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A Syndrome of Severe Mental Retardation, Spasticity, and Tapetoretinal Degeneration Linked to Chromosome 15q24

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Summary

Nine affected individuals are described from a large extended Pakistani family manifesting a syndrome characterized by a triad of varying degrees of spasticity, severe mental retardation, and visual impairment resulting from tapetoretinal degeneration. In all cases, the parents were at least first cousins, since there was complex consanguinity within the pedigree. The clinical features differ from previously reported syndromes involving pigmentary retinal degeneration and appear to represent a new recessively inherited neurodegenerative condition. Linkage to a 4–5 cM-region between markers D15S211 and D15S152 on 15q24 has been established by autozygosity mapping.

Introduction

Pigmentary retinopathy or tapetoretinal degeneration can be a feature of a number of inherited metabolic disorders and syndromes of unknown etiology. The classification depends on the constellation of clinical features and metabolic abnormalities seen in the affected individuals (table 1). Some of the syndromes with an unknown etiology have overlapping features (Norio and Raitta 1986), and it is only when the molecular etiology is known that a comprehensive classification system will be realized. We report a family that has some of the features described in other case reports of syndromes involving retinal pigmentation/degeneration. However, many of the features reported elsewhere are absent, and we propose that this condition represents a new clinical disorder.

The possibility of using consanguineous families to map rare recessive disorders was first published in 1953 (Smith 1953). This concept was expanded in 1987 (Lander and Botstein 1987), but, with the advent of large numbers of highly polymorphic markers, autozygosity mapping only recently has started to fulfil its potential. It has been used to map rare recessive syndromes (Ben Hamida et al. 1993) as well as highly heterogeneous common conditions (Petit 1996). This technique has been utilized in mapping this previously unreported disorder to chromosome 15q24.

We report a family with nine cases, from four related sibships, presenting with a syndrome that is characterized by spasticity of varying degrees, severe mental retardation, and progressive visual impairment caused by a tapetoretinal degeneration. Some affected individuals showed dystonic features, but no additional neurological features or other associated abnormalities were noted by clinical examination. The clinical picture differs from previously described syndromes involving a tapetoretinal degeneration and may represent a previously unrecognized neurodegenerative disorder. The parental consanguinity and pattern of inheritance within the pedigree make autosomal recessive inheritance likely. Autozygosity mapping was used to establish linkage of this family to chromosome 15q24, following a genomewide search using highly polymorphic microsatellite markers.

Subjects and Methods

Subjects

The nine affected individuals are from four related sibships from two generations of a large consanguineous family originating from the Mirpur district of northern Pakistan. There was a high degree of consanguinity within the family (fig. 1).

Sibship 1.—Four affected individuals (VI-1, VI-2, VI-3, and VI-5) were identified. All presented with global developmental delay and visual impairment at 9–12 mo

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Table 1

Disorders in Which Pigmentary Retinopathy Is a Feature

Inherited Metabolic Disorder or Syndrome Associated with Pigmentary Retinopathy	MIM No(s).	Reference(s)
Metabolic disorder:		
Abetalipoproteinaemia (Bassen-Kornzweig)	200100	Bassen and Kornzweig (1950)
Refsum disease	266500	Refsum (1952)
Infantile Refsum disease	266510	Scotto et al. (1982)
Neuronal ceroid lipofuscinosis (Batten disease)	204200	Wisniewski et al. (1992)
Mucopolysaccharidosis type II (Hunter disease)	309900	Gerich (1969)
Mucolipidosis type IV	252650	Amir et al. (1987)
Peroxisomal disorders	...	Moser et al. (1995)
Syndrome:		
Laurence-Moon-Biedl-Bardet syndrome	245800	Bardet (1920)
	209900	Laurence et al. (1866)
Usher syndrome	276900	Hallgren (1959)
Cockayne syndrome	216400	Cockayne (1933)
Alstrom syndrome	203800	Alstrom et al. (1959)
Joubert syndrome	213300	Joubert et al. (1969)
Jeune syndrome	208500	Allen et al. (1979)
Hallervorden-Spatz disease	234200	Hallervorden and Spatz (1922)
Senior-Loken syndrome	266900	Senior et al. (1961)
Boucher-Neuhauser syndrome	215470	Boucher and Gibberd (1969)
Leber amaurosis	204000	Leber (1871)
Cohen syndrome	216550	Cohen et al. (1973)
Mirhosseini-Holmes-Walton syndrome	268050	Mirhosseini et al. (1972)

of age. At the time of examination, ages were 12–17 years, and all showed severe mental retardation. Clinical examination revealed spasticity affecting all four limbs of the oldest three individuals. The youngest (individual VI-5) showed marked muscle wasting but no spasticity. All four were microcephalic, but head circumferences within the normal range had been documented at birth. All showed a retinal dystrophy with marked attenuation of retinal arterioles and secondary optic atrophy. No other dysmorphic features or abnormalities were noted by clinical examination, apart from wide-spaced teeth and a single palmar crease, in all four individuals

Sibship 2.—The affected individual (V-3) presented with global developmental delay and poor vision, which was apparent from 2 years of age. When seen at 23 years of age, she showed a marked spastic paraplegia with dystonic posturing and severe mental retardation. Ophthalmological examination showed mild optic atrophy with gross attenuation of retinal arterioles and subtle retinal pigmentation. Clinical examination was otherwise normal. Two siblings (V-4 and V-6) showed mild developmental delay but no physical abnormalities, and one additional sibling (V-8) was diagnosed with congenital stationary night blindness and mild learning difficulties. He showed no features of spasticity, and, after expert ophthalmic review, he was not considered to demonstrate the same retinal dystrophy as his sister.

Sibship 3.—Two affected individuals (V-9 and V-13) were identified. Both presented with global developmental delay and poor vision within the first 18 mo of life, having appeared normal during early infancy. When seen at 29 and 20 years of age, respectively, both individuals showed a marked spastic quadriplegia, with dystonic posturing evident in individual V-13. Both were severely mentally retarded. Ophthalmological examination showed a severe tapetoretinal degeneration with gross optic atrophy in individuals V-9 and V-13.

Sibship 4.—Two affected individuals (V-14 and V-15) were identified. Both presented within the first 18 mo of life, with global developmental delay and poor vision. When seen at 24 and 22 years of age, respectively, both showed generalized hyperreflexia with dystonic posturing noted and severe mental retardation. Individual V-15 also showed spasticity affecting the lower limbs and was microcephalic. Ophthalmological examination of individual V-14 showed optic atrophy with marked attenuation of retinal arterioles. Mild retinal pigmentation was noted in individual V-15. General examination was otherwise normal.

Families

Affected individuals were visited and clinically examined at home. Ten milliliters of venous blood was

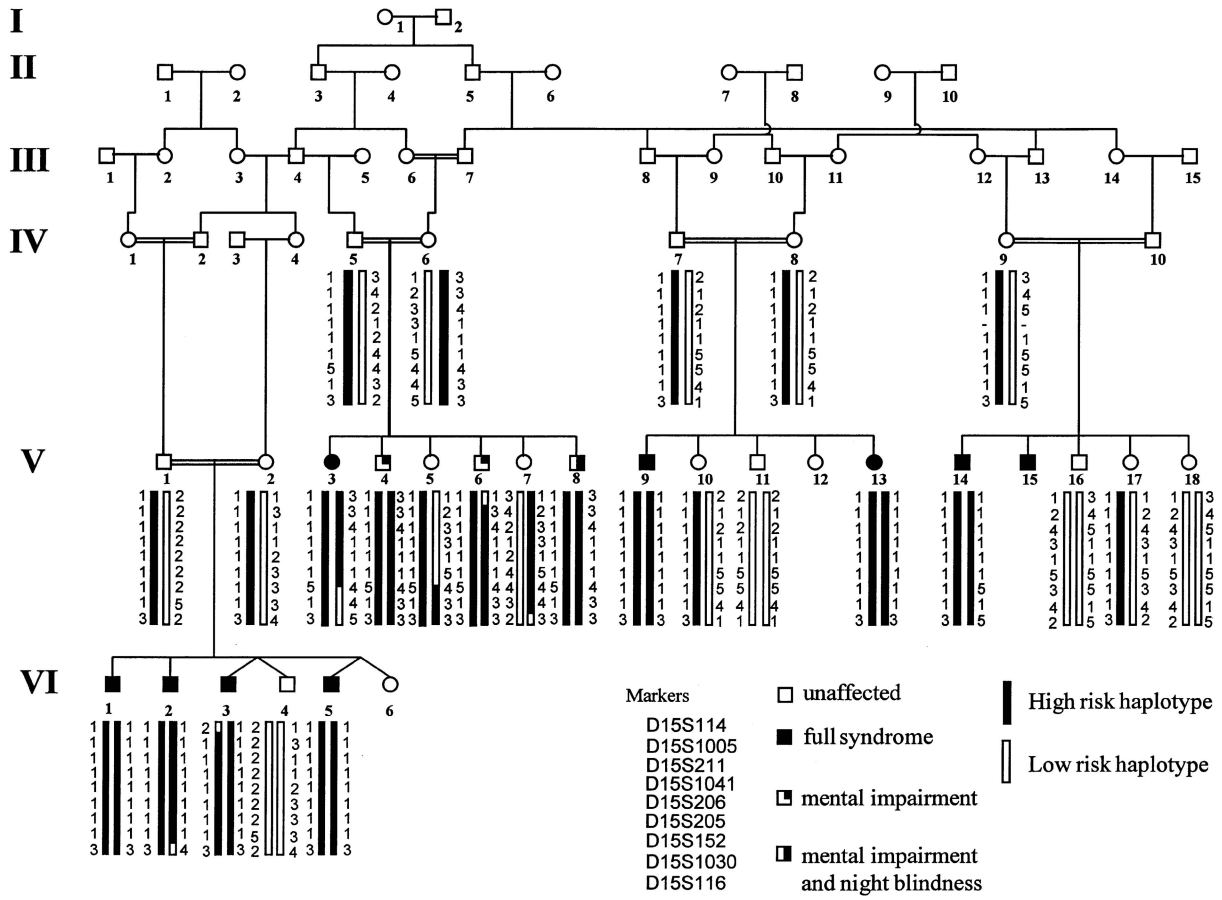

Figure 1 Genotype data for markers (ordered cen–tel) from the region of linkage on chromosome 15q24

collected from all consenting individuals. DNA was extracted by use of standard protocols.

Clinical Investigations

The following clinical investigations were carried out: blood and urinary amino acids, normal; urinary organic acids, normal; white-cell enzymes (hexosaminidase, β-galactosidase, and aryl sulphatase), normal; blood film, no white-blood-cell inclusion bodies; and skin biopsy, electron microscopy normal. Because of the close phenotypic similarities seen, investigations were not duplicated on all affected individuals. None of the affected individuals had undergone cranial imaging at the time of this study. All were severely mentally retarded and would have required heavy sedation or even general anesthesia to facilitate this. It was felt that the risks to the patients could not be justified when the information yielded would be unlikely to influence clinical management or genetic counseling.

Genotyping

A genomewide linkage analysis was performed by use of a set of 254 polymorphic microsatellite markers with an average spacing of 12–14 cM (Reed et al. 1994). Extra markers from regions of interest were obtained from the CEPH-Généthon web site (http://www.cephb.fr/bio/ceph-genethon-map.html). Oligonucleotides were modified with a 5′ fluorescent label, for analysis by use of an automated ABI 377 gene scanner.

PCRs were performed in a total volume of 20 μl of 1 × reaction buffer containing 40 ng of DNA, 0.2 mM dNTPs, 1.5 mM $MgCl_2$, 50 ng each primer, 1 unit *Taq* DNA polymerase, 50 mM KCl, 10 mM Tris-HCl (pH 9.0), and 0.1% Triton X-100. Annealing temperatures were optimized for each primer pair. PCRs were performed as follows: initial denaturing at 95°C/5 min, followed by 30 cycles of 95°C/20 s, annealing temperature/20 s, and 72°C/20 s. Products were analyzed on a 4%-polyacrylamide/6-M urea/1 × Tris borate–EDTA

gel for 2 h/3,000 V/51°C. Data was captured and analyzed by use of the ABI Genescan Analysis software package, and the genotypes were generated by use of the Genotyper software package.

Multipoint analysis was performed by use of the HOMOZ/MAPMAKER program (Kruglyak et al. 1995). The disease gene frequency was estimated to be 1/200. Marker allele frequencies for each of the markers were assumed to be equal.

Results

All the affected individuals were analyzed with a total of 254 highly polymorphic markers. One marker, D15S114, was homozygous in six of the nine affected individuals. Therefore, an additional eight extra markers from this region were identified, from the Généthon map, at spacings of ~1–2 cM (cen–D15S1005, D15S211, D15S1041, D15S206, D15S205, D15S152, D15S1030, D15S116–tel), resulting in a total of nine markers spanning a 15-cM region. The haplotypes generated are shown in figure 1.

Multipoint analysis was performed on each sibship of the family by use of HOMOZ/MAPMAKER, and the results were combined (fig. 2). The maximum LOD score obtained by use of this analysis was 3.4. The LOD scores generated from sibships 1, 3, and 4 were maximal for the pedigree structure; summation of the results for these branches of the family yielded a LOD score of 6.44 between D15S1041 and D15S205 (fig. 2).

Only one member of sibship 2 had the full phenotype and was therefore classified as affected, for the initial analysis. However, three other members of the family had mild mental retardation, and one of these members also had spasticity and night blindness but did not have the unusual retinal dystrophy seen in the other affected members of the family. These individuals initially were coded as unaffected, for the analysis, but they may represent variable expression of the disease phenotype. In order to circumvent this problem, an "affected-individuals-only" analysis was performed, and this analysis generated a maximum LOD score of 5.6 between D15S211 and D15S152. In this sibship, all four individuals with some form of neurological abnormality have the same haplotype at D15S1041–D15S205.

In general, the minimal critical region in autozygosity mapping is the smallest region of autozygosity shared by the affected individuals and not by the unaffected individuals within the pedigree. In order to be confident of the boundaries flanking the locus in this pedigree, only the affected individuals may be used. The only region of autozygosity common to all the affected individuals is between marker D15S211 and D15S152, a distance of ~4 cM. A common haplotype for markers

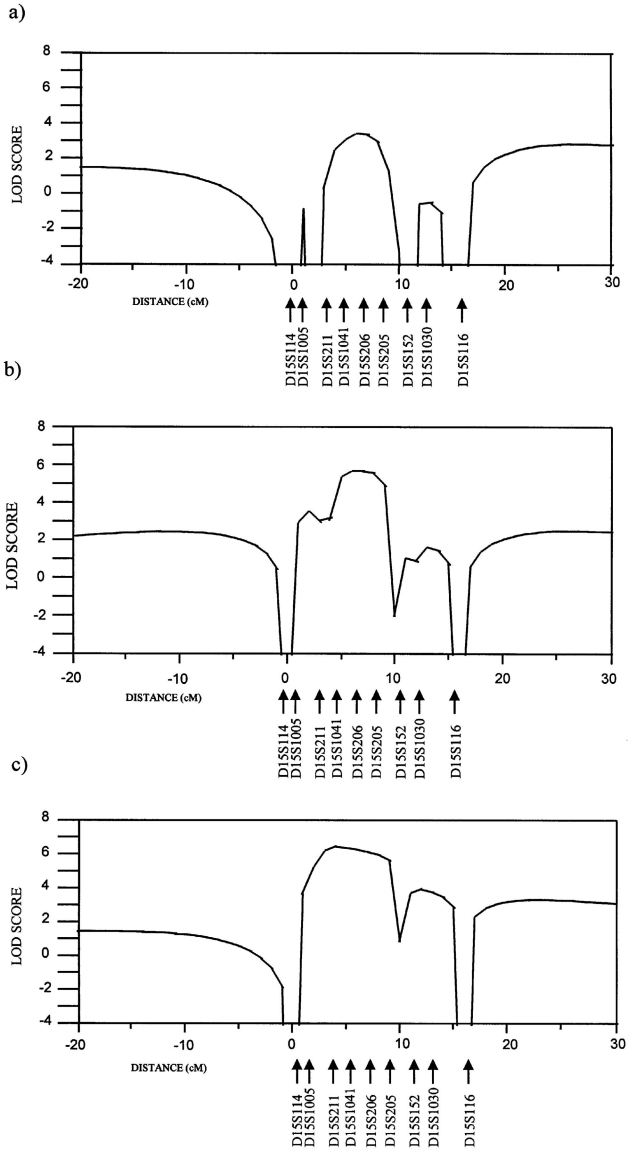

Figure 2 Results of multipoint analysis for the region of linkage. *a,* Entire family. *b,* Affecteds only. *c,* Sibships 1, 3, and 4.

D15S1041, D15S206, and D15S205 can be seen in all the affected individuals (fig. 1).

We have demonstrated linkage of a novel developmental syndrome to chromosome 15q24. This syndrome consists of the unique triad of severe mental retardation, an unusual pigmentary retinopathy, and varying degrees of nonprogressive spasticity.

Discussion

Pigmentary retinopathy or tapetoretinal degeneration is a feature of a number of genetic disorders (table 1).

The normal metabolic investigations, the absence of specific associated abnormalities, and the phenotypic differences in affected individuals distinguish the condition described in this family from disorders described elsewhere.

Reported cases of Mirhosseini-Holmes-Walton syndrome (MIM 268050) (Mirhosseini et al. 1972; Mendez et al. 1985) show some features in common with the cases described in this report, but these previously described cases differ in the occurrence of cataracts, dysmorphic facial appearances, truncal obesity, and joint hypermobility and arachnodactyly. It subsequently has been suggested that these cases may represent variants of Cohen syndrome (MIM 216550) (Norio and Raitta 1986; Steinlein et al. 1991), with clear phenotypic differences from the affected individuals in the family described in this study.

A syndrome of hereditary spastic paraplegia with retinal degeneration (MIM 270700) has been described (Stewart 1937; Evans 1954; Mahloudji and Chuke 1968; MacRae et al. 1974), but adult onset was observed in all cases. Hereditary spastic paraplegia with a pigmentary retinopathy and dementia (MIM 236130) was described by Sjaastad et al. (1976); but, in that condition, the age at onset was 5–20 years, and the retinopathy differed from that in the family described here, presenting with color blindness followed by the development of diffuse retinal pigmentation. Raised levels of homocarnosine were found in the cerebrospinal fluid of affected patients.

The pigmentary retinopathy seen in the family described herein is unique. Affected individuals appeared normal at birth and during early infancy but presented with global developmental delay, visual impairment resulting from a tapetoretinal degeneration, and the development of varying degrees of spasticity during the first 18–24 mo of life. Dystonic features were seen in some patients, but there were no other neurological abnormalities or associated features. There is evidence that the disease follows a progressive course, with the older individuals appearing to be more severely affected and with, in some, the observed development of microcephaly during the first few years of life. Biochemical investigations have not identified an underlying metabolic disorder, and the affected individuals in this extended family may be manifesting a previously undescribed neurodegenerative condition.

By use of an affected-individuals-only analysis, the disorder in this family has been mapped to a 4–5-cM interval on chromosome 15q24, with a maximum LOD score of 5.44 between markers D15S211 and D15S152. In this family, 254 markers were genotyped at an average spacing of 12–14 cM. Only one region was autozygous for an interval >7 cM, in the affected members of the first sibship. The affected members of sibships 3 and 4 also were autozygous for >10 cM of this region. Individual V-3 in sibship 2 was homozygous for markers D15S1041, D15S206, and D15S205 and was heterozygous at both D15S211 and D15S152, giving a maximum autozygous region of ~4–5 cM. The small autozygous region seen in sibship 2 suggests that the disease-causing mutation(s) occurred several generations ago, which increases the likelihood that the disease allele was inherited from one of the more distantly related individuals "marrying into" the family in a recent generation.

Although the degree of spasticity is variable across the whole pedigree, the retinal dystrophy and mental retardation are severe in all the affected members of sibships 1, 3, and 4. Sibship 2 is interesting in that it includes one individual who has all of the severe features seen in the other branches of the family and three additional individuals who have either mild mental retardation or mild mental retardation, spasticity, and night blindness. Spasticity and mental retardation are often variable within single sibships (Mitchell and Bundey 1997), and retinopathies are also known to have variable phenotypes. There are two plausible explanations for the data seen in sibship 2. The most likely explanation is that this is a variable condition and that the other members of the sibship are showing a phenotype that is milder than that shown by individual V-3. The clinical phenotypes were well documented prior to the genotyping information being available. This would map the responsible gene(s) to the interval defined previously. A second explanation is that the disease-causing mutation lies between D15S205 and D15S152 and that a recombination event has occurred between these two markers. This would map the gene to a 1–2-cM region.

Rare familial disease phenotypes can be the result of a permissive mutation within a highly conserved and vital gene, small deletions affecting contiguous genes, or separate mutations in two or more contiguous genes. We have concentrated our search, for candidate genes, on the retinal phenotype seen in this family. Two retinal genes are known to map to this region: the gene for cellular retinoic acid–binding protein (Eller et al. 1992) and the gene for cellular retinaldehyde-binding protein (Maw et al. 1997). The first of these genes is ubiquitously expressed, with particularly high levels of expression in retina and skin. The second gene is that for retinaldehyde-binding protein, which is expressed almost exclusively within the retina, although an expressed sequence tag (EST) has been sequenced from a hippocampal library with an identical 3′ UTR, suggesting that low-level expression may be present elsewhere. Recently, a mutation within this gene has been shown to be involved in retinitis pigmentosa, but there were no associated features within the family described (Maw et al. 1997). Both of these genes are candidates for the disorder that

we describe, although the expression pattern of the gene for retinaldehyde-binding protein suggests that, if this gene is responsible for the retinal disease, then a second gene may well be responsible for the spasticity and mental retardation. There also are five ESTs, expressed in retinal libraries, that map to the critical region (Schuler et al. 1996).

The mapping and subsequent cloning of genes involved in rare recessive conditions will provide unique information about both normal and abnormal development in humans. Increased understanding of the normal developmental pathways within neuronal development hopefully will lead to better treatment and prognosis for patients suffering from a wide variety of nonprogressive neurological conditions and neurodegenerative diseases. Visual impairment is a major handicap, and a better understanding of retinal development offers the hope of delaying and even reversing conditions leading to retinal degeneration.

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