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PITPNM3 is an uncommon cause of cone and cone-rod dystrophies

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Abstract

The first mutation in *PITPNM3*, a human homologue of the *Drosophila* retinal degeneration (*rdgB*¬¬) gene was reported in two large Swedish families with autosomal dominant cone dystrophy. To establish the global impact that *PITPNM3* has on retinal degenerations we screened 163 patients from Denmark, Germany, the UK, and USA. Four sequence variants, two missence mutations and two intronic changes were identified in the screen. Thus, mutations in *PITPNM3* do not appear to be a major cause of cone or cone-rod dystrophy.

Keywords

PITPNM3; mutation; cone dystrophy

The cone (COD) and cone-rod dystrophies (CORD) are a genetically and clinically heterogeneous group of retinal disorders characterized by reduced central vision, defective colour vision and photoaversion. These disorders can be inherited in an autosomal recessive, autosomal dominant or X-linked manner with reported mutations in at least 22 genes including *ABCA4*,[1] *AIPL1*,[2] *CRX*,[3] *GUCA1A*,[4]*GUCY2D*,[5] *PITPNM3*,[6] *RIM1*,[7] and *RPGR*.[8]

In 2007 we reported the first mutation in *PITPNM3*, a human homologue of the *Drosophila* retinal degeneration (*rdgB*) gene in two large Swedish families with autosomal dominant COD.[6] The Swedish patients were found to have a p.Q626H mutation in an evolutionarily

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conserved region in the C-terminal part of PITPNM3. The *Drosophila* rdgB protein is highly expressed in the retina and has been proposed to be required for membrane turnover of photoreceptor cells.[9] Immunoblot experiments showed strong expression of PITPNM3 in rat retina,[10] though human PITPNM3 has so far only been shown to be expressed in brain, spleen, and ovary.[10]

Eleven additional COD patients from Sweden were screened for mutations in *PITPNM3* but no other mutations were detected. With the intention of establishing the global impact that *PITPNM3* has on retinal degenerations, we obtained DNA samples, through collaboration with research groups in Denmark, Germany, the UK, and USA. In the following mutation screen 163 samples were analyzed. Of these were 71 autosomal dominant CORD, 37 autosomal dominant COD, 24 sporadic CORD, and one case was sporadic COD. Thirty patients had various retinal degenerative diagnoses including macular dystrophy, Stargardt disease, central areolar choroidal dystrophy, and pattern dystrophy. The samples were screened by DNA sequencing (Applied Biosystems) as previously described[6] and dHPLC (denaturing high performance liquid chromatography) (Transgenomic) as described by Köhn,[6] using primers from the DNA sequencing. The results are summarized in Table 1.

The p.Q626H mutation found in the Swedish families was also detected in one British family where the mother and daughter presented with macular dystrophy. One additional sequence variation resulting in an amino acid substitution was found in a German patient with autosomal dominant cone dystrophy. A glutamine residue is exchanged for a proline at position 342 in the protein (p.Q342P). Unfortunately there were no family samples available for segregation analysis, but Q342P was absent in 100 matched controls. This substitution is predicted not to be tolerated by SIFT (Sorting Intolerant from Tolerant [http://sift.jcvi.org]) probably because this position is highly conserved in vertebrates. Two intronic sequence variants, c.900 + 60G>T and c.901-45G>A, were also discovered in intron 8 in patients with CORD, see Table 1. None of these are located in any constitutive splice acceptor or donor site but may activate a cryptic splice site. The c.901-45G>A substitution was found in a North American patient but was absent in the patient's unaffected sister and in an unaffected niece. All of the variants except c.900 + 60C>T were screened for but not detected in matched control materials. The c.900 + 60C>T variant was not found among Swedish controls, though it has not been was screened for in the British population. Absence of these variants in matched controls implies that they are disease causing however functional data are necessary to establish if they are truly pathogenic. We conclude from these results that mutations in *PITPNM3* do not appear to be a major cause of cone or cone–rod dystrophy.

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TABLE 1

PITPNM3 mutation screening in 163 patients

Exon	Nucleotide substitution	Amino acid substitution	Patients	Frequency in matchedcontrols
IVS 8	c.900 + 60C>T		1 British CORD	not screened in British population 0/95[1] in Swedish population
IVS 8	c.901-45G>A		1 North American CORD	0/93[1]
9	c.1025A>C	Gln342Pro	1 German COD	0/100[1]
14	c.1878G>C	Gln626His	2 British MD	0/120[1]

CORD – cone-rod dystrophy, COD – cone dystrophy, MD – macular dystrophy.

[1] numbers represent individuals.