

Paparella: Volume I: Basic Sciences and Related Principles

Section 8: General Medical Principles

Chapter 38: Genetic Disorders

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In the past 25 years there has been rapid growth in the understanding of the genetic aspect of both health and disease, with important implications for all facets of otolaryngology. More than 4000 single-gene disorders have now been elucidated and more than 50 different chromosomal abnormalities are recognized. Several of these disorders result in structural and functional anomalies of the ear, nose, and throat. This chapter presents a review of the fundamentals of medical genetics, with special reference to otolaryngology. Further details can be obtained elsewhere (Emery and Mueller, 1988; Connor and Ferguson-Smith, 1984).

Historical Considerations

The hereditary basis for certain characteristics has been known for many centuries, and stone engravings depicting the pedigrees and inheritance patterns of many characteristics in horses have been discovered that date back several millennia. The Old Testament (Genesis, 325-43) recorded the dispute between Jacob and his father-in-law, Laban, over the division of a goat herd. The matter was settled to Jacob's advantage using the identifying skin color characteristics of each animal, which were inherited as recessive traits. Talmudic references, dating from 500 AD, described fatal hemorrhage in boys who were circumcised. As a result, males from these families were exempt from the ritual of circumcision. This was an obvious reference to the X-linked disorder of hemophilia.

Regnier de Graaf, a Dutch scientist, is credited with first recognizing that the essential act of conception is the union of the egg and sperm. It was the Moravian monk, Gregor Mendel (1822-1884), however, who formulated the basic laws of inheritance after his careful experiments on the common garden pea. Mendel concluded that inherited characteristics are determined by "particular elements" in pairs (now called genes), that genes segregated and the pairs assort independently of one another, and that traits are inherited in a statistically predictable manner. Chromosomes were subsequently identified within the cell nucleus by Walther Flemming in 1877, and in 1903 Sutton and Beveri independently postulated that the behavior of chromosomes during the formation of gametes paralleled Mendel's "hereditary units". Chromosomes were shown to consist of nucleic acid, and the structure of deoxyribonucleic acid was delineated by Watson and Crick in 1953.

Basic Principles of Genetics

Functions of DNA

Deoxyribonucleic acid (DNA) is the major component of the cell nucleus. A single strand of DNA consists of a sugar-phosphate backbone with projecting nitrogenous bases - adenine, guanine, thymine, and cytosine. Two such strands, linked at complementary bases by hydrogen bonds (A=T, G=C), are coiled around one another in a helical configuration to

form the complete double-stranded DNA molecule.

Genetic information is stored within the DNA molecule in the form of a linear sequence of triplet codes (three bases), each directing incorporation of a single amino acid into proteins. The amino acid composition of every protein is therefore determined by the specific permutation of base triplets in the gene of interest.

At cell division DNA aggregates into structures called chromosomes. In every somatic (nongonadal) human cell there are 44 autosomes and 2 sex chromosomes. The human genome is thus comprised of a total of 46 chromosomes arranged in 23 pairs of homologous chromosomes, with one chromosome of each pair inherited from the mother and the other from the father. An exception is the sex chromosomes, in which the X in the male must be maternal in origin because the Y is paternally derived.

A major function of DNA is the accurate transmission of genetic information to succeeding generations of cells. Replication of the DNA molecule during nuclear division is achieved by splitting of the hydrogen bonds that hold the base pairs together, thereby separating the two strands. As a result of specific base pairing, each chain then builds its complement from free bases within the nuclear milieu. Therefore, when cells divide, genetic information is conserved and transmitted unchanged to each daughter cell.

Another important function of DNA is the direction of all protein synthesis within the cell. The double strand of DNA splits and one strand serves as a template for messenger ribonucleic acid (mRNA) transcription. The mRNA molecule diffuses into the cytoplasm, where ribosomes direct the construction, or translation, of individual proteins.

A series of hereditary units or genes is arranged along the length of every chromosome. Homologous chromosomes have the genes for specific traits in exactly the same order at precise position called gene loci. Therefore, two genes are present at a particular locus on a pair of homologous chromosomes. Most estimates indicate that there are 50,000 to 100,000 human structural genes in every cell.

Within a population several different forms of a gene (or alleles) can be present, and these alleles can have identical or different effects on a particular trait. The individual with two identical genes is said to be homozygous at that locus, whereas different alleles at the same locus result in a heterozygous state.

Mutation

Normally, DNA replication is completely accurate, but errors or mutations can occur, resulting in the coding of an altered amino acid sequence and a change in the structure and function of the resultant protein product. Mutation is the primary source of new alleles. It can occur spontaneously or be induced by a mutagenic agent, such as radiation. Mutations may be detrimental or neutral, but are rarely advantageous to the individual. If the mutation has a beneficial effect, evolutionary change of the species then follows through the interaction of natural selection and the production of new genetic forms.

If a mutation results in a detrimental dominant gene it is usually eliminated rapidly, because the individual seldom reproduces. Recessive mutations or alleles can be maintained in a population, however, if they produce little reduction in the viability of the heterozygous individual. Detrimental alleles can therefore be retained in a population by an equilibrium between the forces of selection and mutation.

Patterns of Inheritance

Genetic disorders are conventionally grouped according to their mode of inheritance. The following patterns are recognized: autosomal dominant, autosomal recessive, X-linked dominant, X-linked recessive, polygenic, and mitochondrial.

A few important disorders are the consequence of numerical or structural chromosomal abnormalities, such as Down, Turner and Klinefelter syndrome. Most genetic diseases are a result of single gene defect, however, and for the purposes of this discussion only these conditions will be considered further. Because of the rarity of chromosomal anomalies in otologic practice, it is seldom cost-effective or clinically indicated for chromosome studies to be performed.

Autosomal Dominant Inheritance

The autosomal dominant trait manifests itself in the heterozygous state, indicating that at a single gene locus one allele is normal whereas the other is abnormal or mutant. Affected individuals transmit the disorder to 50 per cent of their offspring, and males and females are equally affected. A family history of generation-to-generation transmission is usually forthcoming in autosomal dominant disorders, although mutations may occur *de novo* and are then transmitted to succeeding generations as an autosomal dominant trait. The propensity of elderly fathers to produce offspring with new autosomal dominant conditions is known as the paternal age effect.

Autosomal dominant traits tend to be extremely variable in expression, so that the severity of a disorder exhibited within a kindred can range from mild to profound clinical manifestations. An example is the Treacher Collins syndrome, in which the facial stigmata may differ considerably within a family.

The phenomenon whereby a dominant gene does not express itself in the carrier individual is called nonpenetrance and explains apparent "skipped" generations in certain pedigrees. Careful clinical appraisal however, usually reveals mild stigmata of the disorder in individuals thought to be unaffected.

Many disorders with otolaryngeal manifestations, including Waardenburg syndrome, the mandibulofacial dysostoses, and otosclerosis, are inherited as autosomal dominant conditions.

Autosomal Recessive Inheritance

Unlike autosomal dominant traits, the heterozygote or "carrier" of an autosomal recessive gene is usually healthy. The disorder is only manifest in the homozygous state when

a double dose for the abnormal gene is present. Two parents who are heterozygous carriers for a disorder have a one in four (25 per cent) risk of producing either a homozygous affected offspring or a totally normal child. However, 50 per cent of children from such a union are at risk of being heterozygous carriers, identical to their parents. Because related individuals share a proportion of their genes, parental consanguinity increases the likelihood of offspring manifesting an autosomal recessive disease. Both sexes are equally at risk. A typical pedigree is illustrated. Recessive disorders with otolaryngeal implications include the severe form of osteopetrosis, Usher syndrome, and Pendred syndrome.

X-Linked Dominant Inheritance

In this very rare type of inheritance the condition occurs in both sexes but, because the gene is situated on the X chromosome, all the daughters and none of the sons of a male with the disorder are affected. With an affected female there is a 50 per cent chance of transmission of the gene to any of her sons or daughters. The Xg blood group and vitamin D-resistant rickets are examples of this form of inheritance, but no otolaryngeal disorders of importance are inherited in this manner.

X-linked Recessive Inheritance

In X-linked recessive inheritance only males are affected at a clinical level, but asymptomatic females can be carriers. The carrier female transmits the abnormal gene to 50 per cent of her daughters who, because of the masking effect of the normal X chromosome, are clinically unaffected heterozygous carriers, but 50 per cent of her male offspring manifest the disorder.

Probably 1.5 per cent of genetic deafness is determined by an X-linked gene. These disorders include congenital perceptive deafness, deafness with stapes fixation, and high-tone neural deafness.

Polygenic (Multifactorial) Inheritance

Polygenically inherited conditions are the consequence of the interaction of environmental agents and several abnormal genes, with each contributing a small but additive effect. These genes can be derived from either or both parents. There is no recognizable pattern of inheritance, but the risk of recurrence is proportional to the number of affected members within a family and to the individual's relationship to the affected person. An example of a polygenically inherited disorder with otolaryngeal implications is cleft lip and palate.

Teratogens

All the conditions discussed above are inherited from germinal mutations, which allow generation-to-generation transmission of the abnormality. Not all congenital malformations (ie, those present at birth), however, are hereditary. Some arise from fetal exposure to teratogens that interfere with normal embryogenesis.

Many congenital abnormalities can be a result of non-genetic factors, such as drugs, infection, diet, and irradiation. Teratogenic agents are particularly likely to produce congenital abnormalities if exposure occurs during fetal organogenesis. The pattern or type of malformation produced depends on the fetal gestational age at the time of the insult.

Drugs

Almost all drugs cross the placenta in variable amounts during pregnancy, but most cause no fetal damage. The effects depend on dosage, maternal nutrition, chronicity of usage, genetic predisposition, drug sensitivity, and gestational age. Various drugs have been implicated in otolaryngeal manifestations.

Aminoglycosides. The administration of ototoxic drugs such as streptomycin during pregnancy has occasionally resulted in deafness in the newborn child (Donald and Sellars, 1981). This rare occurrence might be the result of an inherited aminoglycoside sensitivity, as reported in a large South African kindred (Viljoen et al, 1983).

Hydantoin. Some infants born to epileptic mothers receiving hydantoin therapy in the early months of pregnancy have a characteristic constellation of signs. These include craniofacial abnormalities, such as cleft lip and palate, and structural ear anomalies (Hayden, 1978).

Retinoic Acid. Retinoic acid, an analogue of vitamin A, is frequently used for treatment of severe cystic acne and other chronic dermatoses. When administered during the first 10 weeks after conception a high percentage of exposed infants have malformations of the face, cranium, heart, thymus, and CNS (Lammer et al, 1985). Bilateral microtia or anotia and low-set ears were present in 17 of 21 dysmorphic infants (Lammer et al, 1985).

Other drugs that can produce severe fetal malformations when administered in the first trimester include antimetabolites, folic acid antagonists, and steroid compounds.

Fetal Infection

The teratogenic effects of infections such as rubella, cytomegalovirus, toxoplasmosis, the herpes viruses, and syphilis on the early embryo are well documented. These intrauterine infections can cause malformations with otolaryngeal deformities or deafness but, except for rubella, this rarely occurs. The widespread use of an attenuated live virus vaccine against German measles has resulted in a dramatic decline in frequency of occurrence of the rubella syndrome. Maternal hyperthermia in pregnancy has also been implicated in a wide range of fetal defects, including craniofacial malformations (Smith et al, 1978).

Diet

Dietary factors such as maternal malnutrition can have deleterious effects upon the fetus, but there are no specific associated otolaryngeal syndromes. Excessive maternal ingestion of alcohol during pregnancy, however, has been shown to result in a constellation of signs (fetal alcohol syndrome), including craniofacial anomalies, low birth weight, skeletal malformations, and intellectual impairment. Similarly, iodine deficiency in the maternal diet

can produce endemic cretinism with deafness, mental deficiency, and spastic diplegia. The offspring of mothers treated with dietary regimens for phenylketonuria have been described with craniofacial deformities, profound mental retardation, microcephaly, and congenital heart disease (Rohr et al, 1987). Methyl mercury, occasionally consumed in contaminated fish, flour, or meat by pregnant women, can produce the fetal methyl mercury syndrome in newborns, consisting of variable microcephaly, aberrant muscle tone, deafness and blindness (Koos and Longo, 1976).

Irradiation

The major risk of fetal irradiation occurs when extensive radiographic investigations are performed early in pregnancy. There is a direct relationship between the incidence of malformation and the dose of radiation received by the fetus. The resultant wide range of abnormal manifestations reflects the timing of the insult on the developing embryo.

Genetic Counselling

Diagnostic precision, and hence the mode of inheritance, have important implications with respect to genetic counselling and the prevention of genetic disorders. Specialized genetic counselling services are available in most major medical centers. Their primary function is to provide advice to affected individuals and their families concerning the recurrence risks to further offspring and future generations. Accurate diagnosis is crucial for sound genetic counselling, and the combined role of the otolaryngologist and geneticist for optimal patient care is apparent. Affected individuals and their families are counselled regarding the prognosis and management of the disorder, as well as the recurrence risks and possibility of antenatal diagnosis.

Antenatal Diagnosis

Sometimes the clinical state of the fetus in a pregnancy deemed to be at risk for an inherited otolaryngeal disorder can be determined on the basis of genetic precedents. Certain investigations are invasive, however, and the risk of miscarriage should be carefully assessed in conjunction with the potential sequelae of the inherited disorder. Such an investigation must not be carried out unless both parents have been extensively counselled and are in full agreement regarding termination of pregnancy if the fetus is found to be affected. Various antenatal investigative procedures may be carried out.

Fetal Radiography

Radiographic diagnosis of genetic disorders in the fetus is usually limited to severe hydrocephalus or skeletal dysplasias. Individuals with osteogenesis imperfecta (type I form) can have deafness as a syndromic component, and this diagnosis can occasionally be made by demonstrating rib or long-bone fractures radiographically.

Ultrasonography

The use of high-resolution, two-dimensional, ultrasonographic techniques has revolutionized antenatal diagnosis. Many structural defects are now recognizable in the first

trimester of pregnancy using this procedure, and craniofacial malformations such as holoprosencephaly, cleft lip and palate, the Robin anomalad, and other mandibulofacial dysostoses have been diagnosed antenatally. No untoward fetal effects attributable to ultrasonography have been described.

Amniocentesis

Amniocentesis is technically feasible at the 16th week after conception, when sufficient amniotic fluid has accumulated to allow the relatively safe passage of a needle into the amniotic sac. The procedure is undertaken on an outpatient basis and performed under ultrasonographic guidance, with a risk of abortion of less than 1 per cent. Cells derived from the fetus are cultured in the laboratory and their cytogenetic status is then determined. Chromosomal defects that are frequently associated with craniofacial malformation (ie, trisomy 13 syndrome) are readily detectable. An elevated amniotic fluid alpha-fetoprotein level can indicate a neural tube defect. Specific biochemical assays on amniotic fluid can identify many inherited disorders of metabolism, some of which have otolaryngeal implications - for example, Hurler syndrome and Hunter syndrome (Liebaers and Neufeld, 1976).

A major disadvantage of amniocentesis is the relatively late stage at which diagnostic confirmation is achieved. Delay often extends to beyond 20 weeks of gestation in chromosomal disorders for which amniotic cell culture is required.

Chorionic Villi Biopsy

The chorionic villi biopsy procedure can be performed from 6 to 10 weeks postconception, when the natural risk of spontaneous abortion is about 7 per cent. The additive miscarriage rate from the procedure is approximately 3 per cent. Chorionic tissue, which is fetal in origin, can be harvested by the transabdominal or vaginal route. Fetal chromosomal analysis is possible within 48 hours, thereby allowing first-trimester termination of pregnancy for disorders such as trisomy 13 and Down syndrome. The large number of cells obtained by the chorionic villus biopsy procedure provides enough DNA for molecular probe analysis without the time-consuming and expensive need for cell culture. In the foreseeable future, advances in molecular technology will allow the antenatal diagnosis of many genetically determined otolaryngeal disorders. A working knowledge of these molecular techniques is essential to all medical disciplines, but beyond the scope of this text. The subject is well reviewed elsewhere (Weatherall, 1982; Emery and Mueller, 1988).

Fetoscopy

Direct visualization of the fetus using a fiberoptic device is possible at 18 to 20 weeks postconception. The technique is difficult and restricted to a few specialized centers, and the spontaneous abortion rate is less than 5 per cent. Recurrent leakage of amniotic fluid occurs in 4 per cent, and premature labor is a problem in 7 to 8 per cent of women who undergo this procedure.

The method has been used for the antenatal diagnosis of Treacher Collins syndrome (Tolarova and Zwinger, 1981), and provides a means for fetal blood sampling and skin and

liver biopsy. Other craniofacial malformations can also be diagnosed using fetoscopy.

In view of the rapid pace of development of medical genetics and recombinant DNA techniques, more heritable disorders are now being identified. In some instances, patients might be advised to await specific technologic advances before planning their families. The future holds exciting prospects for the use of genetic engineering techniques in the diagnosis and therapy of genetically transmitted and other otolaryngeal diseases.