Deafness Genes

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About 1 in 1,000 children are born deaf, and another 1 in 1,000 develop deafness by adolescence. Although some deafness can arise during development due to external sources, much deafness in children is due to mutations in specific genes. As many forms of deafness are nonsyndromic—there is no other associated abnormality—identification of the responsible genes can lead to characterization of proteins that are essential for the auditory system, and often for the vestibular system, too.

The genes responsible for □90 recessive and □60 dominant nonsyndromic deafness syndromes have been identified in humans (http://hereditaryhearingloss.org), and similar numbers have been identified in mice (Dror & Avraham, 2010). Moreover, a dozen or so syndromes with deafness—associated with other phenotypic abnormalities besides deafness—have also been identified. Some genes are associated with both recessive and dominant deafness, and others are associated with both syndromic and nonsyndromic deafness. Because most genes identified in humans have also been identified in mice, this tally corresponds to about 200 different genes, although the total number of genes associated with deafness may be as large as 500 to 1000.

The deafness syndrome most common in humans, DFNB1, can be caused by mutations in either of two gap-junction connexin genes that are tightly associated on chromosome 13, *GJB2* (connexin 26) and *GJB6* (connexin 30). These connexins play a critical role in establishment of a gap-junction network in supporting cells of the cochlea, which is thought to be important for recycling K+ ions that enter (and leave) hair cells during transduction (Nickel & Forge, 2008).

About one-third of the genes responsible for nonsyndromic deafness encode proteins that

are expressed in stereocilia. Some of these encode structural proteins of the stereocilia (e.g., gamma-actin, TRIOBP and radixin); others encode proteins that regulate the actin cytoskeleton (e.g., myosin-3a, myosin-15a and espin). Additional genes encode proteins that are expressed in stereocilia but have unknown function (e.g., GRXCR1).

Usher syndrome is a deafness–blindness syndrome that is caused by mutations in a number of genes that are essential for stereocilia development and function. Usher syndrome is divided into three classes depending on the severity of the phenotype. Usher I produces profound deafness and vestibular dysfunction, as well as adolescent blindness; in Usher II, deafness is less profound. Usher III is less common; in these patients, hearing and vision loss develop progressively, and vestibular dysfunction is variable.

Of the seven mapped genes underlying Usher type I, five have been identified: *CDH23*, *PCDH15*, *MYO7A*, *USH1C* (harmonin) and *SANS*. Biochemical evidence and phenotypic similarity suggests that these proteins may assemble into a complex (Adato et al., 2005; Lefevre et al., 2008), although conclusive evidence for such a complex is lacking. Moreover, all of these proteins are important for both hair-bundle development and mechanotransduction, suggesting an intimate relationship between the two processes. Usher type II is caused by mutations in at least four genes, three of which—*USH2A*, *GPR98* and *WHRN*—have been identified. The products of the *USH2A* and *GPR98* genes, usherin and the very large G-protein–coupled receptor 1, are large transmembrane proteins that may make up the ankle links, links that interconnect stereocilia at their bases. Whirlin, the product of the WHRN gene, is a scaffolding protein that has been implicated in the control of stereocilia actin dynamics. One gene responsible for Usher type III is *CLRN1*; clarin-1 is a four-transmembrane-domain protein that plays a role in stereocilia development (Yan & Liu, 2010).

Understandably, disruption of hair-cell function at many levels can lead to deafness, so it is expected that deafness genes include those involved in inner-ear development, in ion balance in the endolymph, and in structural integrity of hair cells. However, the deafness-gene approach has not been successful in identifying some constituents of the transduction apparatus, most notably the transduction channel. This is a surprising observation, as the genetic approach relies on few assumptions about the nature of the systems studied. Perhaps the lesson here is that some of the important molecules for transduction play essential roles elsewhere in the organism during development, a sobering observation for those relying exclusively on deafness-gene identification to reconstruct the transduction apparatus of hair cells.

References

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