Choroideremia

Authors: Doctors Hoyng C.B\(^1\), van den Hurk J.A.J.M., Seabra M.C., Cremers F.P.M.
Creation Date: December 2002
Update: October 2004

Scientific Editor: Professor Jean-Jacques De Laey

\(^1\)Department of Human Genetics (417), University Medical Centre Nijmegen, PO. BOX 9101, 6500 HB Nijmegen, Netherlands. C.Hoyng@ohk.umcn.nl

Abstract

Choroideremia (CHM) is an X-linked recessive eye disorder that is characterized by progressive degeneration of the choroid, retinal pigment epithelium (RPE), and neural retina. CHM incidence is estimated to 1 in 100,000. Typically, affected males develop nightblindness in their teenage years, followed by progressive constriction of visual fields and complete blindness by middle age. Fundus changes initially consist of pigmentary stippling and fine atrophy of the RPE in the posterior and equatorial regions. There is also focal atrophy of the choriocapillaris and the larger choroidal vessels around the optic disc and in the equatorial area. Later, the atrophy of the choroid, RPE and retina spreads from the midperiphery inwards and from the disc outwards, whereas the macula is relatively spared. The fundus has a white appearance. Female carriers generally show no serious visual impairment, but they do have conspicuous fundus abnormalities such as pigment changes in the periphery closely resembling the fine mottling, which is characteristic of initial stages of the disease in males. Most frequently clinical signs of CHM in females can be attributed to skewed X-inactivation. Exceptionally homozygosity or disruption of the CHM gene by X-autosome translocations may also result in manifestation of the disease in females. The gene for CHM was localized to Xq21.2. A closely related gene, the CHM-like (CHML) gene, has been identified on chromosome 1q. The CHM and CHML genes encode Rab escort protein-1 (REP1) and -2 (REP2) respectively, which are essential for post-translational lipidation (prenylation) and subcellular localization of intracellular protein trafficking regulators designated Rab GTP-binding proteins. Chorioretinal degeneration is thought to result from deficient prenylation of Rab proteins in the choroid and/ or retina. No treatment is currently available but ongoing studies are focusing on gene therapies. Management is based on low-vision aids.

Keywords

Choroideremia, CHM, choroideremia-like, CHML, rab escort protein-1, REP1, rab escort protein-2, REP2, tapetochoroidal dystrophy, TCD

Definition

Choroideremia (CHM) is an X-linked recessive eye disorder that is characterized by progressive degeneration of the choroid, retinal pigment epithelium (RPE), and neural retina (1,2).
Excluded diseases
- Gyrate atrophy (MIM 258870)
- X-chromosomal recessive retinitis pigmentosa (MIM 602772)
- Bietti crystalline retinal dystrophy (MIM 210370)
- Acquired retina damage due to thioridazine toxicity
- Mitochondrial myopathies

Incidence
Estimated to 1 in 100,000.

Clinical description
Typically, affected males develop nightblindness in their teenage years, followed by progressive constriction of visual fields and complete blindness by middle age. Fundus changes initially consist of pigmentary stippling and fine atrophy of the RPE in the posterior and equatorial regions. There is also focal atrophy of the choriocapillaris and the larger choroidal vessels around the optic disc and in the equatorial area. Later, the atrophy of the choroid, RPE and retina spreads from the midperiphery inwards and from the disc outwards, whereas the macula is relatively spared. The fundus has a white appearance. Female carriers generally show no serious visual impairment, but they do have conspicuous fundus abnormalities such as pigment changes in the periphery closely resembling the fine mottling, which is characteristic of initial stages of the disease in males. Most frequently clinical signs of CHM in females can be attributed to skewed X-inactivation. Exceptionally homozygosity or disruption of the CHM gene by X-autosome translocations may also result in manifestation of the disease in females.

The CHM gene

Positional cloning
The gene for CHM was localized to the Xq13-Xq22 region by linkage analysis. The disease region was further refined by the characterization of cytogenetically visible deletions in patients with CHM, mental retardation, and deafness with a temporal bone defect. Molecular analysis of deletions in patients where CHM is the only clinical feature formed the basis for the positional cloning of the CHM gene (EMBL accession no. X78121) from Xq21.2 (3,4). The CHM mRNA has a length of approximately 5.6 kb. The open reading frame (ORF) is composed of 15 exons spanning a genomic sequence of about 150 kb. The exons range in size from 64 nucleotides to 3.4 kb (5).

Mutation analysis
The spectrum of defects in the CHM gene includes deletions, translocations, and a variety of subtle mutations. Deletions vary in size from a few kilobases removing a single exon, to ~15 Mb comprising the entire CHM gene and large parts of Xq21 (6). Deletions of this size associated with human monogenic disorders are unprecedented. Balanced X;7 and X;13 translocations that disrupt the CHM gene were found in two females with mild clinical signs of choroideremia and ovarian dysgenesis (3,5). In females with reciprocal X-autosomal translocations, the normal X is preferentially inactivated while both translocation fragments remain active. Recently, the CHM gene was reported to show heterogeneous expression from the inactive X chromosome, being subject to inactivation in some females and escaping inactivation to different extents in others (7). The presence of a low level of functional CHM transcript derived from the inactive normal X chromosome in the two females with translocations in the CHM gene, could account for their mild disease course.

Among the subtle mutations that have been detected in the CHM gene are nonsense, frameshift, and splice site mutations. A full-length L1 retrotransposon insertion into the coding region of the CHM gene (exon 6) results in a splice defect and skipping of exon 6, while maintaining the reading frame. The predicted CHM protein lacks L235_Q273del. An intron 4 mutation activates a cryptic exon of 98 bp which is spliced into the CHM mRNA between exons 4 and 5, disrupting the open reading frame and leading to a premature stop codon (8). Most, if not all, of these mutations give rise to a premature termination codon. The only missense mutation that has ever been reported in the CHM gene (9) turned out to be a splicing mutation (10). The conspicuous absence of missense mutations in the CHM gene of choroideremia patients may indicate that in many instances they have no disadvantageous consequences. Also, missense mutations may give rise to a phenotype distinct from choroideremia or they may be lethal.

Related genes – CHML
An autosomal homologue of the CHM gene has been isolated, which was designated CHML (choroideremia-like). The intronless CHML gene (EMBL accession no. X64728) encodes a protein of 656 amino acids that is 72% identical to the CHM protein (11). The human CHML gene was localized to chromosome 1q42-qter, the murine chml gene was mapped to chromosome 1, 5.4 centiMorgan distal to D1Mit15 and 18.3 centiMorgan proximal to D1Mit17.

**The CHM gene product: Rab Escort Protein structure**

The **CHM** gene encodes a protein of 653 amino acids and apparent molecular weight of 72.5 kDa, designated Rab Escort Protein (REP1) on the basis of its known cellular function (12-14). Both REPs, REP1 and REP2 (the product of the **CHML** gene) are ubiquitously expressed. REP proteins are homologous to Rab GDP Dissociation Inhibitor (RabGDI), a Rab-binding protein with a role in intracellular protein trafficking.

Sequence alignments of the known REPs and RabGDIs revealed significant structural homology in three regions termed sequence conserved regions (SCR1, 2 and 3), suggesting that the members of this family may have similar three-dimensional structures. The crystal structure of RabGDI was elucidated recently and found to be organized in two domains, a large complex multisheet domain I, which forms a Rab-binding platform and a globular alpha-helical domain II, which may be involved in the interaction with membrane proteins (15). REP has not been crystallised yet. Modelling studies suggest that REP is composed of three domains: domain I and domain II similar to those in RabGDI, plus a novel domain III formed by an 150 amino acid insert present between domains I and II.

REP proteins are conserved throughout evolution. The yeast **S. cerevisiae** expresses an ortholog, known as **Mrs6p**. **Mrs6p** is an essential gene and appears to have the same function as its mammalian counterparts. REP orthologs have also been found in flies and plants.

**Rab escort protein function and clues into the pathogenesis of CHM**

REP is essential for post-translational lipidation (prenylation) of a large family of intracellular protein trafficking regulators designated Rab GTP-binding proteins. Rab prenylation and membrane-association is critical to their function. The role of REP appears to be binding newly synthesized, unprenylated Rabs and presenting them to Rab geranylgeranyl transferase, which catalyzes the transfer of prenyl groups to Rabs. After prenylation, REP escorts Rabs into the appropriate intracellular membrane, thereby activating them (12-14).

Why does a defect in REP1 lead to retinal degeneration in CHM? The most likely possibility is that the loss of REP protein results in defects in Rab protein prenylation. In the absence of prenylation, dysfunctional Rabs lead to the arrest of one or more intracellular exocytic and endocytic pathways and eventually to cell death. REPs appear to be functionally redundant with respect to the prenylation of most Rabs with at least one notable exception. The Rab27 protein was initially suspected to be more efficiently prenylated by REP1 than by REP2, and therefore to be selectively unprenylated (16). However, it was recently shown that the rates of Rab27 prenylation mediated by REP-1 and REP-2 differ only by 2-fold. The latest model proposed for the molecular mechanisms underlying CHM is based on a low affinity of Rab27 for both isoforms of REP, which does not allow it to compete favorably with other Rabs for prenylation by REP-2, if the total activity REP becomes limiting (17).

**Animal model of CHM**

The current challenge in choroideremia research is the construction of a mouse model to investigate the pathogenesis of the disease and to serve as an experimental system for (gene) therapeutic studies. To this end, a gene targeting approach was used to disrupt the mouse **chm** gene in exon 8, thereby introducing a premature termination codon. Chimeric males transmitted the mutated **chm** gene to their carrier daughters but, surprisingly, these heterozygous females had neither affected male nor carrier female offspring. The targeted **chm** allele was detectable, however, in male as well as in female blastocyst stage embryos isolated from a heterozygous mother (18). Thus, it appears that disruption of the **chm** gene causes embryonic lethality in males; in females it is only lethal if the mutation is of maternal origin. A likely explanation could be that, in mice, expression of the **chm** gene is essential for proper functioning of the extraembryonic membranes. It has been extensively documented that in female mouse conceptuses, the paternal X-chromosome is preferentially inactivated in most of the extraembryonic tissues. As a consequence, female embryos that inherit the mutated X from their mother, lack a functional **chm** allele in their extraembryonic tissues because the wildtype gene on the paternal X is inactive. In contrast, female embryos carrying the targeted **chm** gene on their paternal X chromosome would be healthy because this X chromosome is inactive in their extraembryonic tissues anyway; the only active **chm** gene is the wildtype one on the maternal X. Affected male embryos would die because the **chm** mutation on their single X chromosome results in the absence of functional **chm** gene product in their extraembryonic membranes. A recent study in mutant **chm** mice embryos provided evidence that abnormal development of extraembryonic tissues is indeed the cause for prenatal lethality of the maternally transmitted **chm** mutation. The multiple defects of the extraembryonic tissues in these mutants demonstrate that **chm** is essential for diploid...
trophoblast development and plays a role in the vascularization in placenta and yolk sac (19).
To find evidence for ocular manifestations of the *chm* mutation, eyes of chimeras and their female heterozygous offspring were examined histologically. Heterozygous females demonstrated a clear but rather mild loss of photoreceptors in the retina. In chimeras, the retina showed areas that were relatively well-preserved and areas that were completely devoid of photoreceptors (18). Thus, mutation of the mouse *chm* gene gives rise to ocular changes that are comparable to human choroideremia.

**Treatment**
No treatment is currently available but ongoing studies are developing therapeutic strategies that target REP, Rab proteins and modulate the endocytic pathway (20;21). Management is based on low-vision aids.

**References**

**Suggestions for Further Reading**

http://www.orpha.net/data/patho/GB/uk-choroid.pdf