Genetics of Congenital Deafness

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From 10 to 26 per cent of cases with hearing loss are known to be congenital, that is, present at birth or by early childhood; approximately 52 per cent of these are genetically caused. Although these include rare instances of conductive hearing loss consequent to osseous malformations of the middle ear (such as in branchial arch syndrome), the term congenital deafness in this article refers only to profound, sensorineural hearing loss that is irreversible and bilateral. Estimates of the incidence of genetic congenital deafness in Great Britain, Japan, Germany, and the USA are 1 in 2000 to 1 in 6000 live births.

Some General Principles of Genetics

A specific gene can be inherited from the previous generation or can arise de novo in an individual owing to spontaneous mutation (in the latter, no prior family history of the gene would be likely). Such new mutations can be passed on to the next generation. Specific genes, then, may not always be inherited, but they are heritable. The genetic makeup of an individual is the genotype, the effect of which is the phenotype. The genes are distributed among 23 pairs of chromosomes. One pair of chromosomes, the X and Y, contain some genes determining primary sex differentiation. Females have 2 X chromosomes; males have one X and one Y chromosome. The remaining 22 pairs of chromosomes are the autosomes. Since chromosomes exist in pairs, all genes exist in pairs except those on the X and Y chromosome in males. The X and Y chromosomes are not similar (homologous) genetically or morphologically. A particular gene at each gene locus can exist in several slightly different molecular forms called alleles. Respecting any one pair of genes, the alleles can be identical (homozygous) or not (heterozygous). By the reproductive process (meiosis), one member of each gene pair is passed on from each parent to its offspring.

Autosomal Inheritance

Consider a single pair of genes on an autosome where there are two possible alleles: A and a. Then, respecting this gene pair, an individual can have one of three possible genotypes: AA, Aa, or aa. Suppose that the phenotype AA and Aa are both designated "A" (that is, identical) while the phenotype of aa (designated "a") is different. Then, the effect of allele A dominates that of allele a (the latter is said to be recessive, that is, its phenotype is seen only when homozygous). Respecting such a "simple mendelian trait", there are six possible matings in the population.

First, assume that the dominant allele, A, causes congenital deafness and that the recessive allele, a, results in normal hearing. Then all the offspring of matings type 1, 2, and 3 would be deaf. However, in human beings one rarely finds homozygotes for abnormal autosomal dominant genes (AA in this illustration). Probably such genotypes are lethal to the fetus in utero. Consequently, respecting autosomal dominant deafness, one can assume with confidence that the genotype is heterozygous (Aa), and that the only possible mating types are 4, 5, and 6. Deaf offspring would result only from mating types 4 and 5. The relative

frequency of the three mating types will depend on the frequencies of alleles A and a in the population and the randomness of the matings. For deafness, mating is not random, since about 85 to 90 per cent of congenitally deaf individuals have a congenitally deaf mate. Consequently, mating type 4 would be over-represented compared to a randomly mating population. However, the observed ratio of the phenotype "A" (deaf) to "a" (normal hearig) in offspring from mating type 4 would be 2:1 rather than 3:1 since AA fetuses would not be born. The risk of deaf offspring for mating type 5 would be 50 per cent at each conception.

Next, consider the reverse situation in which the dominant allele, A, causes normal hearing while the recessive allele, a, causes congenital deafness. In this situation, all six mating types are possible but deaf offspring would result only from mating types 4, 5, and 6. Mating type 6 would produce only deaf offspring while the risk of deaf offspring at each conception from mating types 4 and 5 would be 25 per cent and 50 per cent respectively. However, again the frequency of mating type 6 would be over-represented in the population since the congenitally deaf tend to marry each other.

X-linked Inheritance

Since genes on the X chromosome have no mate on the Y chromosome, all X-linked genes act as dominants in the male, that is, they express themselves in the phenotype. In the XX female, however, X-linked genes are all paired just as autosomal genes are all paired. Consequently, only in the female can X-linked genes act as dominants or recessives. The hallmark of X-linked inheritance is that a male cannot pass his X-linked genes on to his sons since a male gives only his Y chromosome to his sons. Conversely, a male passes all his X-linked genes on to his daughters to whom he gives his one X chromosome.

Consider an X-linked gene with two possible alleles, D and d, where D is dominant and produces normal hearing and d is recessive and produces congenital deafness (remember, the alternatives dominant and recessive here apply only to the female). Note that none of these three mating types produces deaf daughters and only mating type 3 would produce deaf (X^dY) sons (50 per cent risk at each male conception).

More Complex Matings

The genetic etiology of congenital deafness is quite heterogeneous. Five or six distinct autosomal recessive traits (such as Pendred and Usher syndromes) account for about 3 per cent of congenital deafness and probably many more rare traits, a few of which may be found in any particular deaf population. Each deafness trait presumably results from homozygosity of an abnormal recessive allele at a different specific gene locus. Likewise, there are several distinct X-linked recessive and autosomal (and possibly X-linked) dominant genes that can result in congenital deafness. Any one individual, then, can bear genes for deafness at several different gene loci which can result in complex mating types. Numerous other complex matings are possible. Of the three examples, type 1 is the most common. This is fortunate since the mating does not result in deaf offspring. Mating types 2 and 3 are more rare but are frequent enough to be considered in genetic counseling, particularly if there is consanguinity. Matings type 2 and 3 illustrate "pseudodominance", that is, although each deafness results from homozygosity of a specific autosomal *recessive* gene, the risk for deaf offspring from the matings is 50 per cent at each conception - the same risk as for an autosomal dominant

gene for deafness (the risk of deafness is 50 per cent whether caused by the recessive allele, a, or the dominant allele, A).

Genetic Syndromes With Congenital Deafness

Fraser found about 50 per cent of cases of congenital deafness to be genetically determined. Autosomal recessive inheritance was the most common (33 per cent), autosomal dominant inheritance was next (15 per cent), and X-linked recessive inheritance was rarest (about 2 per cent). Among Fraser's autosomal recessive cases, the single most common diagnosis was "clinically undifferentiated" (26 per cent); next were Pendred syndrome, deafness with goiter (5 per cent); Usher syndrome, deafness with retinitis pigmentosa (1.2 per cent); and cardioauditory syndrome of Jervell and Lange-Nielsen (0.5 per cent). The remaining 0.3 per cent of autosomal recessive cases consisted of congenital deafness as part of various rare syndromes of congenital abnormalities.

Among the autosomal dominant cases, again the single most common diagnosis was "clinically undifferentiated" (11 per cent). Auditory pigmentary syndromes, such as Waardenburg syndrome, were next most common (4 per cent). Rare entities, such as Alport Syndrome (deafness with nephritis) or deafness with earpits or with optic atrophy, comprised less than 1 per cent of the cases.

All of the 2 per cent of X-linked recessive cases of congenital deafness were diagnosed as clinically undifferentiated. However, congenital deafness is associated with well known X-linked recessive syndromes such as cutaneous albinism. About 0.6 per cent of the congenitally deaf in Fraser's survey (1.2 per cent of the girls) were diagnosed as Wildervanck's syndrome (congenital deafness with abducens palsy, retraction of eyeball, and Klippel-Feil deformity) and female. The genetic etiology of this condition is probably heterogeneous.

Genetic Counseling

Genetic counseling for congenital deafness must be a team effort including, among others, primary care physicians, otolaryngologists, audiologists, and geneticists. Precise genetic counseling is facilitated most by a specific diagnosis and a detailed family history; both often depend most on the efforts of others prior to the formal genetic consultation. For example, if the geneticist sees a deaf couple who both have Usher syndrome, the couple can be counseled with confidence that there is a 100 per cent risk for deaf children. On the other hand, if the diagnosis for one deaf spouse is Usher syndrome and for the other is Pendred syndrome, the couple can be advised with confidence that their risk for a congenitally deaf child is about the same as that of the general population, less than 1 in 1000. Unfortunately, for about 40 per cent of individuals the diagnosis is congenital deafness, clinically undifferenitated, genetically determined (the latter often being decided only by exclusion). Approaches to genetic counseling for these individuals can be illustrated by looking at three different types of matings: when congenital deafness is found in both spouses, only one spouse, or neither spouse.

Both Spouses Congenitally Deaf

This is the most common situation since approximately 85 per cent of congenitally deaf persons marry each other. The risk of these couples for congenitally deaf children ranges from that of the general population to 100 per cent. This range can be narroed if there are offspring whose hearing status is known; but aside from eliminating the extremes, the range of the risk may still remain broad in any one particular case. Fraser estimates that the chance of both spouses being autosomal recessive homozygotes at the same gene locus (mating type 6 with 100 per cent risk for deaf children) is less than 2 to 3 per cent. However, the chance of this increases significantly if the spouses are consanguineous or if both come from a small isolated population which harbors a particular form of autosomal recessive deafness (such as the Jews of Britain).

Even when the deafness is clinically undifferentiated, the family pedigree may provide sufficient information for precise genetic counseling. Evidence for autosomal dominant or X-linked recessive inheritance of the deafness should be searched for carefully. Unfortunately, lack of such evidence does not completely eliminate these possibilities since one deaf partner or the other could represent a new mutation for deafness. Fraser found among clinically undifferentiated deaf persons, new mutants in 10/22 X-linked recessive cases and 127/143 autosomal dominant cases. Another complication is that dominant genes do not always express themselves when present (penetrate), that is, actually produce their phenotype in the heterozygote. The average penetrance of dominant genes for clinically undifferentiated congenital deafness is about 67 per cent; that is, if an individual has the gene, the chance of that individual being congenitally deaf is only 67 per cent, not 100 per cent. Another complication in pedigree analysis is the phenomenon of "pseudodominance".

It should be clear that genetic counseling of a clinically undifferentiated deaf couple often cannot be precise in regard to risk, and the couple should understand that reality. When precise risk calculations are not feasible, empirical risks can be helpful. According to Fraser, the average empirical risk for a clinically undifferentiated congenitally deaf, nonconsanguineous couple having a congenitally deaf child is 10 per cent.

One Spouse Congenitally Deaf

In this less common situation, the risk for a congenitally deaf child ranges from that of the general population to 50 per cent. If the family history is not informative and the deafness of the spouse is clinically undifferentiated, the genetic counseling again is difficult and imprecise. If the deafness is autosomal dominant, the couple's risk for a deaf child still may be less than 50 per cent owing to low penetrance. If the deafness is autosomal recessive, the risk still may be more than that of the general population because of pseudodominance (mating type 3). However, in the absence of consanguinity the incidence of pseudodominance in such matings is only about 1 per cent. If the husband is the deaf spouse, X-linked recessive inheritance must be considered as a cause, although it is less likely than autosomal dominance or recessiveness. If X-linked recessive, however, the increased risk for deaf children would not be for the couple but rather for their daughter's sons (mating 2 and 3). All in all, this couple's empirical risk for a deaf child is about 5 per cent. Their recurrent risk (the risk subsequent to the birth of a deaf child), however, would approach 50 per cent at each conception depending on penetrance.

Neither Spouse Congenitally Deaf

In most instances, these couples seek genetic counseling after the birth of a congenitally deaf child. If the congenital deafness is clinically undifferentiated and there is no informative family history, the risk of recurrence ranges from that of the general population to about 25 per cent. The lower extreme would apply if the child's deafness resulted from a new dominant mutation. The upper extreme would represent recessive inheritance (mating type 4 or, if the deaf child is a male, mating type 3). Unless the parents are consanguineous, the mean empirical recurrent risk is 10 per cent. This empirical recurrent risk is inversely proportional to the birth order of the first deaf child. If the first deaf child is the first born, the recurrent risk is 12.5 per cent; if the second born, it is 10 per cent; if the third born, it is 7.5 per cent; and if the fourth born or higher, the recurrent risk is 5 per cent. After the birth of the second deaf child, the recurrent risk would approach about 25 per cent at each conception.