

PAX3

Human Disease Association

Waardenburg Syndrome Type 1 and 3 (WS1, WS3): Over 90% of individuals with WS1 or WS3 have been shown to have mutations or deletions in *PAX3* ([Milunsky et al., 2007](#)). WS1 individuals display the phenotypes of dystopia canthorum (abnormal placement of the inner canthus of the eye, leading to a wide nasal bridge), high nasal root, synophrys, hypopigmentation (most often manifested as a white patch of hair at the forehead or leukoderma), heterochromia irides, hypoplastic blue eyes, early graying, and sensorineural deafness due to abnormal development of cochlear melanocytes. Two independent studies used genomic sequence analysis of *PAX3* in WS1 patients to demonstrate that *PAX3* mutations are associated with the disease, and that the Splotch mouse mutant models WS1 ([Baldwin et al., 1992](#), [Tassabehji et al., 1992](#)). The report of a phenotypically WS2 family with a *PAX3* mutation reflected heterogeneity of dystopia canthorum ([Tassabehji et al., 1993](#), [Tassabehji et al., 1992](#)); subsequent analysis reclassified this family as WS1 ([Read and Newton, 1997](#)).

Linkage analysis confirmed 100% linkage of *PAX3* with WS1 ([Farrer et al., 1994](#)).

Gel shift assays indicated that *PAX3* mutations associated with WS show impaired DNA binding ([Chalepakis et al., 1994a](#)).

PAX3 mutations associated with WS1 appear to affect protein function differently, as different mutations have varied effects on the promoters of *TRP1* and *MITF*. *PAX3* utilizes both the paired domain and homeodomain to bind to the *MITF* promoter with high affinity, even though the binding sites for both domains are non-canonical and independently show low affinity (ie. the two domains must be within the same protein to bind). In contrast, *PAX3* utilizes only the paired domain to bind the *TRP1* promoter with a more moderate affinity. *PAX3* mutations associated with WS showed disparity in their actions on the two promoters; for example, the same mutation (G48A) showed no change in *TRP1* promoter binding but an increase in *MITF* promoter binding ([Corry and Underhill, 2005](#)).

WS3, also known as Klein-Waardenburg Syndrome, occurs less frequently than WS1 and shows WS I phenotypes in combination with upper limb abnormalities including hypoplasia and/or contractures of limb muscles or joints, syndactyly, or carpal bone fusion. WS3 can be caused by heterozygous or homozygous *PAX3* mutations. **WS3 can be considered an extreme subtype of WS1**, in which *PAX3* levels have fallen below a threshold at which upper limb abnormalities arise, or, in the case of heterozygous *PAX3* mutations, dominant-negative *PAX3* proteins result. The first WS3 individual identified as a *PAX3* homozygote carried a missense mutation (S84F), and survived into early infancy, displaying nearly complete absence of pigmentation, severe upper limb defects, and a severe liver disorder ([Zlotogora et al., 1995](#)). Subsequent genotyping of additional WS3 individuals, including the individual originally identified with Klein-Waardenburg syndrome, showed homozygosity or compound heterozygosity for *PAX3* mutations ([Read and Newton, 1997](#), [Wollnik et al., 2003](#)). One fetus born to parents who both had WS1 displayed severe limb abnormalities, exencephaly, and additional developmental defects; although no mutations were identified by partial analysis of the *PAX3* locus by SSCP, the authors hypothesized that this fetus carried two *PAX3* mutations ([Ayme and Philip, 1995](#)). Three cases of WS3 individuals carrying heterozygous mutations within the *PAX3* paired domain or homeodomain have been described, all displaying milder phenotypes than those of homozygous *PAX3* individuals ([Hoth et al., 1993](#), [Tassabehji et al., 1995](#), [Tekin et al., 2001](#)). The authors suggest dominant negative effects or modifier effects-possibly from other mutations in genes regulating melanocyte development segregating within these families-could cause the increased severity of phenotypes associated with these mutations as compared with WS1-associated heterozygous mutations of *PAX3*.

Craniofacial-deafness-hand syndrome (CDHS): The initial CDHS description was derived from mother and infant daughter, who presented phenotypes of flat facies, hypertelorism, reduced or absent nasal bones, small

nose with thin nares, sensorineural deafness, and ulnar finger abnormalities (Sommer et al., 1983). Sequence analysis of this family, which subsequently included another affected son, found a *PAX3* missense mutation (Asn47Lys) associated with CDHS. A previously described mutation at this residue (Asn47His) has been seen in WS3 (Hoth et al., 1993), suggesting that Lys or His substitutions at residue 47 cause distinct or more severe changes in *PAX3* protein function, possibly through dominant negative effects (Asher et al., 1996b). A follow up study reported an additional CDHS-associated anomaly of nasolacrimal system defects (Sommer and Bartholomew, 2003).

Alveolar rhabdomyosarcoma: A translocation fusing the genomic region that encodes both the paired box and homeodomain of *PAX3* with the region encoding the carboxyl-terminus of the transcription factor *FOXO1A* results in an oncogenic fusion protein (*PAX3-FKHR*). This translocation is seen in the majority of cases of alveolar RMS, a malignant pediatric cancer derived from developing skeletal muscle (Barr et al., 1993, Galili et al., 1993, Shapiro et al., 1993).