

RESEARCH REPORT

Phenotypic observations in “hypotrichosis with juvenile macular dystrophy” (recessive *CDH3* mutations)

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ABSTRACT

Purpose: Recessive mutations in *CDH3* cause “hypotrichosis with juvenile macular dystrophy,” typically recognized by the presence of prominent dermatological features. We report novel phenotypic observations and associated mutations in four patients from three families, including one who did not have frank hypotrichosis.

Methods: Retrospective case series (2010–2014).

Results: Four affected individuals from three consanguineous Arabian families were identified. All four subjects (two sisters and two unrelated males; 5, 13, 17, and 26 years old) had homozygous recessive *CDH3* mutations not previously associated with the condition (c.307C>T; p.R103 in two sisters, c.1859_1862delCTCT in both unrelated males). Symptomatic visual loss was since birth or early childhood. One male subject did not have frank hypotrichosis, but review of symptoms revealed relatively slow hair growth and an inability to conceive children. None had dental or digital findings, although one female noted slow nail growth. All had a circumscribed central maculopathy with borders that did not respect posterior pole horizontal arterioles (typically extending beyond the major arcades) and associated with polygonal pigment clumping. Recognition of this pattern led us to suspect the diagnosis in the male without frank hypotrichosis. Retinal dysfunction was cone-rod (rather than macular only) by ERG in one patient, who developed severe central macular atrophy and a macular hole.

Conclusions: Ophthalmologists should consider the diagnosis of *CDH3*-related retinopathy in individuals with such clinical features whether or not there is frank hypotrichosis.

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Introduction

“Hypotrichosis with juvenile macular dystrophy” is a form of retinal dystrophy defined by early scalp hair loss and subsequent progressive macular dystrophy (On-line Mendelian Inheritance in Man [MIM] #601553). The condition is caused by recessive mutations in *CDH3*, encoding P-cadherin, which is expressed in the retinal pigment epithelium and hair follicles.¹ Recessive *CDH3* mutations also cause another syndrome, that of ectodermal dysplasia, ectrodactyly, and macular dystrophy (MIM #225280).² Most cases of hypotrichosis with juvenile macular dystrophy were reported in the dermatology or genetics literature and were recognized based on the presence of dermatological features.^{1,3–12} The purpose of our study is to further phenotype *CDH3*-related retinopathy by reporting phenotypic features of four Saudi Arabian patients from three families harboring one of two homozygous recessive mutations in *CDH3*, both of which are novel for the syndrome.

Methods

Institutional board approval was obtained for reporting this retrospective consecutive case series (2010–2014) of children and/or young adults referred to a pediatric ophthalmologist for low vision, confirmed to have early childhood-onset retinal

dysfunction, and found to harbor homozygous recessive mutations in *CDH3*. Electroretinography (ERG) was performed using international standards.¹³ Families were specifically questioned regarding any abnormalities of the hair, teeth, nails, and digits, and these structures were inspected for abnormalities in all affected patients. General medical history was recorded, with specific questioning regarding the presence or absence of the following: neurodevelopmental delay, deafness, polydactyly, heart disease, kidney malformation, skeletal disease, and obesity.

Diagnostic genetic testing for individuals in this cohort was either next-generation sequencing of a retinal dystrophy gene panel using previously-described methods¹⁴ followed by confirmatory Sanger sequencing of *CDH3* or direct Sanger sequencing of *CDH3* after we had become familiar with the phenotype. Panel testing covered 44 genes previously associated with retinal degeneration preferentially affecting central regions of the retina such as macular dystrophy, cone dystrophy and cone-rod dystrophy (*ABCA4*, *ACBD5*, *ADAM9*, *AIPL1*, *BEST1*, *C1QTNF5*, *C21ORF2*, *C8ORF37*, *CABP4*, *CACNA2D4*, *CDH3*, *CDHR1*, *CERKL*, *CNGA3*, *CNGB3*, *CNNM4*, *CRX*, *ELOVL4*, *FBLN5*, *GUCA1A*, *GUCA1B*, *GUCY2D*, *HMCN1*, *ITM2B*, *KCNV2*, *MERTK*, *PDE6C*, *PITPNM3*, *PROM1*, *PRPH2*, *RAB28*, *RAX2*, *RDH5*, *RGS9*, *RGS9BP*, *RIMS1*, *RP1L1*, *RPGR* except *ORF15*, *RPGRIP1*,

SEMA4A, *TEAD1*, *TIMP3*, *UNC119*, *WASF3*) and 26 Leber congenital amaurosis genes (*ADAMTS18*, *AIPL1*, *CABP4*, *CEP290*, *CRB1*, *CRX*, *DHX38*, *DTHD1*, *GDF6*, *GUCY2D*, *IMPDH1*, *IQCB1*, *KCNJ13*, *LCA5*, *LRAT*, *MERTK*, *MPDZ*, *MYO7A*, *NMNAT1*, *OTX2*, *RD3*, *RDH12*, *RPE65*, *RPGRI1*, *SPATA7*, *TULP1*) [some genes have been associated with both disease groups and are therefore listed twice]. Bioinformatic programs were used for evaluation of variants' pathogenicity as previously described.¹⁵ Verification of identified variants was carried out by polymerase chain reaction amplification of the corresponding exon, followed by Sanger sequencing. The reference sequence for *CDH3* was NM_001793.4

Results

Four subjects from three Arabian families (two sisters, Subjects 1 and 2, 17 and 13 years old respectively, and

two unrelated males, Subjects 3 and 4, 5 and 26 years old respectively) were identified (Table 1). Only Subject 1 had panel testing followed by confirmatory *CDH3* Sanger sequencing rather than direct *CDH3* Sanger sequencing only, and she did not have any other mutations in the candidate genes tested on the panel. All subjects were from first-cousin marriages, had symptomatic visual loss since birth or early childhood, and harbored one of two recessive homozygous mutations in *CDH3*, both of which are associated with hypotrichosis with juvenile macular dystrophy for the first time in this report: c.307C>T; p.R103 in Subjects 1 and 2 (novel to this report), and c.1859_1862delCTCT in Subjects 3 and 4 (previously associated with digenic hypotrichosis¹⁶). Subject 4 did not have frank hypotrichosis but after specific questioning he admitted to relatively slow hair growth; in addition, review of systems also revealed that he had been unable to conceive

Table 1. Clinical summary of subjects.

Subject	Age	BCVA	CYCLO RNS	Visual history	Additional	ERG	Homozygous mutation	Mutation reference
1	17 y	3/200	−1.75	Difficulty with vision since age 6 y old, but especially bad since 13 y old	Scalp hypotrichosis; no eyelashes; developed atrophic macular hole	Cone-rod dystrophy	c.307C>T p.(Arg103*)	This study
2	13 y	20/60	−4.25 + 2.50 × 090	Difficulty with vision since 8 y old	Scalp hypotrichosis; slow nail growth	WNL	c.307C>T p.(Arg103*)	This study
3	5.5 y	20/100	+1.75	Nystagmus since birth	Scalp hypotrichosis	WNL	c.1859_1862delCTCT	Digenic hypotrichosis ¹⁶
4	26 y	20/80	−0.75	Difficulty with vision since childhood (unable to specify age)	Infrequent haircuts; unable to conceive children	WNL	c.1859_1862delCTCT	Digenic hypotrichosis ¹⁶

BCVA: best-corrected visual acuity in either eye; CYCLO RNS: cycloplegic retinoscopy in either eye; ERG: electroretinography; WNL: within normal limits; y: years.

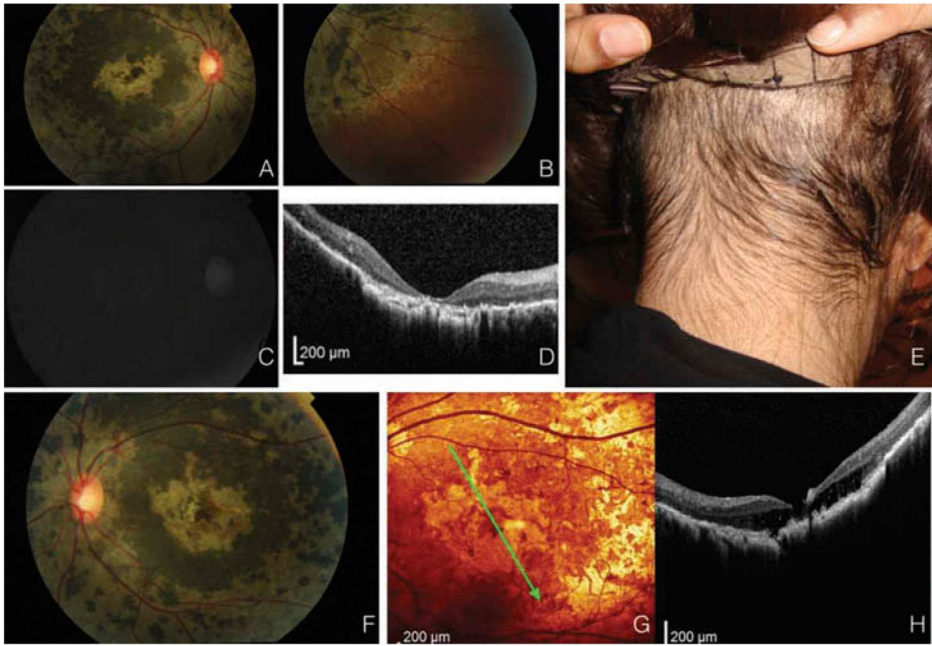


Figure 1. Subject 1: In the right eye (A–D), (A) There is circumscribed retinal atrophy in the macula extending beyond the borders of the retinal arcades. In the central macula, there is a smaller more discolored circumscribed area of atrophy that also does not respect the horizontal arterioles. Atrophy is associated with numerous polygonal pigment clumps. (B) The nasal extent of the retinal atrophy extending beyond the borders of the retinal arcades can be appreciated. (C) There is decreased autofluorescence signal in much of the fundus. (D) Optical coherence tomography of an oblique central macular cut (directed superonasally towards 2 o'clock) shows extensive outer retinal atrophy as well as retinal pigment epithelial atrophy. (E) After *CDH3* mutations were uncovered by next-generation sequencing, the subject was specifically questioned about hair loss and she revealed she had been wearing a wig and false eyelashes; scalp hypotrichosis can be appreciated underneath the wig. In the left eye (F–H), (F) the dystrophic pattern is similar to that of the right eye and (G & H) optical coherence tomography reveals a macular hole in the context of outer retinal and retinal pigment epithelial atrophy.

children (more than 5 years of trying). None had dental or digital findings, although Subject 2 noted slow nail growth. Their clinical features are summarized in Table 1. All had circumscribed central macular dystrophic changes that did not respect the horizontal arterioles, typically extended beyond the posterior pole major arcades, and was associated

with polygonal pigment clumps (see Figures 1–4, corresponding to Subjects 1–4 respectively). It was this pattern of macular dystrophic changes that made us suspect the diagnosis in the male without frank hypotrichosis (Subject 4, Figure 4). All subjects had normal ERGs except Subject 1, who had generalized cone-rod dystrophy and severe central

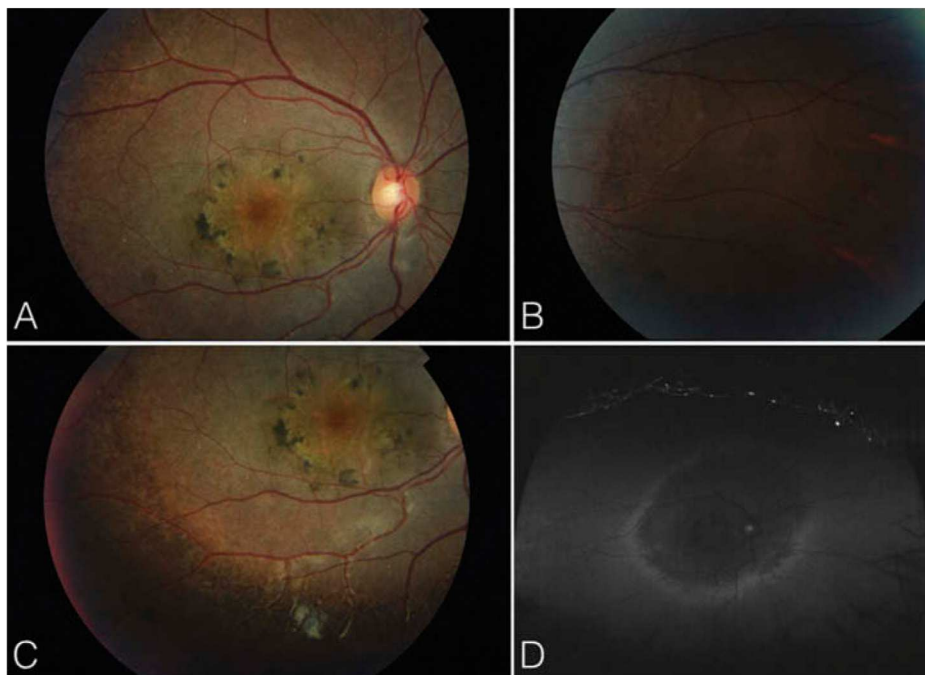


Figure 2. Subject 2: In the right eye (left eye not shown but was similar), (A) There is circumscribed retinal atrophy in the macula extending beyond the borders of the retinal arcades. Centrally, there is a second smaller more discolored circumscribed area of atrophy that also does not respect the horizontal arterioles and is associated with polygonal pigment clumps. (B) The nasal and (C) inferotemporal borders of the circumscribed retinal atrophy can be appreciated. (D) Autofluorescence shows a ring of increased autofluorescence along the border of the circumscribed retinal atrophy extending beyond the borders of the retinal arcades. Within the ring autofluorescence is decreased, and within the smaller central area of atrophy autofluorescence is markedly decreased, in a bull's-eye pattern as is often seen in cone dystrophies.

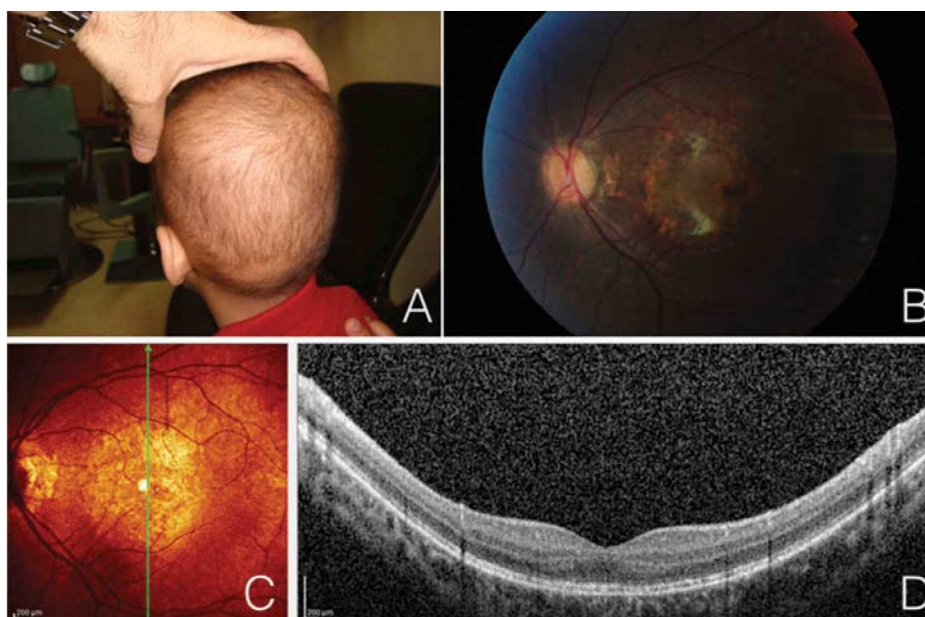


Figure 3. Subject 3: (A) Scalp hypotrichosis is shown. (B) In the left eye (right eye not shown but was similar), vertically extending circumscribed central macular atrophy that does not respect the horizontal arterioles can be appreciated. A polygonal pigment clump can be seen temporally. (C & D) Optical coherence tomography shows loss of outer retinal architecture in the central macula.

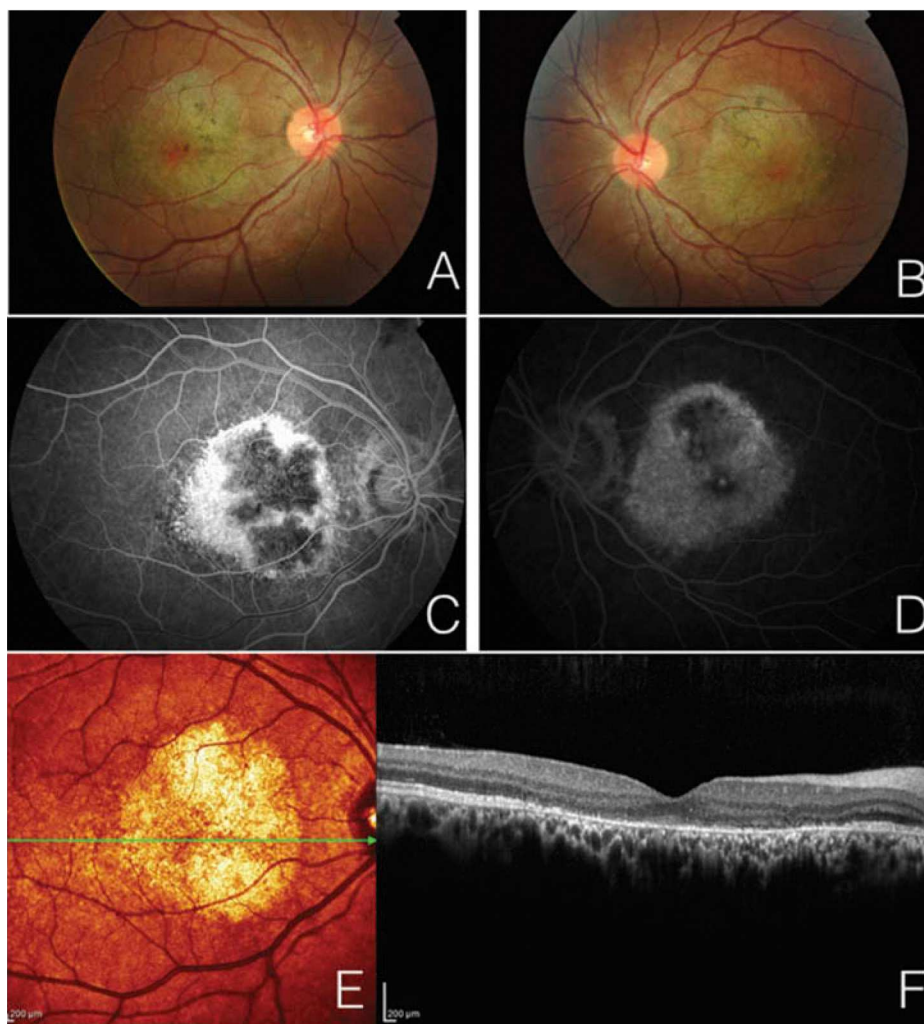


Figure 4. Subject 4: (A) Right and (B) left eyes show vertically oval central circumscribed macular atrophy that does not respect the horizontal arterioles. (C & D) Fundus images of fluorescein angiography of the (C) right and (D) left eyes reveal right arteriovenous phase hyper- and hypo-fluorescence corresponding to the central macular lesion and left late phase staining in the central macular lesion. (E, F) Optical coherence tomography of the right eye shows loss of outer retina in the central macula.

macular atrophy that included a macular hole in her left eye (Figure 1).

Discussion

All four subjects with homozygous recessive *CDH3* mutations in our series had similar circumscribed dystrophic changes that were centered in the central macula with borders which did not respect horizontal arterioles, often extended beyond the arcades of the posterior pole, and were associated with polygonal pigment clumps; one of the four subjects did not have frank hypotrichosis. This pattern of circumscribed dystrophy seems recurrent for *CDH3* mutations and thus should raise suspicion for the mutations in the gene whether or not frank hypotrichosis is present. Other clinical findings noted for the first time in this series are macular hole formation and potential male infertility.

Central cone photoreceptor dystrophy can be isolated or in the context of systemic disease. Isolated cone and cone-rod dystrophies can be dominant (e.g. mutations in genes such as

CRX or *GUCY2D*), recessive (e.g. mutations in genes such as *ABCA4* or *KCNV2*), or X-linked (e.g. mutations in *RPGR*).¹⁷ Cone and cone-rod dystrophies in the setting of systemic disease are rarer and include Jalili syndrome (MIM #217080), spinocerebellar ataxia type 7 (MIM #609270), Alstrom syndrome (MIM #203800), some forms of Bardet-Biedl syndrome,¹⁷ and hypotrichosis with juvenile macular dystrophy. Age of onset and rapidity of progression are variable for both non-syndromic and syndromic forms. Typical early retinal findings are macular atrophy or bull's-eye maculopathy. When such changes are circumscribed in a bull's-eye pattern, they tend to respect the horizontal arterioles. Later, more widespread changes occur such as more peripheral retinal pigment epithelial atrophy, retinal pigmentary changes, and arteriolar attenuation. While there can be considerable phenotypic overlap among these different causes of cone and cone-rod dystrophies, the large circumscribed central macular involvement without respect for the horizontal arterioles in hypotrichosis with juvenile macular dystrophy seems recurrent; thus, this specific diagnosis should be considered when a patient has this particular fundus appearance. However,

probably a more common cause for such a fundus appearance is severe *ABCA4*-related disease (from null mutations).

At least 19 families have been reported with a genetically-confirmed diagnosis of hypotrichosis with juvenile macular dystrophy (Table 2).^{1,3–12} Affected patients were bi-allelic for one (homozygous cases) or two (compound heterozygous cases) of 11 recessive *CDH3* mutations (17 families with homozygous mutations,^{1,3–5,7–12} two families with compound heterozygous mutations⁶). Few reports include ophthalmic details or retinal images; those that do show findings consistent with what we describe here. Two are reports from the ophthalmic literature, a retrospective cohort study¹⁸ of previously-reported families¹ and a case report.¹² The retrospective cohort study¹⁸ was an electroretinographic review of 16 known Israeli Arab patients¹ harboring one of two homozygous recessive mutations. The authors of that report concluded that despite the name associated with the genotype (“hypotrichosis with juvenile macular dystrophy”), *CDH3*-related retinal dystrophy could be a cone-rod rather than a macular dystrophy, consistent with our observation of generalized retinal dystrophy in one of our four subjects. The case report¹² was of a 48-year-old adult (ethnicity not documented) with hypotrichosis, cone-rod dystrophy, and a deletion in *CDH3*. More recently, a case report of a 6-year-old boy (ethnicity not documented) with hypotrichosis and macular dystrophy was published although without results of *CDH3* mutation analysis.¹⁹ However, retinal photographs were included in that report, and findings were similar to what we describe.

In addition to highlighting the pattern of retinal dystrophy characteristic for *CDH3*-related retinal dystrophy, we note additional potential phenotypic features in affected

patients. One is severe central macular atrophy and macular hole formation in Subject 1. Another is lack of frank scalp hypotrichosis in Subject 4. The fact that the condition can occur without frank hypotrichosis raises the possibility that recessive *CDH3* mutations may be a more common cause for retinal dystrophy than is recognized because mutations in the gene are usually not suspected unless hypotrichosis is present. An additional clinical observation was the inability of the 26-year-old male in our series (Subject 4) to conceive children, which raises the interesting possibility that *CDH3* mutations might be associated with male infertility. Previous reports of patients with recessive *CDH3* mutations, many of which were of children, have not addressed this possibility at all. P-cadherin is a component of human semen,²⁰ and there is evidence that cadherins have a role in human male gametes and fertilization.²¹ Yet we cannot prove that inability to conceive a child in our case is related to his *CDH3* mutations. There are multiple potential causes for male infertility, as well as the possibility that his wife was infertile, and the couple has not consented to investigate for potential causes. However, at the very least, the possibility that recessive *CDH3* mutations could be associated with male infertility deserves further study.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the article.

References

1. Sprecher E, Bergman R, Richard G, et al. Hypotrichosis with juvenile macular dystrophy is caused by a mutation in *CDH3*, encoding P-cadherin. *Nat Genet* 2001;29:134–136.
2. Kjaer KW, Hansen L, Schwabe GC, et al. Distinct *CDH3* mutations cause ectodermal dysplasia, ectrodactyly, macular dystrophy (EEM syndrome). *J Med Genet* 2005;42:292–298.
3. Indelman M, Bergman R, Lurie R, et al. A missense mutation in *CDH3*, encoding P-cadherin, causes hypotrichosis with juvenile macular dystrophy. *J Invest Dermatol* 2002;119:1210–1213.
4. Indelman M, Hamel CP, Bergman R, et al. Phenotypic diversity and mutation spectrum in hypotrichosis with juvenile macular dystrophy. *J Invest Dermatol* 2003;121:1217–1220.
5. Indelman M, Leibu R, Jammal A, et al. Molecular basis of hypotrichosis with juvenile macular dystrophy in two siblings. *Br J Dermatol* 2005;153:635–638.
6. Indelman M, Eason J, Hummel M, et al. Novel *CDH3* mutations in hypotrichosis with juvenile macular dystrophy. *Clin Exp Dermatol* 2007;32:191–196.
7. Jelani M, Salman Chishti M, Ahmad W. A novel splice-site mutation in the *CDH3* gene in hypotrichosis with juvenile macular dystrophy. *Clin Exp Dermatol* 2009;34:68–73.
8. Basel-Vanagaite L, Pasmanik-Chor M, Lurie R, et al. *CDH3*-related syndromes: report on a new mutation and overview of the genotype-phenotype correlations. *Mol Syndromol* 2010;1:223–30.
9. Kamran-ul-Hassan Naqvi S, Azeem Z, Ali G, et al. A novel splice-acceptor site mutation in *CDH3* gene in a consanguineous family exhibiting hypotrichosis with juvenile macular dystrophy. *Arch Dermatol Res* 2010;302:701–703.
10. Shimomura Y, Wajid M, Kurban M, et al. Splice site mutations in the P-cadherin gene underlie hypotrichosis with juvenile macular dystrophy. *Dermatology* 2010;220:208–212.

Table 2. Previously-published mutation-positive cases

Reference	Families (patients)	Mutations	Retinal images?
Sprecher 2001 ¹	4 Israeli Druze families (11 patients)	c.981delG	Later in Leibu 2006 ¹⁸
Indelman 2002 ³	1 Arab Israeli family (4 patients)	c.1508G> A (p.R503H)	Later in Leibu 2006 ¹⁸
Indelman 2003 ⁴	5 families (9 patients) – French, Turkish, Turkish Cyprus, 2 Arab Israeli	c.503T> A (p.L168)	No
Indelman 2005 ⁵	1 Arab Muslim family (2 patients)	c.1845T>A (p.Y615*)	Yes
Indelman 2007 ⁶	2 non-consanguineous families (4 patients) – white English and white North American	c.661C>T (p.R221*), c.1510G>A (p.E504K), c.1724A>G (p.H575R), c.160+1G>A	Yes
Jelani 2009 ⁷	1 Pakistani Pashtooni family (6 patients)	c.1425-1G>T	No
Kamran-ul-Hassan Naqvi 2010 ⁹	1 Pakistani family (6 patients)	c.1425-1G>A	No
Shimomura 2010 ¹⁰	2 Pakistani families (7 patients)	c.1796-2A>G	No
Avitan-Hersh 2012 ¹¹	1 Arab Israeli family (1 patient)	c.747C>A (p.Y249*)	No
Halford 2012 ¹²	1 family without described ethnicity (1 patient)	8815bp including exons 12–13	Yes

11. Avitan-Hersh E, Indelman M, Khamaysi Z, et al. A novel non-sense CDH3 mutation in hypotrichosis with juvenile macular dystrophy. *Int J Dermatol* 2012;51:325–327.
12. Halford S, Holt R, Nemeth AH, et al. Homozygous deletion in CDH3 and hypotrichosis with juvenile macular dystrophy. *Arch Ophthalmol* 2012;130:1490–1492.
13. Marmor MF, Fulton AB, Holder GE, et al. ISCEV standard for full-field clinical electroretinography (2008 update). *Doc Ophthalmol* 2009;118:69–77.
14. Eisenberger T, Neuhaus C, Khan AO, et al. Increasing the yield in targeted next-generation sequencing by implicating CNV analysis, non-coding exons and the overall variant load: the example of retinal dystrophies. *PLoS One* 2013;8 (11):e78496.
15. Khan AO, Bergmann C, Neuhaus C, et al. A distinct vitreo-retinal dystrophy with early-onset cataract from recessive KCNJ13 mutations. *Ophthalmic Genet* 2015;36:79–84.
16. Basit S, Wali A, Aziz A, et al. Digenic inheritance of an autosomal recessive hypotrichosis in two consanguineous pedigrees. *Clin Genet* 2011;79:273–281.
17. Michaelides M, Hardcastle AJ, Hunt DM, et al. Progressive cone and cone-rod dystrophies: phenotypes and underlying molecular genetic basis. *Surv Ophthalmol* 2006;51:232–258.
18. Leibu R, Jermans A, Hatim G, et al. Hypotrichosis with juvenile macular dystrophy: clinical and electrophysiological assessment of visual function. *Ophthalmology* 2006;113:841,7.e3.
19. Mason JO 3rd, Patel SA. A case of hypotrichosis with juvenile macular dystrophy. *Retin Cases Brief Rep* 2015;9:164–167.
20. De Paul AL, Bonaterra M, Soler AP, et al. Soluble P-cadherin found in human semen. *J Androl* 2005;26:44–47.
21. Vazquez-Levin MH, Marín-Briggiler CI, Caballero JN, et al. Epithelial and neural cadherin expression in the mammalian reproductive tract and gametes and their participation in fertilization-related events. *Dev Biol* 2015;401:2–16.