
Homozygous Deletion in CDH3 and Hypotrichosis With Juvenile Macular Dystrophy

Hypotrichosis associated with juvenile macular dystrophy (HJMD; OMIM 601553) is a rare autosomal recessive disorder characterized by short scalp hair from birth and progressive macular degeneration. Loss of central vision usually occurs between the second and fourth decades of life. Mutations in the P-cadherin gene (CDH3; GenBank NM_001793) were first reported to underlie HJMD by Sprecher et al1; splice, missense, and nonsense mutations have since been described.2-5

Report of a Case. A 48-year-old man had a 21-year history of deterioration of central vision. The original diagnosis was Stargardt disease. Initial symptoms at age 17 years included photosensitivity, abnormal color vision, and central scotomata. His sister has the same phenotype and the parents were likely to be related. The proband and his sister both gave a history of having very fine, sparse hair that never thickened, with a persistently visible scalp (Figure 1A). Funduscopy in the proband revealed bilateral symmetrical macular degeneration with sparing of the peripheral retina (Figure 1B and C). Visual acuities were 6/760 OD and 6/96 OS. Goldmann visual field testing showed bilateral central scotomata (Figure 1D). Electrophysiology showed extinguished pattern electroretinograms, normal scotopic responses, and significant reduction in amplitudes of both a and b waves in the standard flash electroretinogram and photopic responses. The electro-oculogram light rise was normal in both eyes.

Figure 1. Clinical spectrum of the patient with hypotrichosis associated with juvenile macular dystrophy. A, Sparse hair in the proband at age 48 years. B, Color fundus photograph showing macular degeneration. C, Color fundus photograph of the same eye showing degeneration confined to the macular and peripapillary regions, sparing the mid and peripheral retina. D, Left visual field showing extensive central scotoma (the findings are similar in the right eye).
The phenotype prompted us to undertake mutation screening of \textit{CDH3}, which comprises 16 exons spanning approximately 55 kilobases of genomic DNA (Figure 2A). Exons 1 through 11 and 14 through 16 were successfully amplified using primers as described by Kjaer et al.\textsuperscript{6} No nucleotide changes were detected by sequencing. Failure to amplify exons 12 and 13 in the patient, compared with a control, led us to speculate that there could be a small intragenic deletion. Primers located in introns 11 and 14 amplified a 1607–base pair (bp) fragment from the patient, the expected size being 10,422 bp. Sequencing confirmed

\begin{table}[h]
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\begin{tabular}{|c|c|}
\hline
\textbf{Exon, bp} & \textbf{Intron, bp} \\
\hline
1 & 86 \\
2 & 144 \\
3 & 156 \\
4 & 176 \\
5 & 186 \\
6 & 225 \\
7 & 207 \\
8 & 129 \\
9 & 148 \\
10 & 2054 \\
11 & 380 \\
12 & 1054 \\
13 & 3829 \\
14 & 391 \\
15 & 2299 \\
16 & 210 \\
\hline
\end{tabular}
\caption{Exon and intron sizes.}
\end{table}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure2.png}
\caption{Mutation screening. A, Schematic diagram of the genomic structure of \textit{CDH3}. Boxes indicate exons; lines, introns; and bp, base pairs. All are to scale except for regions of intronic DNA larger than 1 kilobase, which are represented as slashed lines. Exon and intron sizes are marked, as are the start and stop codons. The exons encoding the calcium-binding domains are shaded blue. B, Sequence of the deletion break point showing intron 11 spliced directly to intron 13 (not present in the Database of Genomic Variants). C, Expression of \textit{CDH3} in lymphocytes from the patient and a control by reverse transcription–polymerase chain reaction amplification of RNA using gene-specific primers spanning the junctions of exons 10 and 11 (forward) and 14 and 15 (reverse); human retinal complementary DNA was used as a control. The wild-type fragment should be 729 bp; the fragment amplified from the patient is 297 bp, lacking the 432 bp from exons 12 and 13. Lane 1 is the marker; 2, patient with reverse transcriptase; 3, patient without reverse transcriptase; 4, control with reverse transcriptase; 5, control without reverse transcriptase; 6, human retinal complementary DNA; 7, human genomic DNA; and 8, no-template control. D, Confirmation by sequence analysis. E, The domain structure of \textit{P-cadherin} is represented diagrammatically. The protein consists of 5 extracellular calcium-binding domains (EC1–EC5), a transmembrane region, and a short intracellular tail that binds to \textit{\(\beta\)-catenin}. The predicted mutant protein missing EC4, EC5, and part of the transmembrane domain is shown below.}
\end{figure}
a homozygous deletion of 8815 bp in both siblings with break points in introns 11 and 13 resulting in loss of exons 12 and 13 (Figure 2A and B). Further examination of the region showed a 34-bp repeat (differing by only 1 bp) flanking the break points, suggesting homologous recombination as the mechanism for generating this deletion. The predicted result of this deletion would be that exon 11 splices directly to exon 14 and remains in frame, resulting in a protein of 685 amino acids, compared with the wild-type protein of 829 amino acids (Figure 2E). This was confirmed using complementary DNA from patient and control lymphocytes and sequencing the products (Figure 2C and D).

Comment. Hypotrichosis associated with juvenile macular dystrophy is caused by mutations in CDH3, which encodes P-cadherin, a member of the classic cadherin family. We report here, to our knowledge for the first time, an intragenic deletion causing HJMD that results in the homozygous loss of exons 12 and 13 of CDH3. The resultant transcript has exon 11 spliced directly to exon 14, and although it remains in frame, the predicted protein loses extracellular calcium-binding domains 4 and 5 and part of the transmembrane domain and would therefore be nonfunctional.

Kjaer et al9 have shown that mutations in CDH3 also cause ectodermal dysplasia, ectrodactyly, and macular dystrophy (EEM; OMIM 225280); they also discuss possible mechanisms for this phenotypic variation. Both HJMD and EEM have very similar hair and retinal defects, but patients with EEM have additional limb abnormalities. Hypotrichosis associated with juvenile macular dystrophy is a rare condition with 1 previous report in the ophthalmology literature.7 This case highlights the importance of assessing patients with inherited retinal degeneration for extraocular features and the fact that HJMD should be considered if early-onset macular degeneration is diagnosed in the context of hypotrichosis.

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**Bilateral Ophthalmic Artery Occlusions Due to Probable Varicella-Zoster Virus Vasculopathy**

Varicella-zoster virus (VZV) vasculopathies account for almost one-third of arterial ischemic strokes in children.1 Visual complications are rare, with previous reports occurring secondary to unilateral central retinal artery2 or posterior ciliary artery3 occlusion. We describe the first case, to our knowledge, of an immunocompetent child who became blind due to bilateral ophthalmic artery occlusions secondary to probable VZV vasculopathy.

**Report of a Case.** A 6-year-old boy visited his local emergency department with a history of sudden painless bilateral visual loss. He was otherwise in good health apart from a history of chickenpox 8 weeks previously. His father had been treated for culture-negative mediastinal tuberculosis a year earlier. Initial examination in the emergency department showed visual acuity of counting fingers OU, a moderate bilateral panuveitis, and diffuse bilateral retinal edema with sheathing of both retinal arteries and veins. The optic discs were not swollen. Neurological examination findings were otherwise normal. Initial management aimed to treat a possible tuberculosis optic neuropathy and/or vasculopathy, using oral prednisolone, rifampin, pyrazinamide, and isoniazid. Initial investigations showed no abnormality on hematology and biochemistry tests of peripheral blood. Cytomegalovirus and VZV IgG were both detected on testing of serum, but polymerase chain reaction results for the respective DNA were negative. Evidence of tuberculosis infection was not found, with negative results on both enzyme-linked immunosorbent spot and Heat tests and