The Boon Becomes the Bane: The Ballad of the Blue-eyed Boy

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Beauty lies in the eyes of the beholder. However, beauty can also literally be due to a person's eyes, especially the eye colour. In South India, the population generally has black-coloured irises and hence, a different hue, especially blue or green, is a matter of great pride and wonder. However, even something as innocuous as a different colour of the iris can herald an underlying genetic syndrome which might affect future generations to come, as illustrated by this report.

The proband, a 3-month-old male child, the first child of a non-consanguineous marriage, was born at term with a birth weight of 2.9 kg. At birth he was noticed to have a white forelock of hair, a depigmented patch on the forehead and brilliant blue irises of both eyes. He was admitted in the neonatal intensive care unit (NICU) for 3 days in view of mild respiratory distress which resolved. He did not pass his preliminary otoacoustic emissions (OAE) test, and brainstem evoked response audiometry (BERA) and auditory steady-state response (ASSR) tests which were done further were suggestive of bilateral profound sensorineural hearing loss. Since his features were phenotypically suggestive of Waardenburg syndrome, genetic testing was planned for confirmation of the diagnosis. Clinical exome sequencing unveiled a heterozygous nonsense variant c.667C>T (p.Arg223Ter) in exon 5 of the *PAX3* gene (NM_181457), which is classified as a 'pathogenic' variant as per the American College of Medical Genetics and Genomics/ Association for Molecular Pathology (ACMG/AMP)criteria, confirming the diagnosis of Waardenburg syndrome type 1. This variant is predicted to cause loss of normal protein function through protein truncation. Loss-of-function variants in *PAX3* are known to be pathogenic (Wildhardt et al., 2013). Parental segregation analysis showed that the father had the same heterozygous mutation, and the mother did not have it.

Pedigree analysis of the family (**Figure 1**) reflects the high degree of variability in the clinical phenotype caused by the mutation in the family. The first known affected member in the family was the proband's great grandmother with history of premature greying of hair and blue eyes. She had seven children of whom two children were unaffected and four had blue eyes with early greying of hair. The proband's grandfather had only premature greying. It was interesting to note that the grandfather had premature greying, the father additionally had blue eyes and the proband had all the classical features of Waardenburg Syndrome. Since many family members had blue eyes without any other features it was considered a matter of pride within the family; they considered themselves to be unique. However, it was only after the birth of the proband with a white forelock and hearing loss, that the family realized that there were probable repercussions to bear along with the beauty of blue eyes! The child is on hearing aids at present and cochlear implant is being planned. The parents and rest of the family are now concerned about blue-eyed children and genetic counselling has been advised to all members of the family.

Waardenburg syndrome (WS) is a group of genetic conditions that can cause hearing loss and changes in coloring (pigmentation) of the hair, skin, and eyes. The hearing loss in WS1, observed in approximately 60% of affected individuals, is congenital, typically non-progressive, either unilateral or bilateral, and sensorineural. Most commonly, hearing loss in WS1 is bilateral and profound (>100 dB). Majority of individuals with WS1 have either a white forelock or early greying of the scalp hair before the age of 30 years. The classic white forelock observed in approximately 45% of individuals is the most common hair pigmentation anomaly seen in WS1.

In this family reported here, multiple

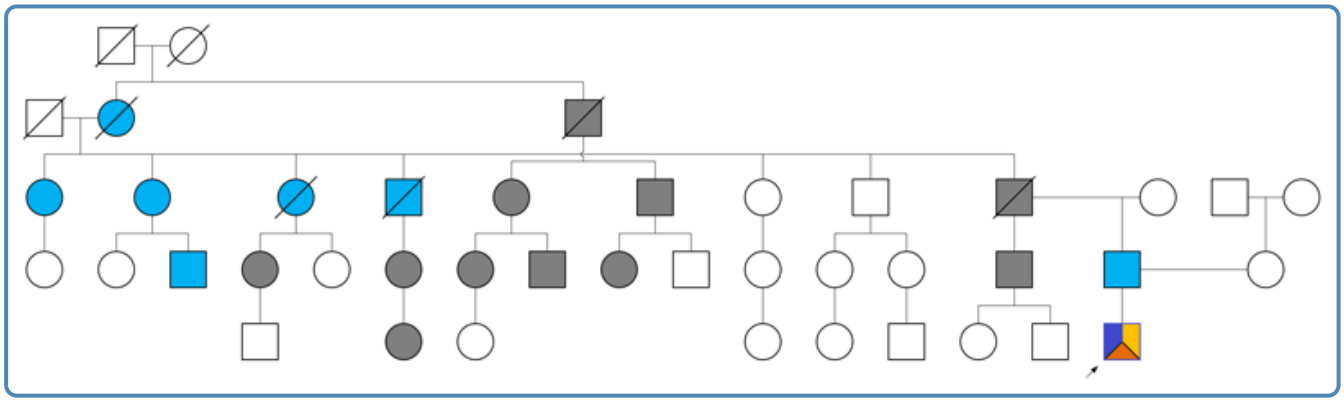

Figure 1 Five-generation pedigree of the family showing multiple affected members of the family with variable expressivity of the disorder.
Light blue shading represents affected members with blue irises and premature greying.
Grey shading represents affected members with only premature greying of hair.
Dark blue shading represents blue irises.
Yellow shading represents white forelock of hair.
Orange shading represents sensorineural hearing loss.

generations of the family had individuals with blue irises with or without other classical features of Waardenburg Syndrome. However, until the proband was born, there was no member of the family with a white forelock or hearing loss and hence, the members of the family were never seen from a genetic angle for many generations. This case illustrates the variable expressivity of a novel mutation in Waardenburg Syndrome type 1 and its implications in a family over multiple generations.

Waardenburg syndrome is notorious for variable expression and hence, can go undetected in multiple generations of a family if hearing loss or significant hypopigmentation is not present. Therefore, even if a person with blue eyes/ heterochromia irises comes to a clinic for an unrelated issue, it would be beneficial to ask a family history of premature greying, hearing loss, and/or hypopigmentation. It can be useful in picking up a hidden syndrome with more ominous symptoms.