

# Notch Mutations

There are at least four homologues of the *Notch* gene in humans, but *Notch3* is the only protein that appears to have naturally occurring mutations in the human population. Notch proteins can use several ligands, and mutations of some of these ligands have been found.

## Mutations in the Receptor Protein, Notch

### ***Notch-1***

*Notch-1* is critically important and there are no human mutations known in this gene. Indeed, there do not seem to be any known mutations of Notch 2 or 4, either. Mice made homozygous for loss-of-function alleles of *Notch-1* die between embryonic day 10 and 12, and no homozygous embryos were recovered past embryonic day 12 (Conlon et al., 1995; Huppert et al., 2000).

### ***Notch-3***

Mutations of *Notch-3* in humans causes the CADASIL syndrome. This syndrome is characterized by Cerebral Autosomal Aominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy. It involves a type of stroke and dementia of which key features include recurrent subcortical ischemic events and vascular dementia associated with diffuse white-matter abnormalities. CASADIL is hereditary, but not congenital (at birth). Rather, it is a disease whose onset isn't until adult life. Joutel and colleagues (1996, 1997, 2000) were able to map the gene to a small interval of chromosome 19 and then show that the gene for *Notch-3* fell in this region. A panel of 58 unrelated patients were then checked for point mutations of the *Notch-3* gene. Mutations were discovered in these genes and were found to segregate with the presence of the syndrome in families.

## Notch Ligand

### ***Jagged-1***

*Jagged-1* is a ligand for the *Notch-1* protein. Mutations of this gene in humans produce the Alagille Syndrome, consisting of liver anomalies, prominent forehead, pointed chin, defects in retinal pigmentation, heart valve abnormalities, and abnormal "butterfly" vertebrae (Li et al., 1997; Oda et al, 1997).

### ***Jagged-2***

Jiang et al. (1998) examined the in vivo role of the *Jag2* gene by making a targeted mutation that removed a domain of the *Jagged-2* protein required for receptor interaction. Mice homozygous for this deletion died perinatally because of defects in craniofacial morphogenesis. The mutant homozygotes exhibited cleft palate and fusion of the tongue with the palatal shelves. They also exhibited syndactyly of the fore- and hindlimbs. Mutant homozygotes also displayed defects in thymic development and impaired differentiation of T cells. These results demonstrated that Notch signaling, mediated by *Jag2*, plays an essential role during limb, craniofacial, and thymic development in mice. No human mutations of this gene have been found.

## Delta

Mutations of the Delta-Like Ligand-3 gene in humans causes autosomal recessive spondylocostal dysostosis (SCDO; Bulman et al., 2000). This syndrome has characteristic vertebral anomalies, including hemivertebrae and block vertebrae accompanied by deformity of the ribs. Affected children have difficulty breathing and often die of respiratory infections under 1 year of age. Using homology of synteny and linkage data suggesting that the SCDO locus is on chromosome 19q13.1-q13.3 and that a mouse region containing the Notch ligand delta-like-3 gene is mutated in the mouse mutant 'pudgy,' causing a variety of vertebral and rib defects similar to the SCDO phenotype, Bulman and colleagues (2000) cloned and sequenced human DLL3 to evaluate it as a candidate gene for SCDO. They identified mutations in 3 autosomal recessive SCDO families. These mutations in a human delta homologue highlight the critical role of the Notch signaling pathway and its components in patterning the mammalian axial skeleton.

## Literature Cited

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