreceptor dystrophy involving both cones and rods called cone-rod dystrophy (CRD) has been localised to chromosome 18q21.1-q21.3 by deletion mapping of mentally retarded children with this disorder.[140] More recently, Evans *et al*[141] mapped a locus for autosomal dominant CRD to chromosome 19q13.1-q13.2 in another family. A third locus on chromosome 17q has been proposed be-

Genetic mapping of primary ocular diseases involving the retina, choroid, and vitreous

Category	*Disorder*	*MIM*	*Mode*	*Location*	*Gene/protein*
Tumours	Retinoblastoma	180200	AD	13q14	RB1: retinoblastoma gene (p105(Rb))
Colour blindness	Protanopia	303900	XL-R	Xq28	Red cone opsin
	Deuteranopia	303800	XL-R	Xq28	Green cone opsin
	Tritanopia	190900	AD	7q31.3-32	Blue cone opsin
	Blue cone monochromatism	303700	XL-R	Xq28	Red and green cone opsins
	Rod monochromacy, achromatopsia	216900	AR	14	nk
Night blindness, congenital stationary (CSNB)	CSNB, Rhodopsin type	180380.0031	AD	3q21-q24	Rhodopsin (rod opsin)
	CSNB PDEB type	180072.0005	AD	4p16.3	Rod cGMP phosphodiesterase, β subunit
	CSNB with myopia	310500	XL-R	Xp11.3	nk
Ocular albinism (OA)	OA, type 1	300500	XL-R	Xp22.3	nk
	OA, type 2	300600	XL-R	Xp21.3-p21.2 or Xp11.3-p11.23	nk
	OA, type 3	203310	AR	6q13-q15	nk
Retinitis pigmentosa (RP)	RP-1	180100	AD	8p11-q21	nk
	RP-2	312600	XL-R	Xp11.23	nk
	RP-3	312610	XL-R	Xp21.1	nk
	RP-4	180380	AD/AR	3q21-q24	Rhodopsin (rod opsin)
	RP-6	312612	XL-R	Xp21.3-p21.2	nk
	RP-7-Human homologue of mouse *rds*	179605	AD	6p21.1-cen	Peripherin/retinal degeneration slow (RDS)
	RP-8	180103	AD	19q13.4	nk
	RP-9	180104	AD	7p15.1-p13	nk
	RP-10	180104	AD	7q	nk
	RP-Human homologue of mouse *rd*	180072	AR	4p16.3	Rod cGMP phosphodiesterase, β-subunit
	RP-cGMP channel protein-1 (CNGC)	123825	AR	4p14-q13	Rod cGMP-channel protein
	RP-digenic	18072	Digenic	11p13/ 6p21.1–cen	RDMI, Peripherin/RDS
RP and congenital hearing loss	Usher syndrome, type 1A	276900	AR	14q32	nk
	Usher syndrome, type 1B	276903	AR	11q13.5	nk
	Usher syndrome, type 1C	276904	AR	11p15.2-p14	nk
	Usher syndrome, type 2A*	276901	AR	1q42-ter	nk
Retinal dystrophies	Cone dystrophy*, X linked	304020	XL-R	Xq28 Xp21-p11.1	Red cone opsin nk
	Cone dystrophy*, dominant	180020	AD	6q25-q26	nk
	Cone-rod dystrophy*	120970	AD	18q21-q22.2 19q13.1-q13.2 17q	nk nk nk
	North Carolina macular dystrophy	136550	AD	6q14-q16.2	nk
	Macular dystrophy, vitelliform, Best disease*	153700 179605	AD AD	11q13 6p21.1-cen	nk Peripherin/RDS
	Macular dystrophy, atypical vitelliform type	153840	AD	8q24	nk
	Macular dystrophy*	179605	AD	6p21.1-cen	Peripherin/RDS
	Patterned dystrophy of the RPE* Butterfly shaped macular dystrophy*	179605.0009	AD	6p21.1-cen	Peripherin/RDS
	Retinitis punctata albescens*	179605.0005	AD	6p21.1-cen	Peripherin/RDS
	Fundus flavimaculatus*	179605	AD	6p21.1-cen	Peripherin/RDS
	Macular degeneration, juvenile*, Stargardt disease (fundus flavimaculatus)	248200	AR AD	1p21-p13 13q34 6q13-q16.2	nk nk nk
	Sorsby's fundus dystrophy	136900	AD	22q13.1-qter	nk
	Cystoid macular dystrophy	153880	AD	7p21-p15	nk
Chorioretinopathies	Choroideremia	303100	XL-R	Xq21.1-q21.2	RAB geranylgeranyl transferase, component A
	Gyrate atrophy of the choroid and retina	258870	AR	10q26	Ornithine aminotransferase
Vitreoretinopathies	Familial exudative vitreoretinopathy (FEVR)	133780	AD	11q13.5-q22	nk
	Neovascular inflammatory vitreoretinopathy	193235	AD	11q13	nk
	FEVR, X linked	310600	XL-R	Xp11.4	Norrie disease protein
	Norrie disease	310600	XL-R	Xp11.4	Norrie disease protein
	Retinal dysplasia, primary	312550	XL-R	Xp11	nk
	Retinoschisis, juvenile	312700	XL-R	Xp22.2-p22.1	nk
	Stickler/Wagner syndromes*	120140	AD	12q13.11-q13	Collagen, type II, alpha-1-polypeptide

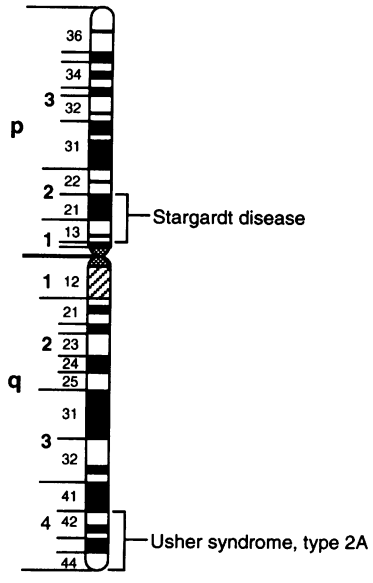
nk: not known, AD: autosomal dominant, AR: autosomal recessive, XL-R: X linked recessive, *non-allelic heterogeneity, MIM: *Mendelian inheritance in man* (11th edition, 1994)

cause one case of CRD also had neurofibromatosis type I.[142]

MACULAR DYSTROPHIES

North Carolina macular dystrophy is an autosomal dominant macular dystrophy with onset during infancy. The disease is usually non-progressive. The phenotype is completely penetrant but the expressivity is highly variable. Generally, the macular lesions are bilateral and symmetrical. The unidentified locus responsible for this disorder designated MCDR1 has been mapped to chromosome 6q16.[143–145]

A distinct macular dystrophy, Best disease or vitelliform macular dystrophy, is characterised by the early onset of a confluent yellow mass resembling an egg yolk within the macula. Over time, the vitelliform lesion becomes increasingly non-confluent and variably pigmented with accompanying atrophy of the retinal pigment epithelium. Funduscopic changes precede visual impairment. Central visual loss is progressive. Electro-oculography can be used to identify affected persons even before the onset of fundus abnormalities. The unidentified gene responsible for this disorder has been mapped to chromosome 11q13 by linkage analysis.[146] A form of retinal dystrophy known as atypical vitelliform macular dystrophy involves the peripheral and peripapillary retina more extensively than Best disease and the yellow lesions tend to be smaller. This disease was mapped by linkage analysis to chromosome 8q24.[147] A retinal dystrophy with macular vitelliform lesions similar to Best disease has been associated with mutations in the peripherin/RDS gene.[108 113] Other autosomal dominant retinal dystrophies associated with mutations in the peripherin/RDS



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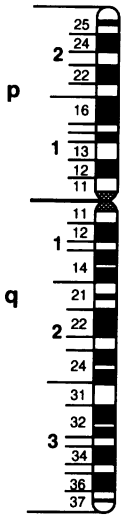

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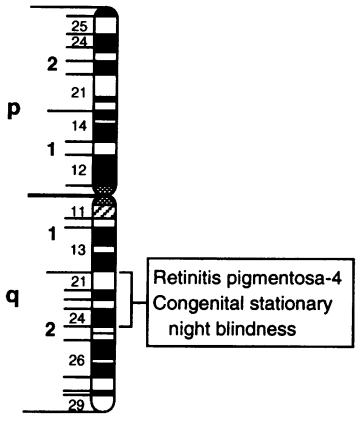

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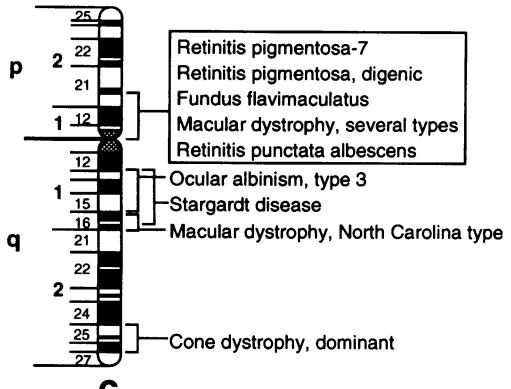

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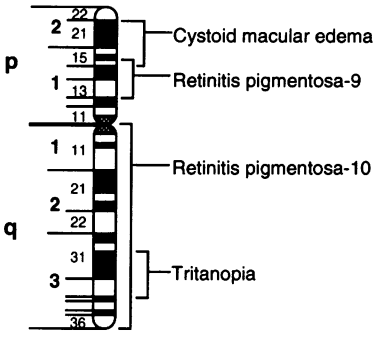

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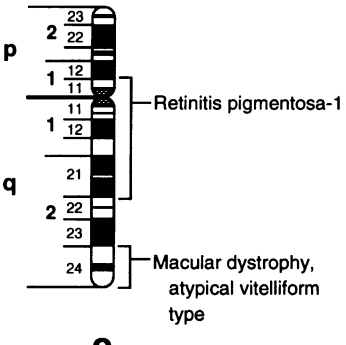

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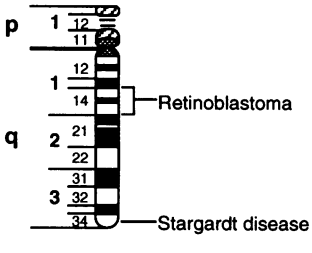

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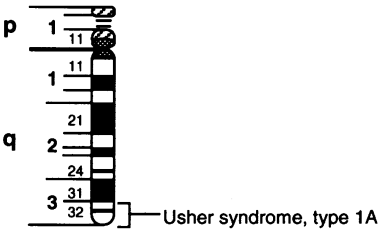
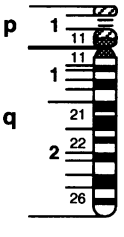


14 Rod monochromacy



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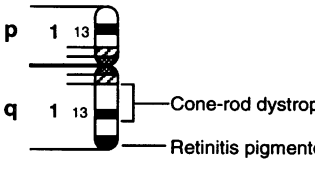

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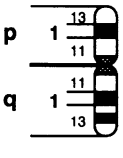

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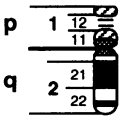

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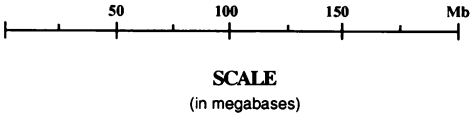
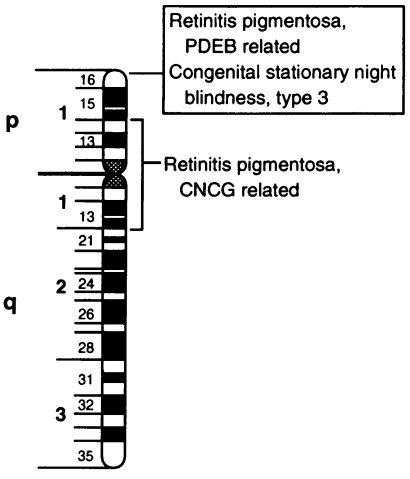
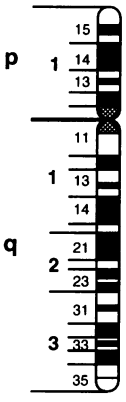
FIGURE 1

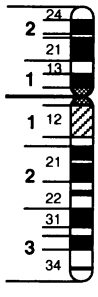
THE HUMAN GENE MAP

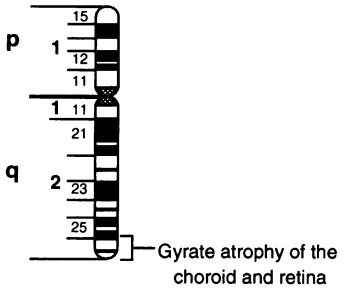
Primary ocular diseases involving the retina, choroid, and vitreous

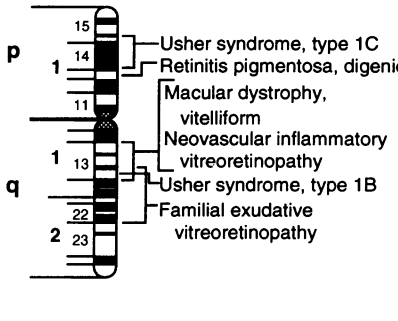


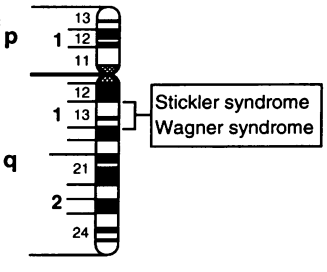


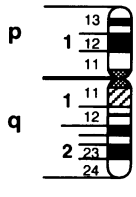


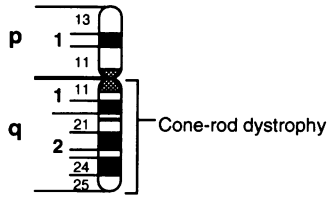


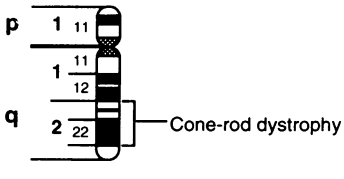


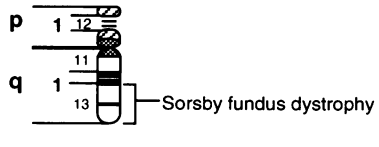


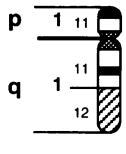


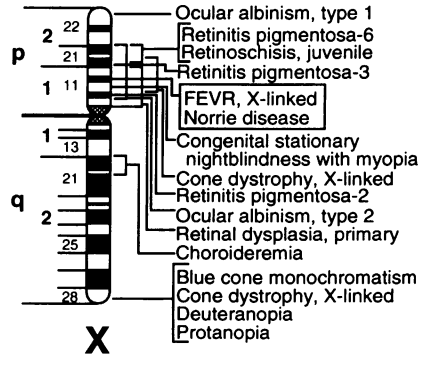












gene include butterfly shaped pattern dystrophy,[109 113 114 148] macular dystrophy,[108] retinitis punctata albescens,[112] and fundus flavimaculatus.[109] An autosomal recessive form of fundus flavimaculatus with juvenile onset and severe progressive visual loss known as Stargardt disease has recently been mapped to the short arm of chromosome 1.[149 150] Autosomal dominant forms of this disease have been mapped to chromosome 13q34[151] and to the long arm of chromosome 6 between loci D6S313 (6q13-q16.2) and D6S252 (6q14-q16.2).[152] Linkage to the North Carolina macular dystrophy gene on chromosome 6 was excluded in this family with autosomal dominant Stargardt-like disease.

Chorioretinopathies

CHOROIDEREMIA

Choroideremia (CHM), an X linked recessive disorder, causes constriction of peripheral vision and reduction of night vision. There is progressive loss of central vision leading to blindness usually in the fourth to fifth decade of life owing to progressive degeneration of the retina, the retinal pigment epithelium, and the choroid. While heterozygous women are usually asymptomatic, they may have irregularly pigmented fundi and peripapillary chorioretinal atrophy. Rarely, they may also lose vision. The disease locus was mapped to band Xq21 by both linkage analysis of pedigrees and cytogenetic analysis of patients with detectable chromosomal translocations and deletions.[153 154] Mutations in a gene encoded within this region, the CHM gene, have been identified in families with choroideremia.[153-158] The predicted sequence of the putative CHM gene product was found to be homologous to a bovine protein that inhibits the exchange of GTP for bound GDP on Rab 3A, known as Rab3A-GDP dissociation inhibitor (Rab3A-GDI).[159-161] Subsequently, the CHM gene was found to be homologous to component A of rat Rab geranylgeranyl transferase.[162] Further support for the function of the CHM gene product was obtained by showing functional deficiency of Rab geranylgeranyl transferase component A from lymphoblast extracts prepared from choroideremia patients.[163] Supplementation of these extracts with wild type component A restored normal levels of geranylgeranyl transferase activity supporting the conclusion that the choroideremia gene encodes at least one form of component A.

GYRATE ATROPHY

Gyrate atrophy is an autosomal recessive retinal degeneration that is usually diagnosed in late childhood. The characteristic fundus lesions are sharply demarcated circular areas of chorioretinal atrophy in the periphery of the retina. Early peripapillary atrophy and myopia may also be evident. Other clinical findings include constricted visual fields, raised dark adaptation thresholds, and small or non-detectable electroretinographic responses. During the second and third decades of life, the scalloped edges of chorioretinal degeneration progress towards the posterior pole. One hallmark of this disease is hyperornithaemia which can be partially alleviated in some patients by the administration of pyridoxine (vitamin B6). A deficiency of the mitochondrial enzyme ornithine aminotransferase (OAT) in patients with gyrate atrophy was first identified by Valle *et al.*[164] This is one of the few genetic eye disorders where the discovery of a biochemical defect preceded the molecular genetic identification of mutations.[165 166] Using cDNA probes encoding OAT, Ramesh *et al*[167] and Barrett *et al*[168] mapped the gene to chromosome 10q26 and family linkage data supported this locus as the cause of gyrate atrophy.[169 170] The OAT structural gene was shown to span 21 kilobases and encode a 2·2 kilobase mRNA consisting of 11 exons.[171] Numerous mutations within the gyrate atrophy gene have been reported and extensive allelic heterogeneity exists in both the vitamin B6 responsive and non-responsive phenotypes.[166 172-187] Unlike many hereditary ocular diseases where the defective genes are expressed primarily in the affected tissues, OAT is expressed throughout the body. The reason systemic defects in OAT lead specifically to degeneration of the choroid and retina is unknown.

Vitreoretinopathies

FAMILIAL EXUDATIVE VITREORETINOPATHY, NEOVASCULAR INFLAMMATORY VITREORETINOPATHY, NORRIE DISEASE, AND PRIMARY RETINAL DYSPLASIA

Familial exudative vitreoretinopathy (FEVR) can be inherited as an autosomal dominant or X linked recessive disease. The disease shows nearly 100% penetrance but variable expressivity with onset any time from infancy to late adulthood. FEVR closely resembles retinopathy of prematurity but there is no history of premature birth or oxygen therapy. The disease is characterised by incomplete vascularisation of the peripheral retina with atypical vessels lying adjacent to a more anterior avascular zone. Retinal exudation, neovascularisation, and fibrovascular proliferation develop at the periphery followed by traction and exudative retinal detachments, falciform retinal folds, a "dragged disc" and macula, and vitreous haemorrhage. Patients with FEVR usually reach a stationary stage and total blindness is uncommon. A locus for autosomal dominant FEVR was mapped by linkage analysis to chromosome 11q13.5-q22.[188 189] Autosomal dominant neovascular inflammatory vitreoretinopathy (ADNIV) is another disease characterised by traction retinal detachment. Linkage analysis has mapped this disorder to chromosome 11q13, the same region as autosomal dominant FEVR,[190] suggesting that FEVR and ADNIV are allelic. If so, future identification of the locus will be necessary to explain why ADNIV is a phenotypically distinct disease characterised by developmentally normal retinal vessels. Other clinical characteristics that distinguish ADNIV from FEVR include ocular inflammation, retinal and iris

neovascularisation, cystoid macular oedema, fundus pigmentation, and a selective loss of the ERG B wave.

When compared to autosomal dominant FEVR, the X linked recessive form of FEVR usually has an earlier onset of symptoms. The adult female gene carriers show no evidence of disease. Fullwood *et al*[191] identified a family with X linked FEVR and mapped the responsible locus by linkage analysis to either Xq21.3 or Xp11.4-11.3. The Xp11.4-11.3 region also contains the Norrie disease gene which has been cloned.[192 193] Norrie disease is an X linked recessive disorder characterised by retinal dysplasia followed by retinal detachment and blindness. Norrie disease is a neurodevelopmental disorder associated with other ocular abnormalities such as microphthalmia, cataract, corneal opacities, congenital blindness, and bulbar atrophy. Extraocular manifestations include progressive sensorineural hearing loss and variable degrees of mental retardation. The Norrie disease gene encodes a mucin-like protein with a tertiary structure similar to that of transforming growth factor β[194] and mutations within this gene have been identified in families with Norrie disease.[195–200] Surprisingly, a point mutation within this Norrie disease gene was found to cosegregate in a family with X linked FEVR studied by Chen *et al.*[201] This finding suggests that the genes for X linked FEVR and Norrie disease are allelic, and once again shows the phenomenon of "gene sharing" between phenotypically distinct diseases. Another disease known as primary retinal dysplasia also has a tight linkage relationship with the Norrie disease locus.[202] Like FEVR and Norrie disease, primary retinal dysplasia is an X linked recessive disorder characterised by retinal detachment. The raised retinal fold characteristic of primary retinal dysplasia arises from the optic disc and involves the macula as it extends to the temporal fundus. Mutations responsible for primary retinal dysplasia have not as yet been reported.

JUVENILE RETINOSCHISIS

Juvenile retinoschisis (RS) is an X linked recessive disorder characterised by cystic degeneration of the peripheral and central retina resulting in the splitting of the nerve fibre layer. A cystic maculopathy with a stellate appearance is a characteristic finding in affected males. Phenotypic expression is highly variable but onset is usually during infancy and there is a slow deterioration throughout life with mild visual impairment until after the age of 40. The disease progresses to retinal detachment, retinal atrophy, choroidal sclerosis, and possibly total blindness. Vasculature abnormalities and vitreous degeneration are associated features. Female carriers of this disease are usually asymptomatic. Multipoint linkage analysis has been used to map the gene responsible for this disease to within the Xp22.1-22.2 locus.[203–208] It is not known at this time if the variable expressivity of this disease can be explained on the basis of allelic heterogeneity, as the gene has not been identified.

WAGNER VITREORETINAL DEGENERATION

Wagner syndrome is an autosomal dominant disorder that has the same ocular features as Stickler syndrome but none of the non-ocular manifestations. Wagner syndrome is characterised by degeneration of the vitreous gel and the retina. These patients appear to have an optically empty vitreous cavity on slit lamp biomicroscopy. Other associated ocular features include retinal detachment, myopia, and cataract. Stickler syndrome has the additional features of progressive arthropathy, cranio-orofacial abnormalities, and deafness. It is unclear whether the Wagner and Stickler syndromes should be considered two distinct clinical disorders or whether they represent variable expressivity of one disease. This debate has been complicated by the fact that Stickler syndrome is a genetically heterogeneous disease. Some families with Stickler syndrome have defects in the COL2A1 gene that encodes for type II α procollagen.[209–214] However, about half of the families reported so far with Stickler syndrome do not show cosegregation with the COL2A1 locus.[215–218] To confuse the issue further, one family with Wagner syndrome has been excluded from the COL2A1 locus[216] and another family has been linked to the COL2A1 locus.[219] Körkkö *et al*[219] proposed that premature termination mutations within the COL2A1 gene may cause the more severe Stickler syndrome while certain amino acid substitutions may cause a milder phenotype like Wagner syndrome. The extent of the relationship between the Stickler and Wagner syndromes remains to be resolved.

Conclusion

The primary genetic disorders of the retina, choroid, and vitreous discussed in this review are summarised along with their MIM (*Mendelian inheritance in man*) number in the accompanying table and idiograms. If a locus has been identified as a cause for a disorder, the MIM number for that disease is assigned according to the identified disease gene. The phenomenon of locus or non-allelic heterogeneity can be appreciated in the table by the different MIM numbers and genes that are assigned to the same clinical disorder. The prevalence of "gene sharing" allelism between clinically distinct disorders is evident by the repeated reference to the same gene or MIM number for different diseases and the presence of grouped disorders adjacent to a chromosomal location in the idiograms. This summary shows a genetic complexity to the mapping of ocular disorders that could not have been appreciated by using clinical classification schemes alone.

Note added in proof

Since this review was submitted, several noteworthy chromosomal loci associated with posterior segment ocular disorders have been published. A digenic form of retinitis pigmentosa was reported in three unrelated families.[220] In these families, affected subjects were double heterozygotes with mutations in the

unlinked peripherin/RDS and ROM1 genes. A heterozygous missense mutation in the rod cGMP phosphodiesterase β-subunit genes was reported to cosegregate with autosomal dominant stationary night blindness in one family.[221] The Bardet-Biedl syndrome was mapped to a second locus on chromosome 11q.[222] An autosomal dominant macular degeneration known as Sorsby's fundus dystrophy was mapped to chromosome 22q13-qter.[223] The locus for autosomal dominant cystoid macular dystrophy was mapped to chromosome 7p15-p21.[224]

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