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Congenital Malformations and Developmental Disabilities in Ataxia-Telangiectasia, Fanconi Anemia, and Xeroderma Pigmentosum Families

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SUMMARY

Heterozygous carriers of an ataxia-telangiectasia (A-T), Fanconi anemia (FA), or xeroderma pigmentosum (XP) gene may be predisposed to some of the same congenital malformations or developmental disabilities that are common among homozygotes. To test this hypothesis, medical records, death certificates, and questionnaires from 27 A-T families, 25 FA families, and 31 XP families were reviewed. Eleven XP blood relatives (out of 1,100) were found with moderate or severe unexplained mental retardation, a significant excess compared to the FA and A-T families (3/1,439). There were four microcephalic XP blood relatives and none in the FA or A-T families. In the A-T families, idiopathic scoliosis and vertebral anomalies were in excess, while genitourinary and distal limb malformations were found in the FA families. A-T, FA, or XP heterozygotes may constitute an important proportion of individuals at risk for specific malformations or developmental abnormalities.

INTRODUCTION

Many congenital malformations and developmental disabilities have familial aggregation. While the familial clustering of such disorders often has a genetic basis, it has been difficult to demonstrate the genetic mechanism. One possibility is that some genes that predispose in single dose to congenital malformations or developmental disabilities may be identified because they cause a distinctive autosomal

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recessive syndrome in the homozygous state. A substantial proportion of genes that predispose to serious common disorders may be detectable using this principle [1].

Patients with Fanconi anemia (FA) often have diverse congenital malformations, especially skeletal and genitourinary, in addition to growth retardation, abnormal skin pigmentation, progressive pancytopenia, and a tendency to develop leukemia or carcinomas [2]. Ataxia-telangiectasia (A-T) is characterized by progressive cerebellar ataxia and skin and conjunctival telangiectasia. A-T patients frequently have immunoglobulin deficiencies and oculomotor apraxia; skeletal malformations are infrequent, although several A-T patients with vertebral defects have been reported. Deaths from leukemia, lymphoma, or other cancers are common [3]. Sun-sensitivity and multiple skin cancers arising from exposure to uv light are the cardinal features of xeroderma pigmentosum (XP). A substantial fraction of XP patients have neurological abnormalities, including mental retardation, sensorineural deafness, and seizures. Some are microcephalic [4].

For FA, A-T, and XP heterozygotes, only the association with increased cancer risk has been studied systematically [5–8]. Heterozygous carriers of the genes for one of these syndromes may be predisposed to other clinical abnormalities commonly found in homozygotes. We have re-examined data collected from 27 families of A-T patients, 25 families of FA patients, and 31 families of XP patients to see if specific congenital malformations or developmental disabilities were in excess among A-T, FA, or XP blood relatives.

METHODS

The diagnostic criteria for homozygotes, procedures for identifying the families, and methods of data collection have been described [6–8]. The original sample included 5 generations of family members, but in order to maximize detail and accuracy for incidents of early life, this analysis was confined to the 3 youngest generations: the aunts, uncles, parents, siblings, first cousins, nieces, and nephews of the homozygotes.

Living family members completed questionnaires for themselves that contained personal demographic information, medical histories, and a checklist of illnesses and disabilities. For deceased persons and those unable to complete the questionnaire, the form was filled out by the closest living relative. Records for stillbirths were not available. Checklist items of particular relevance to this analysis were "any condition present since birth," "permanent stiffness or deformity of the foot, leg, fingers, arm, or back," and "repeated trouble with back or spine." Respondents reported all hospitalizations, and medical records for major illnesses and operations were obtained when available. Death certificates were collected for more than 95% of all persons who died in the United States or Canada between 1930 and the close of each study.

For this analysis, all congenital malformations and developmental disabilities reported on questionnaires, medical records, or death certificates were counted. The source of information about each case is noted in table 1.

Proved or probable homozygotes for the autosomal recessive syndromes were not included. Probands' sibs or other relatives with malformations were included in statistical analyses only if their age and detailed medical information made it implausible that they were homozygotes.

Cases of "unexplained" mental retardation were counted after excluding two persons whose retardation was ascribed to traumatic delivery, one with erythroblastosis fetalis, four with hydrocephalus, and two with Down syndrome. Because most scoliosis of mild degree

would be missed by our survey technique, the analysis was restricted to severe or treated cases. Scoliosis associated with spina bifida, malformed vertebrae, or neuromuscular or neurological disease (including severe mental retardation) was also excluded.

Preliminary tables of malformations and disabilities were based on the International Classification of Diseases (ICD codes 740–759). Pyloric stenosis, cardiac or gastrointestinal defects, talipes deformities, or cleft lip or palate did not occur unusually often in any set of families compared to population incidence data. The remaining malformations were grouped into the broad categories of table 1. For each classification in apparent excess in one set of blood relatives, the observed incidence in that family set was compared with the combined incidence in the other two family sets using a 2×2 contingency table (one-sided test).

RESULTS

There were 741 blood relatives in the A-T study (378 males and 363 females), 698 in the FA families (354 M and 344 F), and 1,100 in the XP families (543 M and 557 F). In each of the three studies, approximately 32% of the sample were aunts, uncles, or parents of probands, 62% siblings or first cousins, and 5% offspring, nieces, or nephews. However, the XP relatives were somewhat older at the end of the study than were the FA or A-T relatives, with 9.6% of the XP blood relatives age 65 or older, compared to 3.6% in the FA families and 3.2% in the A-T families.

Mental Retardation, Microcephaly, and Neurological Diseases

There were 11 XP relatives identified as mentally retarded, three of them microcephalic, compared to one in FA and two in A-T (see table 1). The 11 belonged to 10 separate families. The proportion of identified mentally retarded persons among the XP relatives (11/1,100) was significantly greater than that in the combined set of FA and A-T relatives (3/1,439; $P = .008$).

Five mentally retarded XP relatives had no reported congenital malformations or additional neurological manifestations. Only one uncomplicated case of mental retardation was reported in the FA and A-T families. XP relatives in two families were noted to be exceptionally short as well as mentally retarded. A seizure disorder was associated with mental retardation in one XP relative and two A-T family members; none were reported in the FA families.

Four XP relatives were microcephalic. A proband's brother (XP24 AIV5) was noted to be microcephalic but his records did not describe his level of intelligence or function. He was *not* counted among the mentally retarded relatives. His first cousin, XP24 BIV4, was microcephalic and retarded. Another microcephalic child (XP27 AIV36) had a first cousin (XP27 AIV30) who had mental retardation but no microcephaly. No microcephalic A-T or FA relatives were found. The proportion of microcephalic persons in the XP families (4/1,100) was significantly greater than the 0/1,439 found in the FA and A-T families ($P = .02$).

Five of the 31 XP families had retarded probands. Three of these families (XP8, XP16, XP24) also contained retarded relatives. The probands in two of them (XP16 and XP24) had the only clear-cut cases of de Sanctis-Cacchione syndrome in the study. The proband in the third family (XP8) had progressive mental and growth retardation from age 4. The retarded relatives in families XP8 and XP24

were microcephalic, and in XP16, the retarded individual was noted to be dwarfed. Probands in families XP3 and XP22 were moderately or severely retarded, but no retarded relatives were identified.

The complementation groups of the proband's cells were known in 10 of the 31 families. We compared the incidence of retardation in the three families of groups A and D with that in the seven families belonging to all other complementation groups. In these seven families (four group C, two variant, one group B) with a total of 330 blood relatives, one retarded person was found. In contrast, among the 60 blood relatives in the three families whose probands were known to belong to groups A or D, there were three retarded individuals. The proportion of retarded relatives in the latter families was significantly greater than that in the other families of known complementation group ($P < .001$). The group D probands (XP8 and XP16) are described above; the group A proband (XP9) is of normal intelligence.

Vertebral Column Abnormalities

Among the 741 A-T relatives, there were five cases of severe idiopathic scoliosis, all in female members of different families (see table 1). No other congenital anomalies, mental retardation, or named syndromes were reported in these patients. Single cases were found in the XP and FA families. The median age at treatment was 13. The proportion of A-T relatives with severe idiopathic scoliosis (5/741) was significantly greater than that in the combined set of FA and XP relatives (2/1,798) ($P = .014$).

TABLE 1

A-T, FA, AND XP BLOOD RELATIVES WITH SPECIFIC CONGENITAL MALFORMATIONS AND DEVELOPMENTAL DISABILITIES

Study	Pedigree no.	Abnormality and information source	Age and status at close of study	Sex and relationship to proband
		Mental retardation with no other reported abnormalities		
FA	5 BIII2.....	"Retarded" (sib)	29 L	Uncle
XP	27 AIV30	"Mental retardation; IQ at 5½ yrs was 43" (HR)	13 L	Cousin (M)
XP	9 BIII2.....	"Severely mentally retarded and unable to communicate" (HR)	39 L	Aunt
XP	11 AIII5.....	"Mentally retarded; disabled" (HR)	61 L	Uncle
XP	4 BIII8.....	"Mentally retarded—never married; did odd jobs" (sib)	50 D	Uncle
XP	23 BIII6.....	"Retarded; worked all his life outdoors" (sib)	25 L	Uncle
		Mental retardation with short stature		
XP	14 BIII10.....	"Dwarflike; impaired mentally; finished 6th grade but poorly" (HR)	60 L	Half-uncle
XP	16 AIV3.....	"A midget, mentally and physically" (sib)	42 L	Cousin (M)

TABLE 1 (*continued*)

Study	Pedigree no.	Abnormality and information source	Age and status at close of study	Sex and relationship to proband
		Mental retardation with seizure disorder		
AT	5 AV3.....	"Mentally retarded; low set ears; hyperextensible joints; smooth thin skin; question of seizure disorder" (HR)	8 L	Nephew
AT	8 AIV1.....	"Mental retardation, severe to profound; epileptic—seizures controlled"; structural defects of foot; abnormal facies (HR)	33 L	Sister
XP	18 BIV20.....	"Full scale IQ of 67; seizures, frequent" age 15 (HR); "scoliosis, right, with 35° residual curve" treated with brace age 11 (HR)	20 L	Cousin (F)
		Microcephaly		
XP	27 AIV36	"Microcephaly, head below the 3rd percentile; markedly posteriorly flattened head" at 8 mos; "seizure disorder; developmental delay—not walking at 23 mos; congenital biliary atresia" manifest at 5 mos; birth wt. 5 lb 8 oz; normal perinatal period (HR)	5 L	Cousin (M)
XP	24 BIV4	"Microcephalic" at age 10; developmental delay; "spastic cerebral palsy"; epicanthal folds; seizures; birth wt. 6 lb 6 oz; normal perinatal period (HR); head measurement not recorded	25 L	Cousin (M)
XP	8 BIII2.....	"Microcephaly" (skull film) at age 20; "marked degree of hypophrenia; marked dorsal scoliosis; cerebral spastic disease; generalized convulsive seizures"; 4 wks premature; Caesarean section for placenta praevia; brief hypoxia (HR); head measurement not recorded	37 L	Aunt
XP	24 AIV5.....	"Microcephalic" (2.5 SD below mean at 10 yrs) (HR); intellectual status and developmental history not known	16 L	Brother
		Idiopathic scoliosis		
AT	5 BIV18.....	"Curvature of spine" age 14—surgery; died following scoliosis surgery (parent; confirmed by DC)	14 D	Cousin (F)
AT	11 BIII1.....	"Right scoliosis" age 14—surgery (HR)	49 L	Aunt
AT	28 AIV32	"Idiopathic scoliosis; main thoracic curve pattern" age 11—brace (HR)	22 L	Cousin (F)
AT	25 AIV38	"32° scoliosis; set in brace; 18° improved alignment" age 14 (parent)	17 L	Cousin (F)
AT	3 BIII2.....	"Marked scoliosis of thoracic spine; rib cage asymmetrical due to scoliotic feature" noted on X-ray at age 40 (HR)	46 L	Aunt
FA	3 BIV12.....	"Chronic back curvature" treated age 15 (parent); course of treatment not specified	17 L	Cousin (F)
XP	18 BIV20.....	See "Mental retardation with seizure disorder"		

Table 1 continued on p. 786

TABLE 1 (*continued*)

Study	Pedigree no.	Abnormality and information source	Age and status at close of study	Sex and relationship to proband
		Spina bifida		
AT	23 AIV4.....	"Hydrocephalus; spina bifida" (DC)	2 days D	Sister
AT	14 BIV8.....	"Hydrocephaly; spina bifida" (DC); "clubfoot; heart on wrong side" (parent)	4 mos D	Cousin (M)
AT	2 BIV7.....	"Spina bifida next to last lumbar vertebra; deformed last lumbar vertebra"; "left scoliosis" (HR)	23 L	Cousin (M)
XP	26 AIV14	"Spina bifida; meningomyelocele; arrested hydrocephaly" (HR)	27 D	Sister
XP	26 AIV17	"Spina bifida with meningocele" (HR)	25 L	Sister
		Other vertebral defects		
AT	19 AIV19	"Fused vertebrae in neck; split uvula; extra thumb" (parent)	29 L	Cousin (M)
AT	5 BIV12.....	"Joints are deformed in back; an undersized vertebra at base of spine; slight curvature" (self); "torsion of left kidney; probable double kidney and ureter on left" (IVP, HR)	32 L	Cousin (F)
		Genitourinary		
AT	5 BIV12.....	See "Other vertebral defects"		
FA	2 AIV15	"Multiple congenital strictures of urinary tract with hydronephrosis; hypospadias; Sprengle's deformity of scapula" (HR)	17 L	Brother
FA	6 BIV43.....	"Urethral stricture" (HR)	12 L	Cousin (M)
FA	17 AIV10	"Hydrocele; atrophic testis" (HR); "slight hip and knee deformity" (parent)	13 L	Cousin (M)
FA	30 BIV2	"Incomplete double uterus with double cervix and septate vagina" (HR); "congenital glaucoma" (self)	37 L	Cousin (F)
FA	30 AIII3.....	"External skin flap on left side of vagina missing" (self)	59 L	Aunt
XP	18 BIII6.....	"Bifid uterus" (HR)	50 L	Aunt
		Hands		
AT	19 AIV9.....	"Born with extra thumb, left hand-amputation" (parent)	22 L	Cousin (M)
AT	19 AIV19	See "Other vertebral defects"		
AT	28 AIV20	"Syndactylism, right hand" (HR)	28 L	Cousin (F)
AT	30 AIV53	"Distal and middle phalanx of many fingers and digits of many toes are missing" (HR)	44 L	Cousin (F)
FA	12 BIV11.....	"Two thumbs crooked at birth—was operated on" (parent)	24 L	Cousin (F)
FA	8 BIII6.....	"Deformity in the little fingers: hollow in the knuckle at base of fingers" (self)	28 L	Aunt
FA	18 BIV9	"On each hand two fingers are crooked; cranial synostosis; breast bones prematurely fused; will only have five adult teeth; lower jaw growing out of proportion" (parent)	7 L	Cousin (F)

TABLE 1 (*continued*)

Study	Pedigree no.	Abnormality and information source	Age and status at close of study	Sex and relationship to proband
		Hands		
FA	8 AIV9.....	"Finger deformity" (parent)	11 L	Cousin (F)
FA	8 AIV10	"Finger deformity" (parent)	6 L	Cousin (F)
FA	8 AIV11	"Finger deformity" (parent)	3 L	Cousin (F)
FA	6 AIV6.....	"Finger deformity" (self)	33 L	Brother
XP	28 BIII3.....	"Deformed knuckles" (self)	55 L	Aunt
XP	4 AV8.....	"Supernumerary digits, both hands and left foot; lobster toe right foot" (HR); familial trait on side of family which does not carry XP gene	4 L	Nephew
		Feet		
FA	15 AIV36	"Feet growing in—corrected at 6 mos" (parent)	1 L	Cousin (M)
FA	3 BIV13.....	"Excessive inward pronation of both feet—casts" (self)	22 L	Cousin (M)
FA	3 BIV15.....	"Overlapping of both little toes; also pointed upwards—surgical correction; convergent strabismus—surgery" (parent)	18 L	Cousin (F)
FA	7 AIII10	"Foot surgery" (self)	33 L	Mother
FA	3 AIV9.....	"Extreme pigeon toe, corrected with cast" (parent)	14 L	Cousin (M)
XP	10 BIV11.....	"Both feet turned in; brace and corrective shoes" (parent)	6 L	Cousin (M)
XP	10 BIV12.....	"Needs brace and shoes because both feet turn in" (parent)	3 L	Cousin (M)
		Multiple malformations not listed above		
FA	2 AV10	"Clubfoot" (parent); "esotropia" (HR)	8 L	Nephew
FA	15 AV1.....	"Congenital heart disease; hypertrophic pyloric stenosis" (HR)	2 L	Niece
XP	24 BIV3	"Pyloric stenosis; cleft palate" (HR)	20 L	Cousin (F)

NOTE: Pedigree no. includes type of family under study (AT, FA, XP), no. assigned to each extended family within a study, maternal (A) or paternal (B) side of the proband's family, generation within each family by Roman numerals (III: parent, aunt, or uncle; IV: first cousin or sibling; V: offspring, nephew, or niece), and place in birth order by Arabic numerals. Abbrevations: HR = hospital record, DC = death certificate, L = living, D = deceased.

Spina bifida was seen in three A-T children. One (AT23 AIV4) was a fraternal twin to an A-T proband. She died at age 2 days, so she must be considered a possible A-T homozygote. No cases of spina bifida were found in the FA families, and spina bifida with meningomyelocele was reported in two sibs of an XP proband.

Two other persons with vertebral abnormalities were found in the A-T families. Both had other congenital malformations as well. No similar disorders were reported in the other family sets.

Genitourinary Anomalies

Genitourinary anomalies were reported in five relatives of FA probands (described in table 1). Three of these FA family members also had malformations in other developmental fields. There were single reports of genitourinary abnormalities in the XP and A-T family sets. The proportion of persons with these defects in the FA families (5/698) was significantly greater than that in the combined set of A-T and XP relatives (2/1,841) ($P = .009$).

Malformations of Hands and Feet

Finger malformations reported in the FA relatives appear to be greater in number and different in kind from those found in the XP and A-T families, although detailed medical records to document the nature of an abnormality were usually not available (see table 1). Seven FA relatives reported finger anomalies, as did four A-T and two XP relatives. No polydactyly or syndactyly was found in the FA families, while these were the most common defects in the other family sets.

Foot deformities (other than clubfoot) requiring treatment were found in five FA blood relatives, while in the A-T and XP families only two persons, siblings who were first cousins to an XP proband, had such malformations. The FA families had a significant excess of hand and foot malformations ($P = .001$).

Multiple Malformations

Multiple malformations were found significantly more frequently in the FA relatives than in the other families ($P = .016$). (Cases not listed with multiple malformations in table 1 are found under genitourinary, hands and feet, mental retardation, or vertebral anomalies.) Seven persons in the FA families reported malformations of more than one developmental field. Genitourinary abnormalities were found in three of the seven, and four had anomalies of hands or feet. Three XP relatives had multiple malformations; two of them were mentally retarded. The two A-T family members with multiple malformations both had vertebral anomalies.

Other Manifestations

The data were not sufficiently detailed to detect an excess among the blood relatives of the eye movement abnormalities, hearing loss, or seizure disorders that are seen in homozygotes for these autosomal recessive syndromes. There was no one in the A-T families, apart from some probands, who experienced the repeated infections typically associated with immunodeficiency. There was one person with unexplained thrombocytopenia and no cases of anemia or pancytopenia leading to hospitalization or death among the 698 FA blood relatives.

DISCUSSION

If heterozygous carriers of genes for a specific autosomal recessive syndrome are predisposed to a particular common disorder, that disorder should be found in excess among the close blood relatives of persons with the syndrome. With such evidence, an association between the disorder and heterozygosity for the gene in

question is more likely if the disorder is commonly found in homozygotes. The present review of questionnaires, hospital records, and death certificates found a significant excess of severe scoliosis and vertebral malformations in 27 A-T families, of genitourinary and distal extremity anomalies in 25 FA families, and of mental retardation and microcephaly in 31 XP families.

A substantial proportion of XP homozygotes have neurological abnormalities, the commonest of which is mental retardation [4]. Microcephaly is seen in a smaller fraction of XP homozygotes. Although there are several case reports of retardation in close relatives of XP probands [9–11], the present study provides the first evidence that an XP gene predisposes the heterozygous carrier to mental retardation or microcephaly.

The number of mentally retarded persons we identified in the extended families of XP, A-T, and FA probands is certain to be less than the actual number for several reasons. First, the questionnaires did not ask specifically about mental retardation. Second, hospital records for a retarded person may have been unavailable because that person was never hospitalized or was hospitalized so long ago that the records were destroyed. Not all hospital records for a retarded individual include mental retardation among the diagnoses. Third, persons with mild or moderate retardation often are assimilated into the general population as they reach adult age [12]. Finally, some retarded persons may never have been evaluated.

None of these reasons explain the striking difference between the observed number of retarded persons in the XP families on the one hand, and the FA and A-T families on the other, since they apply to all three studies equally. In fact, if the true proportion of retarded persons among XP blood relatives was equal to that in the A-T and FA families, we might have found fewer retarded persons in the XP sample, because these families contained the highest proportion of older persons, who are more likely, if retarded, to be assimilated into the population.

Although our techniques are less likely to detect retardation than those used in surveys that assessed the proportion of retarded persons in various populations, it is useful to note that about 3/1,000 persons were found to be severely retarded (usually IQ < 50) in reliable population surveys [13]. The observation of 11/1,100 retarded persons in XP families cannot be compared to that figure directly, since it includes some persons of unknown IQ or IQ > 50. On the other hand, the population surveys included a substantial proportion of persons with identifiable forms of mental retardation (e.g., Down syndrome, retardation secondary to birth trauma or hypoxia), conditions that were excluded from our analysis.

XP homozygotes differ in neurological symptoms across a broad spectrum: some have normal or superior intelligence, while there are severely retarded microcephalic individuals at the other extreme. In the United States, XP patients with neurological deficit are almost always of complementation group A or D [4, 14]. The present data suggest that the risk for mental retardation in XP heterozygotes is also greater for groups A and D.

While siblings with XP usually appear to have the same degree of neurological involvement, there are two reported families in which affected individuals differed

in having microcephaly or mental retardation [15, 16]. We have, subsequent to the family study reported here, observed a family in which one XP child was microcephalic and died at age 6 of a progressive neurological disorder, while her sibling has only mild retardation in addition to the skin manifestations. Specific environmental factors could produce more severe neurological symptoms in some XP homozygotes. These factors may also be causally related to the retardation or microcephaly in heterozygotes. Thus many XP heterozygotes would escape neurological deficit, either because of genetic heterogeneity or because they were not exposed to causal agents.

Mild retardation is found in a substantial proportion of FA and A-T patients [3, 17]. There was no evidence for an excess of moderately or severely retarded persons in the FA or A-T families. We did not personally examine any of the XP, FA, or A-T blood relatives, nor did we measure IQs, so there is no information about the number of persons with mild retardation.

Family studies of heterozygote predisposition to mental retardation have a built-in bias against detecting severe retardation, since persons who qualified for the sample because they were married (the probands' parents in these studies) could not have been severely retarded. Further, the parents of our XP probands were probably somewhat selected for normal intelligence, because an XP patient whose parents are retarded is less likely to reach the National Institutes of Health or the major medical centers that referred cases for this study. In studying the hypothesis that genes associated with retardation in the general population may cause autosomal recessive syndromes in homozygotes, it is important in each case to select methods that will detect the type and degree of intellectual deficit suspected in the heterozygous carriers.

For one other genetic syndrome, autosomal recessive microcephaly, there is evidence that heterozygous carriers are likely to be mentally retarded [18–20]. Because of differences in methodology, the familial incidence of retardation in these 31 XP families cannot be compared to that in recessive microcephaly. Qazi and Reed [18] estimated that about 0.34% of the general population is mentally retarded because they carry a gene for recessive microcephaly. It is not possible to estimate the relative risk of mental retardation for XP heterozygotes from our family data, since, as noted above, mild cases were almost certainly not identified by examining medical records and death certificates. Consequently, it is impossible to estimate the overall contribution of XP genes to mental retardation in the general population.

Scoliosis is common among A-T homozygotes, as it is among patients with various genetic ataxias [3]. Vertebral malformations and spina bifida have also been reported in A-T homozygotes [3], although the true incidence of vertebral anomalies in A-T is not known. Among the A-T blood relatives, the proportion of persons with severe idiopathic scoliosis (6.7/1,000) was significantly greater than that observed in the FA and XP families (1.1/1,000). Rogala et al. [21] found 2.75/1,000 persons with scoliosis requiring treatment by examining school children and following them for two years, while prevalence rates for severe scoliosis of 1.33/1,000 [22] and 1.8/1,000 [23] were found in two other surveys.

It would be unwise to draw any conclusion about the relationship of spina bifida to the A-T gene in heterozygotes from the observation of three cases among our 741 A-T blood relatives, particularly since one of them was a possible homozygote. Still, this incidence is comparable to that observed in the most highly predisposed populations (e.g., [24]; 4.13/1,000 births in South Wales), despite our exclusion of stillbirths. The suggestion from these observations that A-T heterozygotes are predisposed to vertebral malformations is supported by our observation of different vertebral abnormalities in two other persons.

Gmyrek and Syllm-Rapoport [25] called attention to several case reports in which relatives in FA families had hematological abnormalities or limb malformations. In the 25 FA families we studied, there was a significant excess of persons with multiple malformations, especially genitourinary or limb anomalies, but no excess of hematological disorders. The genitourinary system and the limbs are, of course, frequent sites of abnormality in FA homozygotes [2], so the observation of an excess among the blood relatives lends support to the hypothesis that the FA gene predisposes the heterozygous carrier to such malformations.

Many XP homozygotes have progressive hearing loss and some have seizures [4]. Almost all A-T homozygotes have a distinctive oculomotor apraxia, and many FA homozygotes have disorders of eye movement or diminished hearing [3, 2]. Perhaps future family studies will distinguish between hearing loss of various types and detect any excess of disorders of eye movement or of seizures.

The present analysis of A-T, FA, and XP family data must be regarded only as preliminary evidence for the associations discussed above. For A-T, a new study of 100 families is underway to answer questions about the association of specific cancers with the A-T gene. It will provide additional evidence about the possible association of the A-T gene in heterozygotes with scoliosis or vertebral column abnormalities. In future studies, it will be important to compare the incidence of mental retardation and microcephaly in XP families of different complementation groups. In general, all associations detected in this analysis could be verified most reliably if a specific test were developed to identify heterozygous carriers of each of the three genes.

The importance of these observations derives in large part from the prevalence of heterozygotes in the general population. While accurate figures for the incidence of homozygotes for XP, A-T, or FA are available only for limited populations, it is almost certain that the heterozygote frequencies for each of these conditions falls between .01 and .001, so that heterozygous carriers of each gene are relatively common [5–7]. Thus these heterozygotes are a substantial portion of the population that may be at a special risk for specific congenital malformations or development disabilities.

If the associations noted in this analysis are confirmed in future studies, perhaps the most intriguing question is how these genes in heterozygotes interact with ordinary environmental events to produce congenital malformations or developmental disabilities. Understanding these environmental-genetic interactions would be of great use in preventing such disorders in genetically predisposed persons and perhaps shed light on the pathogenesis of similar disorders in other individuals.

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