Genetic Studies of Deafness and of Retinitis Pigmentosa

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In experimental animals where the generation time is short and matings can be controlled experimentally, it is a relatively simple task to determine whether a trait is genetic, how it is inherited, and where the causal gene pair is located. However, in human genetics, inferences must be drawn by pooling observations on many small families in which the trait of interest has occurred. The condition may be etiologically heterogeneous, resulting from environmental causes in some families and showing variable patterns of inheritance in others. Hereditary deafness and retinitis pigmentosa (RP) provide instructive examples of the problems involved in the genetic analysis of family data in man.

Hereditary Deafness

It is now clear that the interactions of literally hundreds of genes are required to provide the information needed to form a normal ear, and that a defect in any one of many genes can result in deafness.[1] Well over 100 specific syndromes have been described showing dominant, recessive, and sex-linked patterns of genetic transmission in which hearing loss is a major finding.[2] On the other hand, many environmental causes of deafness are known, such as rubella, prematurity, and ototoxicity, and in a given case, in the absence of a recognizable syndrome or a positive family history, it may be difficult to be sure whether the cause is genetic or nongenetic.

The problem is complicated by the fact that hu-

man families are so small that with recessive deafness (the most common genetic type) there may be only one affected child in the family. Table 1 shows the expected proportion of families that would have no affected children, one affected child (simplex families), and more than one affected child (multiplex families), with a recessive trait. The multiplex families are the "obvious" genetic cases, and the task of the geneticist is to estimate what proportion of the simplex families are, in fact, genetic cases in which by chance only one affected child has occurred. The remaining simplex cases are sporadic; they arise from nongenetic causes and are not associated with an appreciable recurrence risk. The proportion of nongenetic or sporadic cases is designated by the letter x. A second problem in the analysis of data from human families relates to ascertainment biases. In the case of a recessive trait, a large proportion of the families at risk will have no affected children (Table 1). Since there may be no way for us to discover these families, we must base our conclusions about the expected proportion of affected children on an incomplete or truncated sample of families which has been ascertained because there has been at least one affected child in the family. In order to accurately estimate the recurrence risk, we must allow, in an appropriate manner, for the families with no affected children that we had no way of discovering.

The parameter π is the probability that an affected individual will be independently discovered by the sampling procedure. The value of π can vary from nearly zero to one and is a measure of the completeness of the sampling procedure. Finally, we wish to estimate p, the recurrence risk or segregation ratio. If the estimate of p is close to 0.25, we might conclude

TABLE 1
Expected Proportion of Families with no Affected,
One Affected, and Multiple
Affected Offspring in Matings
Between Carriers of a Recessive Gene.

NUMBER OF CHILDREN IN FAMILY	FAMILIES WITH NO AFFECTED CHILDREN (%)	FAMILIES WITH AFFECTED CHILDREN (%)	
		ONE (SIMPLEX)	MORE THAN ONE (MULTIPLEX)
1	75	25	0
2	56	37	7
3	42	42	16
4	32	42	26
5	24	40	36
6	18	35	47
7	13	31	56
8	10	27	63

that the data agreed satisfactorily with the hypothesis of recessive inheritance.

The process by which the three parameters π, x, and p are estimated is known as *segregation analysis*.[3] With the use of a high-speed computer, we can estimate what values of x, π, and p provide the best explanation for any given set of data containing information on the number of affected and normal individuals and index cases in each of a large series of families.

The results of segregation analysis of data from 11,968 families of deaf children are shown in Table 2. In the first line we see that in the case of 86 consanguineous matings, the hypothesis of recessive in-

heritance with no sporadic cases (that is, $p=0.25$ and $x=0.0$) provides a satisfactory explanation for the data. The relatively low X^2 values in the last two columns indicate a good fit of the hypothesis to the data. This means that whenever we elicit a history of consanguinity, it is safe to assume that we are dealing with recessive deafness even if there is only one affected child in the family. This result is not surprising since parental consanguinity is the hallmark of recessive inheritance. When present, it may indicate that the affected child has inherited two copies of the same rare recessive gene carried by one of the common ancestors of the parents.

In the second and forth lines, we see that the hypothesis that all of the children in 11,900 nonconsanguineous matings have recessive deafness is resoundingly rejected as indicated by the enormous X^2 values. However, when we allow x to assume the best fitting value of 0.6 in the families with a negative family history, the hypothesis that the remaining cases are recessive (that is, $p=0.25$) fits very well indeed (line three). This tells us that among these nonconsanguineous families, 40% are genetic and probably recessive while 60% are nongenetic. It is of considerable interest that among families in which there was a remote history of deafness, in a grandparent, aunt, uncle, or a cousin for example, the estimated proportion of sporadic or nongenetic cases was much smaller ($x=0.2$), as shown in line five. Similar analysis can be performed for deaf children arising from deaf by normal matings, which presumably are attributable to dominant inheritance, as well as for affected children arising from deaf by deaf matings, which may include both dominant and re-

TABLE 2
Results of Segregation Analysis on 11,986 Hearing X Hearing Matings with Deaf Children ($\pi = 0.325$)

MATING TYPE AND HYPOTHESIS TESTED	NUMBER OF SIBSHIPS	NUMBER OF CHILDREN		X_P^2	X_X^2
		DEAF	HEARING		
Hearing X hearing consanguineous					
H_0: $p = 0.25$, $x = 0$	86	150	148	2.1	3.4
Negative family history					
H_0: $p = 0.25$, $x = 0$	10,509	12,712	28,739	5,289.6	5,832.8
H_0: $p = 0.25$, $\hat{x} = 0.6$	10,509	12,712	28,739	1.9	—
Positive family history					
H_0: $p = 0.25$, $x = 0$	1,391	2,142	3,496	97.0	103.9
H_0: $p = 0.25$, $\hat{x} = .2$	1,391	2,142	3,496	0.05	—

TABLE 3
Summary Results of Segregation Analysis in 12,661 Informative Families with Deaf Children.

MATING TYPE	NUMBER OF FAMILIES	NUMBER OF DEAF CHILDREN	CHILDREN WITH SPORADIC DEAFNESS	CHILDREN WITH GENETIC DEAFNESS	
				RECESSIVE	DOMINANT
Hearing X hearing	11,986	15,004	8,126	6,650	228
Deaf X hearing	254	478	0	0	478
Deaf X deaf	421	989	0	451	538
TOTAL	12,661	16,471	8,126	7,101	1,244
% of Total			49.3	43.1	7.6
% of Genetic				85.1	14.9

cessive phenotypes. Table 3 provides a tally sheet for the segregation analysis of a large sample of 16,471 deaf children. Although there were multiple affected children in only about 6% of the families, it can be seen that our best estimate is that almost exactly half of the cases are in fact genetic in etiology. Most educators and physicians who work with the deaf find this estimate to be surprisingly high. Few otolaryngologists consider themselves to be geneticists in spite of the fact that half of the young children they see with profound hearing loss are deaf because of genetic reasons. The frequency of patients with simply inherited genetic traits in this group is actually larger than that observed among children who are referred to a typical human genetics clinic for evaluation and counseling.[4]

Unfortunately, it is not always possible to identify those simplex cases that are genetic. As an aid to diagnosis in these cases, we have begun to establish a Genetic Registry of Hereditary Deafness. The Registry is based upon pedigree data from a sample of about 5,000 matings among the deaf that were collected by E. A. Fay, a professor of Gallaudet College in Washington, D.C., before the turn of the century. The Registry contains detailed information on about 30,000 individuals that was collected by Fay and is supplemented by data on current pedigrees. In about 7% of patients with genetic deafness, we find that it is possible to establish a geneologic linkage with someone listed in the Registry. Thus in some cases, use of the Registry can help establish the genetic nature of the disorder in situations where it might not be apparent from the clinical evaluation or the immediate family history.

The Registry should also promote the recognition of genetic heterogeneity which, as previously mentioned, is known to be extensive in hereditary deafness. An autosomal recessive form of hereditary deafness known as Usher syndrome provides an excellent example of heterogeneity even within a single clinical entity. In this condition affected persons suffer from progressive blindness due to retinitis pigmentosa (RP) in addition to sensorineural hearing loss. Our studies suggest that the classic delineation of Usher syndrome with early-onset, severe sensorineural deafness and RP may have to be modified.

We are collecting data on affected individuals using two different methods of ascertainment. The first involves ophthalmologic screening of students in schools for the deaf. About 4% to 6% of this group have an associated RP. Since these students tend to have severe hearing loss, our ascertainment is biased with regard to degree of hearing loss. To circumvent this problem we are also documenting the hearing status of a population of affected patients identified through the National Retinitis Pigmentosa Foundation. Our preliminary data indicate that considerable clinical and genetic heterogeneity exist in these families.[5] Of great interest is the disparity in degree of hearing loss in probands and their affected sibs in the multiplex sibships. Table 4 shows that in 29 sibships

TABLE 4
Hearing Loss in Affected Sibs of Probands

DEGREE OF HEARING LOSS IN PROBANDS	DEGREE OF HEARING LOSS IN AFFECTED SIBS OF PROBANDS*		
	NONE	MILD	SEVERE
Mild	21	8	0
Severe	8	6	1

* numbers refer to sibships

TABLE 5
Syndromes Characterized by Retinitis Pigmentosa (RP)

NAME	MODE OF INHERITANCE	SOME TYPICAL FINDINGS
Usher	AR	Profound deafness; RP
Refsum	AR	Neuropathies; EKG abnormalities; ichthyosis; deafness; RP; hyposmia
Bassen-Kornzweig	AR	Abetalipoproteinemia; RP; acanthocytosis; gastrointestinal disease
Laurence-Moon-Bardet-Biedl	AR	Mental retardation; obesity; polydactyly; hypogonadism; RP
Cockayne	AR	Dwarfism; mental retardation; hearing loss; unusual facies; RP; dermatitis

the probands had either mild or severe hearing loss, but the sibs affected with RP had no hearing loss; and in six sibships the probands reported severe hearing loss while the sibs had only a mild loss.

Thus Usher syndrome may represent only part of a broad clinical spectrum of disability involving these two sensory modalities, and our Registry should not only promote the recognition of such heterogeneity but improve the quality of medical, genetic, and educational research on such diseases by providing rosters of affected individuals who are etiologically homogeneous.

Retinitis Pigmentosa

The term retinitis pigmentosa refers to a group of genetic disorders in which there is a progressive loss of vision associated with a characteristic pigmentary degeneration of the retina, nyctalopia, and progressive loss of peripheral vision, often leading to blindness. The genetic heterogeneity of this group of disorders is well documented. First, it is known that RP may be inherited in all three Mendelian modes: recessive (80% to 90% of cases), dominant (5% to 10%), and X-linked (1% to 5%).[6] Second, several specific genetic syndromes, of which RP is a part, have been identified (Table 5). More evidence for genetic heterogeneity comes from the study of many animal models for RP which indicate that the phenotype seen in these degenerative disorders may be produced by various primary lesions.[7]

In collaboration with the National Retinitis Pigmentosa Foundation, we are conducting a nationwide survey in order to clinically and genetically characterize a sample of probands with RP. Systematic questionnaire data on family history, age of onset and progression of the symptoms, and associated abnormalities, have been analyzed on 670 individuals, forming a data base of 12,348 members of families including 1,390 affected individuals.

Nyctalopia was the most frequently noticed first symptom, especially in the younger age groups. The most common extraocular finding was hearing loss, reported by 30.4% of the probands, 10.6% indicating their loss was severe. This finding in our large proband sample reemphasizes the association between hearing loss and RP.

Segregation analysis has been performed on 405 informative proband sibships with no recognizable syndromes. Table 6 summarizes the results of these analyses, showing estimates of the segregation frequency and proportion of sporadic (nongenetic) cases. The estimate of penetrance in the case of the dominant mode of inheritance was 0.58. The finding of a low segregation ratio for both the recessive and dominant forms of RP is not surprising in view of the natural history of these disorders. The decreases in these ratios reflect the fact that the age of onset may not have been reached by many sibs, the median onset age for probands being nearly 15 years. Perhaps

TABLE 6
Segregation Analysis on Retinitis Pigmentosa Sibships

MATING TYPE	NUMBER OF SIBSHIPS	SEGREGATION RATIO	PROPORTION SPORADIC CASES	PENTRANCE
Normal X Normal Nonconsanguineous	312	0.17 ± .06	0.11	—
Normal X Normal Consanguineous	18	0.45 ± .12	0	—
Normal X Affected	71	0.29 ± .04	0	0.58

the most significant finding from the segregation analysis is the evidence it provides that a small proportion of the cases are nongenetic in etiology.

In conclusion, genetic registries, such as the one described in this article, could have a nationwide impact on the diagnosis of hereditary disease and on genetic counseling for affected individuals and their families. Our research applies an innovative technique for the diagnosis of genetic diseases that could serve as a prototype to demonstrate the practical value of categoric genetic registries. This research will almost certainly lead to the recognition of new forms of hereditary deafness and retinitis pigmentosa which could be the first step in the development of specific therapies.

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The Genetic and Environmental Effects on Diabetes in Humans and Animals: An Overview

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Despite intense scrutiny the precise etiology of diabetes mellitus remains unclear. There appear to be two major forms of diabetes: juvenile-onset or in-

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sulin-dependent diabetes, and late-onset or insulin-independent diabetes[1,2]; the late-onset form, in itself, may be etiologically heterogeneous.[3] Either form may occur at any age, with a clear distinction between the two often being difficult to make. Juvenile-onset diabetes, representing 5% to 10% of all cases, is charac-