Tietz syndrome (hypopigmentation/deafness) caused by mutation of MITF

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Abstract

Patients with Tietz syndrome have congenital profound deafness and generalised hypopigmentation, inherited in a fully penetrant autosomal dominant fashion. The pigmentary features and complete penetrance make this syndrome distinct among syndromes with pigmentary anomalies and deafness, which characteristically have patchy depigmentation and variable penetrance. Only one family has been reported with the exact features described in the original report of this syndrome. This family was reascertained and a missense mutation was found in the basic region of the MITF gene in family members with Tietz syndrome. Mutations in other regions of this gene have been found to produce Waardenburg syndrome type 2 (WS2), which also includes pigmentary changes and hearing loss, but in contrast to Tietz syndrome, depigmentation is patchy and hearing loss is variable in WS2.

In 1963, Tietz described an autosomal dominant syndrome of hypopigmentation and deafness in a large three generation family (MIM 103500). There were no further reports of this syndrome, and Reed et al suggested the cosegregation of the two features had been coincidental in that family.

We were contacted by a family who suspected they had a unique form of deafness, and they wanted to know if there were any other families with similar findings. In particular, they wanted to locate a branch of their family which had become separated in the mid 1800s.

This family has traced their ancestry in the USA to North Carolina in the mid 1700s and believe the founder in the USA emigrated from Derry, Ireland. They described themselves as having profound congenital deafness along with blonde hair and white eyelashes and eyebrows, transmitted through at least seven generations. Review of published reports and comparison with the pedigree information provided by the family indicated that this was a separate branch of the same family reported by Tietz (fig 1).

Eleven family members were personally examined and audiograms were obtained on all of them. Six of these 11 family members had more extensive tests at Boys Town National...
The gene MITF (microphthalmia associated transcription factor) is known to be in this region, and mutations of this gene can produce the Waardenburg syndrome type 2 phenotype. Heteroduplex analysis was used for mutation detection in MITF, with direct sequencing to define the mutations. This detected sequence variations in affected subjects in intron 5 and exon 6. The PCR amplimer from exon 5 and adjacent intron sequence included a change of a C to G at nucleotide +9 in the 5' end of intron 5. This places the mutation out of the 5' splice consensus region, so that it should not have an effect on the normal maturation of the mRNA.

In exon 6, affected subjects were heterozygous for a G to C point mutation at nucleotide 600. This would result in substitution of lysine for asparagine (Asn210Lys) in the mutant protein. This suggests vestibular dysfunction, as adults with white eyebrows and eyelashes may have reddish freckles and some subjects reported they can even tan slightly with very careful exposure to sun.

All affected subjects have blue eyes and ophthalmological examination showed hypopigmented fundi, but there is no nystagmus or other visual problems and no heterochromia irides. Hearing loss is always bilateral, congenital, polar amino acid, while lysine is basic. This basic portion of the molecule is involved in dimerisation with itself or other proteins and the helix-loop-helix and zipper motifs stabilise dimerisation with itself or other proteins in the same subfamily. The change in exon 6 of MITF in this family would produce a substitution of lysine for asparagine in the basic region of the transcribed protein. Asparagine is a neutral, polar amino acid, while lysine is basic. Since the basic region of the MITF protein is important for binding to the major groove of DNA, these changes in size and charge would be predicted to interfere with that function. In the heterozygote, the mutant MITF protein would be expected to dimerise effectively with itself or with a normal allele product; however, the resulting dimer would bind to DNA poorly, so the overall effect of the mutation should be dominant negative. In contrast, mutations of MITF that produce WS2 either truncate the product or affect its dimerisation by disrupting the helix-loop-helix or zipper motifs. As shown by in vitro studies of WS2 mutations in the heterozygous state, these mutations do not interfere with the product of the normal allele, which is still free to form a normally functioning protein. Thus, the mechanism for WS2 appears to be through haploinsufficiency. MITF is homologous to the Mitf (mi) gene in the mouse. Mutations of this gene produce a range of phenotypes including white spotting or pigmentary dilution, inner ear abnormalities, bone resorption problems, and small
eyes. In mice, there are three mi mutations in the basic region which are inherited in a semi-
dominant fashion, mi, Mitf-M, and Mitf. The mi mutation is analogous to the arginine deletion
seen in the family with Tietz syndrome reported by Tassabehji et al and Amiel et al and
the other two mutations each involve either an asparagine (Mitf-M, Ile212Asn) or a lysine
(Mitf-M, Arg216Lys), indicating that changes involving these amino acids in this critical
region have a functional effect. These mutations are felt to act in a dominant negative
fashion and produce both dilution of pigmentation and spotting in the heterozygote. A
fourth mutation, Mitf-M, deletes much of the basic region and also acts as a dominant negative in
vitro; however, the phenotype is recessively inherited. It is possible that the defective
protein is unable to enter the nucleus and does not dimerise, in effect eliminating the domi-
nant negative action. Mutations in other regions in the mouse gene are recessive, with
normal regions in the heterozygote despite the reduced levels of functional protein. This is
an interesting contrast to the dominant inheritance of WS2, indicating that at least certain
tissues in humans (the stria vascularis, irides, and forelock region, for example) are more
sensitive to reduced levels of the MITF protein. This sensitivity to amount of protein has also been seen in the hamster. The Wh (anophthalmic white) mutation of the
mitf gene in the Syrian hamster has been reported to produce a white bellied phenotype with
inner ear deafness. The mutation is the result of a point mutation which
truncates the protein in the loop region, interfering with dimerisation. Thus, this mutation
appears to act through haploinsufficiency in the heterozygote.

Yajima et al have called attention to a novel type of mutation in their description of the
Mitf(bw) mouse, which is white with black eyes and has severe hearing loss. This phenotype
was found to be the result of an insertion of an L1 retrotransposable element in intron 3. This
resulted in the decrease in production of two Mitf isoforms, Mitf-A and Mitf-H, and absence of
a third isoform, Mitf-M. These isoforms differ in the inclusion of amino acids 5' to exon 2,
and have different tissue distributions, with Mitf-A increased in the retinal pigment epithe-
lium (RPE), Mitf-H predominant in the heart, and Mitf-M increased in melanocytes. Since
the RPE is normal in the Tietz syndrome reported by Tassabehji et al and Amiel et al and
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