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GENETIC SYNDROMES CAUSING CONGENITAL HEART DISEASE - A COMMONLY UNRECOGNIZED GROUP OF DISORDERS

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As with diseases affecting other body systems, genetic factors play a significant role in the pathogenesis of most forms of congenital heart disease. In those congenital heart lesions resulting from either a chromosomal abnormality (such as Down syndrome) or a single gene mutation (such as Noonan syndrome), the genetic effects are clearly discernible and easy to analyze. In many of the "garden-variety†" forms of congenital heart disease (such as isolated ventricular septal defect), the role of hereditary factors is less clear-cut with most such disorders having a multifactorial etiology arising from a complex interplay of multiple genetic and environmental factors.

CHROMOSOMAL ABERRATIONS

About 5% of all congenital heart malformations can be traced to a chromosomal aberration (1). In virtually all cases in which a congenital heart malformation is associated with a chromosomal defect, it occurs as a part of a multiple malformation syndrome. Moreover, congenital heart disease is a characteristic feature of most chromosomal disorders, such as trisomy 13, trisomy 18, trisomy 21 (Down syndrome), deletion of the short arm of chromosome 4, deletion of the long arm of chromosome 13, deletion of the long arm of chromosome 18, and the XO Turner syndrome. The one chromosomal syndrome that does not show an increased frequency of congenital heart disease is the XXY Klinefelter syndrome. The two most common chromosomal syndromes that regularly cause congenital heart disease, Down syndrome and Turner syndrome, are discussed below.

1. Down Syndrome

The trisomy 21 form of Down syndrome (mongolism) is the most common chromosomal aberration in man, occurring in approximately 1 in every 600 newborns. Congenital heart disease is found in as many as 50% of patients with this disorder and is a major source of much of the morbidity and mortality in this syndrome (2-5).

The two most common cardiac lesions in Down syndrome are ventricular septal defect and endocardial cushion defect. Since the endocardial cushion defect is a relatively uncommon cardiac lesion that rarely occurs in other situations, it is considered a unique and characteristic feature of the disorder (5). Secundum atrial septal defect, tetralogy of Fallot, and isolated patent ductus arteriosis are also observed in patients with the Down syndrome. Transposition of the great vessels and coarctation of the aorta are rarelyn. Most patients with Down syndrome who have congenital heart disease have a single lesion. However, as many as 30% of those with heart disease may have multiple cardiac defects (4).

The decision to repair surgically a congenital heart lesion in a patient with Down syndrome is often a very complicated one. Multiple factors must be considered, including the seriousness of the defect, whether the patient is living at home with relatives or is institutionalized, and the patient's degree of cooperation. Although it used to be believed that patients with Down syndrome would be poor operative candidates because of their increased susceptibility to infections, recent surgical followup studies suggest that their postoperative

mortality is no higher than that of a non-Down syndrome population with similar cardiac lesions (6).

The most important factor is preventing the birth of a child with the trisomy 21 form of Down syndrome relates to the marked increase in incidence of trisomy 21 that occurs with children born to older mothers. The calculated risk figures for mothers below 30 years of age are less than 1 per 1,000 births, for mothers of 30-34 years between 1 and 2 per 1,000 births, for mothers of 35-39 years between 2 and 5 per 1,000 births, for mothers of 40-44 years between 5 and 10 per 1,000 births, and for mothers above 45 years between 10 and 20 per 1,000 births (7).

The recurrence risk to a couple who has had one child with the trisomy 21 form of Down syndrome is 2%, i.e., there is a 1 in 50 chance that the next child will also have the trisomy 21 form of Down syndrome (7). Once a couple has had one child with trisomy 21 Down syndrome, the recurrence risk is 2% regardless of whether the mother is young (age 20) or old (age 45) (7). All women who are 36 years of age and older and all women who have had one child with trisomy 21 Down syndrome should have each of their subsequent pregnancies monitored by amniocentesis so that a prenatal diagnosis can be performed.

The trisomy 21 aberration accounts for virtually all cases of Down syndrome born to women above age 30 and for 90% of all cases born to women below age 30. The remaining 10% of patients with Down syndrome born to women below age 30 usually have a translocation form of Down syndrome. On karyotype analysis, such patients have the normal number of 46 chromosomes, including two normal chromosomes No. 21, one normal chromosome No. 14, and an unpaired large chromosome that represents one chromosome No. 21 joined to one chromosome No. 14. There are no clinical differences between children with the trisomy 21 form of Down syndrome and those with the translocation form (8).

Studies of the parents of children with the translocation form of Down syndrome show one of two situations: (1) in about 90% of cases both parents will have normal karyotypes in which circumstance the translocation is assumed to have originated during gametogenesis and there is no more than a 2% risk of recurrence to subsequent children; or (2) in the remaining 10% of cases one of the parents will have a karyotype consisting of 45 chromosomes with one normal chromosome No. 14, and one normal chromosome No. 21, and a large chromosome that contains fused copies of both the 14 and 21 chromosomes. About 5 to 20% of the live-born offspring of an individual who is a "balanced" translocation carrier for the 14/21 chromosome will have Down syndrome, depending on whether it is the father (5%) or the mother (20%) who carries the "balanced" translocation (8).

Overall, the inherited translocation form of Down syndrome is extremely rare, especially as compared to the trisomy 21 form of the disorder. Nevertheless, it is important to identify all such cases so that the pregnancies of all family members who are translocation carriers can be appropriately monitored by amniocentesis.

2. Turner Syndrome

The Turner syndrome is characterized by the occurrence in a phenotypic female of the following clinical features: shortness of stature, amenorrhea due to gonadal dysgensis, shield-shaped chest, pigmented nevi, webbing of the neck, cubitus valgus, shortening of metacarpals and metatarsals, renal abnormalities, and cardiovascular abnormalities. About 60% of patients with the above clinical features will have cells that are deficient in one of the two X chromosome (45 X form). The remaining 40% includes patients whose cells show either X chromosomal mosaicism (such as 45 X/46 XX) or structural abnormalities in one of the two X chromosomes (such as a single isochromosome X or a single ring X chromosome). Most fetuses with the 45 X form of Turner syndrome are spontaneously aborted. Recent studies indicate that the 45 X chromosomal abnormality occurs in as many as 5% of all spontaneous abortions and in about 1 in 2,500 female live births (9).

Cardiovascular abnormalities occur in 35 to 50% of all patients with the 45 X form of Turner syndrome (10-13). Coarctation of the aorta is by far the most common abnormality that is encountered, occurring in 70% of patients with cardiac anomalies. Several other congenital malformations that are occasionally seen include bicuspid aortic valve, idiopathic hypertrophic subaortic stenosis, ventricular septal defect, mitral valve prolapse, and dextrocardia (10-14). Pulmonic valve stenosis is rarely, if ever, seen in Turner syndrome. This is in striking contrast to findings in Noonan syndrome in which coarctation of the aorta is rarely encountered and pulmonic valve stenosis is the cardinal cardiac manifestation (13).

Patients with Turner syndrome due to either an isochromosome X or to a ring X differ clinically from patients with a 45 X karyotype in two respects: 1) webbing of the neck is absent and 2) coarctation of the aorta is absent (10,12). Coarctation of the aorta is observed in patients with mosaic Turner syndrome; however, the frequency with which this cardiac lesion is seen in these patients is considerably less than in the 45 X patients.

Adults with Turner syndrome are prone to systemic hypertension. This association between Turner syndrome and hypertension occurs in the absence of coarctation of the aorta and appears to be unrelated to the karyotypic abnormality (10). The mechanism underlying the hypertension has not been defined.

Family studies have revealed a high frequency of both diabetis mellitus and thyroid autoantibodies in the chromosomally normal relatives of patients with Turner syndrome (10). These findings have suggested that a genetic tendency to autoantibody formation in parents may predispose to the occurrence of chromosomal abnormalities in their offspring.

Unlike in Down syndrome, elevated maternal age does not appear to predispose to offspring with the Turner syndrome. Once a couple has had one child with the Turner syndrome, the recurrence risk to the subsequent offspring is virtually zero.

SINGLE GENE DISORDERS

At least seven forms of congenital heart disease are now recognized to be caused by a different single gene mutation. Together, these seven disorders account for about 5% of all forms of congenital heart disease. In six of these disorders, the responsible mutation causes a distinct multisystem syndrome of which congenital heart disease is only one component. Five of these mutations produce developmental anomalies affecting either the pulmonic valve (as in Noonan syndrome and LEOPARD syndrome) or the atrium (as in Holt-Oran syndrome, familial atrial septal defect with AV conduction abnormality, and Ellis-van Creveld syndrome). Each of these single gene mutations presumably disrupts the function of a unique developmental protein whose action is necessary for normal embryogenesis of the heart. Virtually nothing is known about how these mutant genes act at the molecular and cellular level.

The identification of any one of these seven single gene disorders in a given individual enables the cardiologist to apply knowledge of the genetics of the syndrome to the identification of further cases in the same family and to provide genetic counseling to appropriate family members.

1. Noonan Syndrome

The eponym Noonan syndrome describes a distinct clinical entity characterized by shortness of stature, mild mental retardation, a unique facial appearance, webbing of the neck, vertebral anomalies, cubitus valgus, cryptocrchidism, renal anomalies, and congenital heart disease (15-20). Affected individuals superficially resemble patients with Turner syndrome in that shortness of stature, webbing of the neck, cubitus valgus, skeletal anomalies, renal abnormalities, and congenital heart disease are present in both disorders. Because of these clinical similarities, Noonan syndrome has frequently been referred to in the literature as "male Turner syndrome", "Turner phenotype with normal chromosomes", and "XX and XY Turner phenotype" (15-19).

However, there are several striking genetic and clinical differences in Noonan syndrome and Turner syndrome that clearly separate these two disorders as distinct entities. These differences are as follows: 1) unlike in Turner syndrome, both males and females are affected in Noonan syndrome and the karyotype in both sexes is normal (15-19); 2) coarctation of the aorta, which rarely occurs in Noonan syndrome, is the most frequent cardiac lesion in the Turner syndrome; conversely, pulmonic stenosis, which does not occur in Turner syndrome, is the most common cardiac lesion in Noonan syndrome (14-22); and 3) Noonan syndrome is determined by a single mutant gene inherited as an autosomal dominant trait (16,18,19,23-25).

Approximately 50% of patients with Noonan syndrome have congenital heart disease (20). The most common lesion is valvular pulmonary stenosis, occurring in about 60% of those patients who have a congenital cardiac malformation. The

stenotic pulmonic valve is frequently dysplastic. Characteristically, the annulus is of normal size, but the cusps are thickened and immobile (14-22).

Atrial septal defect and hypertrophic cardiomyopathy each occur in about 20% of Noonan patients who have congenital heart disease. The cardiomyopathy is most often an eccentric hypertrophy of the left ventricle and could easily be missed during cardiac catherization limited to the right side of the heart (26-29). While the majority of patients show a single heart defect, some show pulmonary stenosis in combination with either atrial septal defect or hypertrophic cardiomyopathy.

In addition to anomalies of the heart itself, abnormalities of the systemic arteries have also been reported in patients with Noonan syndrome. These include fistulae of the coronary arteries, peripheral pulmonic stenosis, anomalous pulmonary venous septum, hemangiomas, peripheral lymphedema, and intestinal lymphangiectasis (22).

Patients with Noonan syndrome undergoing cardiac surgery are particularly vulnerable to several complications: 1) high operative mortality because of the dysplastic nature of the pulmonic valve, often necessitating total valve replacement; 2) difficulty in establishing outflow drainage during total cardiopulmonary bypass because of the systemic venous anomalies; 3) increased risk of malignant hyperpyrexia during general anesthesia; and 4) development of persistent chylothorax because of pulmonary lymphangiectasis (22).

The evidence for a genetic etiology of Noonan syndrome is provided by its occurrence in multiple siblings and in multiple generations of the same family. Family studies are consistent with autosomal dominant inheritance of a single mutant gene (16,18,19,23-25). Figure 1 shows a pedigree of a family with Noonan syndrome. In this family, the mutant gene segregated through three generations, and one affected woman had affected children with two different husbands. As with most autosomal dominant traits, the Noonan gene shows a marked variation in its clinical expression, some affected individuals showing only minor abnormalities (such as epicanthal folds and low set ears) while others in the same family showing the full syndrome with severe congenital heart disease.

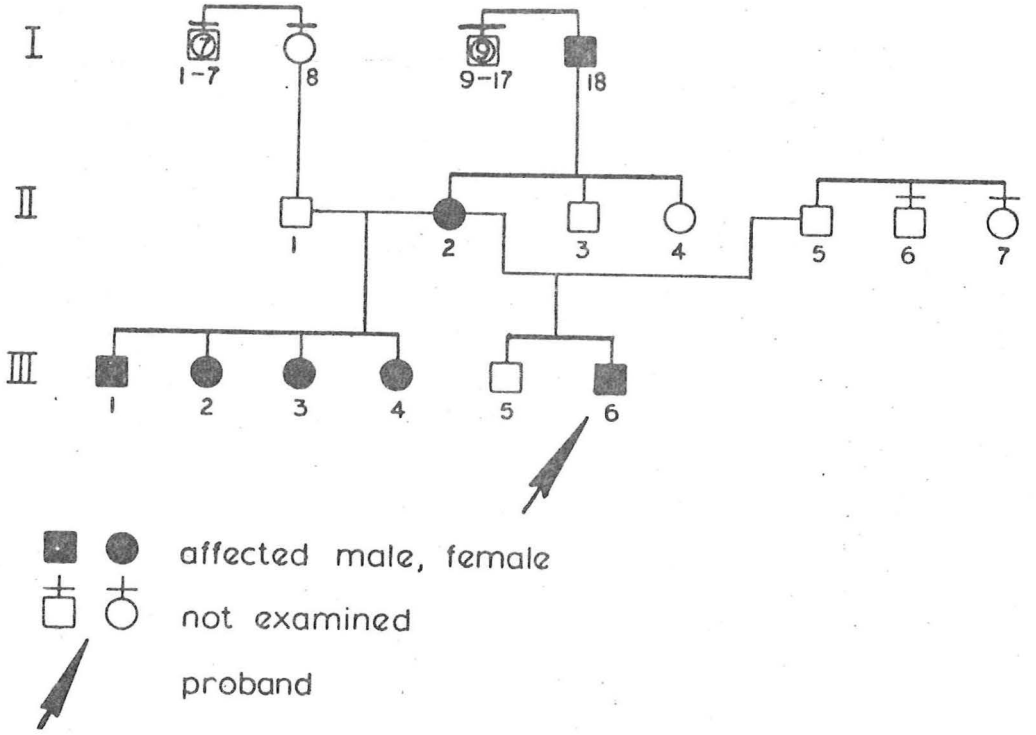

Fig. 1

Pedigree of a family with Noonan Syndrome

Although male-to-male transmission of the mutant gene has been documented in several pedigrees (23-25), most affected males, unlike affected females, show a deficiency in the number of offspring. This deficiency can be attributed to two factors: 1) males appear to have a higher frequency of severe cardiac lesions than do females and would therefore have less chance of surviving to reproductive age, and 2) about 75% of affected males have bilateral cryptorchidism whereas the affected females appear to have normal ovarian function (15-25). This striking diminution in reproductive fitness in Noonan males is consistent with observations that as many as 50% of all cases of the Noonan syndrome present clinically as sporadic cases. Such sporadic cases presumably represent new mutations.

Despite its relatively recent delineation (in 1968) as a distinct clinical and genetic entity that is separate from Turner syndrome, more than 500 cases of Noonan syndrome have been reported in the literature. It has been estimated that the disorder may occur more frequently than 1 in 1000 persons in the population (30). The basic biochemical defect underlying Noonan syndrome is unknown. Considering its apparent frequency, it is likely that the disorder is genetically heterogeneous and that different biochemical defects in different families will ultimately be discovered.

2. LEOPARD Syndrome

The LEOPARD syndrome is a single gene-determined complex of congenital malformations affecting the cardiovascular system, the skin, the inner ear, and somatic and sexual development (31-35). The cardinal features of the disorder are embodied in the mnemonic device LEOPARD, whose letters denote: L, lentigenes; E, electrocardiographic conduction defects; O, ocular hyperteleorism; P, pulmonary valve stenosis; A, abnormalities of genitalia; R, retardation of growth, and D, deafness, sensorineural (31).

Cardiac abnormalities, which are a common feature of the disorder, consist of anatomic malformations as well as electrocardiographic conduction defects. Stenosis of the pulmonary valve appears to be the most frequently encountered cardiac lesion. It may exist as an isolated anomaly or be combined with aortic stenosis. Other cardiac defects that have been reported include endocardial fibroelastosis and hypertrophic cardiomyopathy (31-35). The cardiac disease characteristically has its onset early in childhood and it usually runs a progressive course. The most common electrocardiographic defects include prolonged PR interval, left anterior hemiblock, widening of the QRS, and complete heart block. The functional significance of these EKG abnormalities is highly variable from patient to patient, being well tolerated in some or sufficiently serious to produce sudden death in others.

The most distinctive and striking feature of the syndrome and the one that is diagnostic when present are the numerous lentigenes. These small (up to 5 mm in diameter) dark-brown spots, which spare only the mucosal surfaces, are most concentrated over the neck and upper trunk. In some patients, the lentigenes are present at the time of birth, while in others they appear shortly after

birth. In all patients, the number of lentigenes increases with age. Lentigenes differ from freckles in several respects: 1) they appear before age 5, whereas freckles usually appear at 6 to 8 years of age, 2) they do not increase in numbers with exposure to sunlight, whereas freckles do, and 3) microscopically, they differ from freckles in terms of the quantity of melanocytes and the distribution of melanin in the pigmented and adjacent nonpigmented skin (31).

The LEOPARD syndrome is inherited as an autosomal dominant trait. The clinical findings are highly variable from patient to patient both within the same family as well as between affected individuals from different families. The most frequently encountered manifestations of the mutant gene are those relating to the cardiovascular system, occurring in at least 95% of affected subjects. About 80% have lentigenes. Deafness and the abnormalities of genitalia (hypospadias and undescended testes in the male) occur in about 20% of patients.

The population frequency of the gene causing the LEOPARD syndrome is presumably very rare. Nothing is currently known about the relative proportion of cases arising from familial transmission of the mutant gene versus those arising from new mutations. Moreover, nothing is known regarding the biochemical action of the mutant gene.

3. Holt-Oram Syndrome

Although atrial septal defect almost always occurs as a sporadic disorder, there are occasional families in which the pedigree pattern suggests the operation of a single mutant gene. The Holt-Oram syndrome and familial atrial septal defect with prolonged AV conduction are two such examples of rare autosomal dominant disorders that are hidden among the more common "garden-variety" cases of atrial septal defect.

The cardinal clinical manifestation of the Holt-Oram syndrome is the occurrence of an upper limb deformity in a patient with congenital heart disease (36-41). Atrial septal defect of the secundum type is the most frequently encountered congenital heart malformation in affected individuals. This is usually accompanied by one or more electrocardiographic abnormalities, such as first degree atrioventricular block, right bundle branch block, or bradycardia. Ventricular septal defect is the second most commonly encountered congenital heart lesion. Although virtually any form of congenital heart disease has been reported to occur in the syndrome, 70% of affected individuals have either an atrial septal defect or a ventricular septal defect.

Many different upper limb deformities have been observed in association with the congenital heart disease in the Holt-Oram syndrome (42). These limb deformities are typically bilateral but not necessarily symmetrical. The most characteristic anomaly involves the thumbs. They may be absent, hypoplastic, triphalangeal, or fingerlike. The latter anomaly is referred to as "digitalization of the thumbs". The radius and the forearm are variably involved, the defects ranging in different patients from absent or hypoplastic radii to phocomelia.

While deformities of the thumb are the best known features of the syndrome, they neither occur in every case nor are they pathognomonic (42). Bilateral thumb abnormalities may also occur in the Blackfan-Diamond syndrome, in Fanconi's anemia, or in Thalidomide embryopathy (42). The most frequently encountered and specific upper limb abnormalities - namely, the presence of an abnormal scaphoid bone and/or accessory carpal bones - are detected on radiographs of the wrists (42). Various abnormalities also occur in the shoulder. The most common finding is a rotation of the scapula. Deformities of the humeral head and accessory ossicles around the shoulder have also been frequently noted (42).

As in many dominantly inherited syndromes, individuals inheriting the Holt-Oram gene show varying degrees of clinical severity. Intrafamilial variability appears as great as does interfamilial variability (43). Although the biochemical action of the mutant gene has not been defined, it presumably acts by disrupting a critical embryonic developmental event common to both the upper limbs and the heart. The population frequency of the Holt-Oram syndrome has not been determined. However, the disorder is probably greatly underdiagnosed, most cases being mistakenly considered as "garden-variety" atrial septal defect. The importance of separating the patient with the Holt-Oram syndrome from those cases of atrial septal defect that are not determined by a single gene mechanism cannot be overemphasized, especially in view of the different types of genetic counseling that are required in the two situations.

4. Familial Atrial Septal Defect with Prolonged AV Conduction

The syndrome of atrial septal defect with prolonged AV conduction represents a second example (the first being the Holt-Oram syndrome) of a single gene-determined form of atrial septal defect. Pedigree studies of at least 20 large families leave little doubt about the autosomal dominant inheritance of this disorder (44-47). The mutant gene shows a high degree of penetrance and there is surprisingly little pleiotropy in that the mutant gene appears to cause only atrial septal defect and an abnormality of the AV conduction system. The latter is manifest clinically as either first or second degree heart block. Rarely, complete heart block occurs.

In the absence of a biochemical marker for the mutant gene, the diagnosis can be made only by careful clinical examination of family members of suspected cases. "Garden-variety" atrial septal defect can be ruled out both by a family pedigree showing dominant inheritance and by electrocardiographic evidence of AV conduction block. The Holt-Oram syndrome can be ruled out by a normal clinical and radiologic examination of the upper extremities.

5. Ellis-van Creveld Syndrome

The Ellis-van Creveld syndrome produces a rare form of congenital heart disease that is inherited as an autosomal recessive trait. Affected individuals manifest abnormalities not only of the heart but also of the skeletal system, the nails, and the teeth (48-50).

Congenital heart disease occurs in 50 to 60% of patients and is a frequent cause of infant death. The most common cardiac lesion involves the atrium, either as a single atrium or as a large atrial septal defect. The atrial lesion may occur alone or may be associated with another cardiac defect, such as aortic atresa, hypoplastic ascending aorta, or hypoplastic left ventricle.

The skeletal findings in the disorder are characteristic. The patients have a small stature of prenatal onset with a striking shortening in the distal part of the extremities. Bilateral polydactyly of the fingers and fusion of the carpal bones are also usually present. Additional findings include the presence of hypoplastic nails, upper lip frenula, and dental dysplasia.

About one-half of affected individuals die in early infancy as a result of cardiorespiratory problems. The majority of survivors have normal intelligence. The eventual stature of adults is in the range of 45 to 60 inches.

Although the Ellis-van Creveld syndrome is a very rare disorder, its genetics have been well delineated (49). The following observations support an autosomal recessive inheritance pattern: 1) the disorder occurs with equal frequency in males and females; 2) only siblings are affected in a given family; and 3) about one-third of all cases are the result of parental consanguinity. Most cases of the disorder in the United States occur in the Old Order Amish, an inbred religious isolate in Lancaster County, Pennsylvania (49).

The underlying biochemical defect responsible for the Ellis-van Creveld syndrome has not yet been identified. Nonetheless, since affected individuals always manifest bilateral polydactyly of the hands, it is possible to make a prenatal diagnosis in pregnancies at risk by inspecting the fetus in utero with fetoscopy and determining whether or not polydactyly is present (51).

6. Familial Supravalvular Aortic Stenosis

Supravalvular aortic stenosis can occur as a component of two different clinical entities: 1) as a nonfamilial syndrome resulting from fetal hypercalcemia and characterized by elfin facies (antiverted nostrils and patulous lips), mental retardation, dental anomalies, and congenital supravalvular aortic stenosis (52); and 2) a familial syndrome transmitted as an autosomal dominant trait and characterized by the presence of pulmonary and systemic arterial stenosis in the absence of mental retardation and elfin facies (52-56). Although these two syndromes are often discussed in textbooks as representing a "spectrum of the same disease", they are clinically and genetically distinct disorders. Since the first syndrome is not transmitted by a single gene mechanism but rather results from excessive exposure or excessive hypersensitivity of fetal tissues to vitamin D, it will not be discussed further.

Patients with familial supravalvular aortic stenosis can exhibit a wide range of arterial abnormalities. Although supravalvular aortic stenosis is the "typical" lesion, many affected individuals have pulmonary artery stenosis (peripheral or supravalvular), brachiocephalic arterial stenosis, hypoplasia or coarctation of the descending aorta, and dilitation and tortuosity of the coronary arteries. Like most dominant traits, the mutant gene is variably expressed even among affected persons in the same family.

Most patients initially come to attention because of an asymptomatic heart murmur. Clinical signs of dyspnea, angina pectoris, syncope, or claudication do not usually begin until after age 20 years. Those patients who manifest coarctation of the descending aorta may first present with signs of renovascular hypertension. Since affected individuals are at risk for bacterial endocarditis and should receive antibodies at appropriate times, it is important to identify all affected relatives as early in life as possible.

7. Kartegener Syndrome

The Kartegener syndrome consists of the triad of sinusitis, bronchiectasis, and situs inversus with dextrocardia (57-60). The disorder is inherited as an autosomal recessive trait; males and females are affected with equal frequency. In addition to the classic triad mentioned above, affected males are infertile as a result of immobile spermatozoa.

Since individuals with the Kartegener syndrome are homozygous for a mutant gene, the clinical course is remarkably uniform in different affected persons. Affected individuals initially come to attention as infants because of mucopurulent nasal discharge and repeated bouts of upper respiratory infections, otitis media, and pneumonia. By the preschool years, most patients have persistent sinusitus, chronic bronchitis, and bronchiectasis. As many as 90% of affected individuals have complete situs inversus, a mirror image reversal due to a sinistral instead of a dextral rotation of the viscera occurring between the tenth and fifteenth days of gestation.

In most affected individuals, dextrocardia is the only cardiac manifestation. Occasionally, one or more associated cardiac anomalies are present, such as transposition of the great vessels and triloculor or bilocular heart.

The Kartegener syndrome occurs in about one person in 68,000. Of all persons with bronchiectasis, about 1.4% have the Kartegener syndrome, and of all persons with situs inversus, about 15% have the Kartegener syndrome (61). The absence of any manifestations of the disorder in the parents or in the children of affected individuals, the presence of a higher than normal frequency of consanguinity among the parents of affected individuals, and the absence of any male-to-male transmission all support an autosomal recessive mode of inheritance.

Recent electron microscopic studies show that the cilia and sperm obtained from affected individuals are both normal in all respects except that the so-called dynein arms are not present (61). Dynein arms are structures that in normal cilia and sperm tails form temporary cross bridges between adjacent microtubules. (Fig. 2). These structures are believed to be necessary for

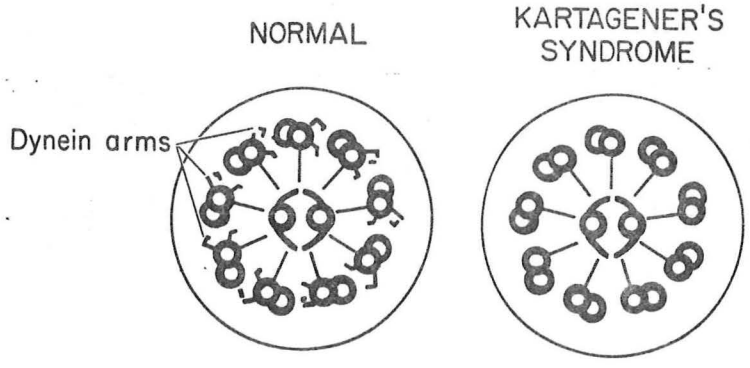

Fig. 2. Cross-sectional view of cilia showing the absence of dynein arms in the cilia of patients with Kartegener syndrome.

generating the movements of cilia and sperm tails. On the basis of the observations showing a lack of dyenin arms in the Kartegener syndrome, it has been suggested that the mutation involves the gene responsible for the synthesis either of the dynein protein itself or of a protein that binds dyenin to the microtubules (61). The absence of dyenin arms presumably produces immobility of sperm and respiratory cilia, accounting for the clinical findings of infertility, sinusitis, and bronchiectasis. The molecular basis of the situs inversus is less certain, but it is not unreasonable to suppose that a malrotation of the visceral tissues occurs in the embryo when the ciliary movements of visceral epithelia are missing.

MULTIFACTORIAL DISORDERS

The chromosomal abnormalities and single gene disorders that produce congenital heart disease account for no more than 5 to 10% of all cases of congenital heart diseases (1). The remaining "garden-variety" cases are believed to result from developmental defects involving multiple genes and possibly environmental factors. Hence, the genetic predisposition in most cases of congenital heart disease is multifactorial (62-64).

In general, congenital heart defects produced by chromosomal errors (as in Down syndrome) and by single gene mutations (as in Noonan syndrome and Kartegener syndrome) are a part of a multisystem disorder. On the other hand, congenital heart defects with multifactorial inheritance typically occur as a discrete lesion that is not a part of a multisystem disorder.

As in other disorders showing multifactorial inheritance, the recurrence risks to first-degree relatives of a patient with a "garden-variety" type of congenital heart disease is considerably less than the 25 to 50% risks that occur in single gene-disorders. Although the relative risk to the siblings and offsprings of such a patient is 3 to 40 times the estimated population frequency, the overall absolute risk for these first-degree relatives is low, in the range of 1 to 4% (62,65). Table I lists the expected recurrence risk for siblings and offspring of patients with the 13 most common forms of congenital heart disease. While these empiric data are very useful in the genetic counseling of families that have had only one child with a congenital heart disease, they do not apply in families with more than one affected person. With two affected first-degree relatives, the recurrence risk doubles or triples and with three affected, risks reach 10 to 20%. It is not yet prossible to predict when the first case is diagnosed in a given family whether that family is at risk for multiple occurrences of congenital heart disease.

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