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A distinct autosomal recessive ataxia maps to chromosome 12 in an inbred family from Jordan

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Abstract

Autosomal recessive ataxias are a heterogeneous group of rare disorders characterized by early onset ataxia associated with neurologic, ophthalmologic or systemic signs. The ataxias associated with myoclonus, epilepsy and progressive neurological degeneration are usually included with the progressive myoclonus epilepsies, one of which is Unverricht-Lundborg disease. We identified four siblings with ataxia, juvenile onset progressive action tremor and atonic seizures from a Jordanian family. The mode of inheritance of this syndrome is autosomal recessive. We performed a genome-wide screen for linkage and fine mapped the region that contains the disease locus. The four affected siblings have ataxia noted at the onset of walking with dysarthria and bulbar features, but no cerebellar hypoplasia on MRI. They all developed a fine tremor that progressed to a coarse action tremor, as well as atonic seizures. Treatment with valproate fully controlled the seizures and improved the tremor, but did not change the course of the ataxia. We mapped the gene responsible for this disorder to the pericentromeric region of chromosome 12. A recently described autosomal recessive variant of Unverricht-Lundborg disease also maps to the same region. We discuss the similarities and differences between our family and the family with the Unverricht-Lundborg disease variant.

Keywords

Ataxia; Action tremor; Linkage analysis; Atonic seizures; Chromosome 12; Progressive myoclonus epilepsy; Epilepsy

1. Introduction

Autosomal recessive ataxias are a heterogeneous group of rare disorders characterized by progressive or non-progressive early onset ataxia associated with neurologic,

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ophthalmologic or systemic signs [1]. A few of these ataxias are genetically and molecularly characterized and the pathogenesis is 'loss of function' of cellular proteins involved in metabolic homeostasis, cell cycle or DNA repair [1]. The ataxias associated with myoclonus, epilepsy and progressive neurological degeneration are usually included with the progressive myoclonus epilepsies (PME) [2]. PME are a heterogeneous group of rare neurogenetic disorders that include Lafora disease (OMIM # 254780), lipidoses and a subgroup of degenerative PME. Of the degenerative forms Unverricht-Lundborg disease (ULD) (OMIM # 254800) is the most common [3,4] and is due to mutations in the cystatin B gene [5,6]. It is clinically characterized by myoclonic or tonic-clonic seizures starting around the age of 10 years and progressing to become more severe and disabling. There is associated myoclonus and ataxia; both are also progressive. Although ULD appeared to be a homogeneous disease, a new clinical and molecular form has been described recently as a ULD variant. This form of ULD is characterized clinically by myoclonic or tonic-clonic seizures or both, action myoclonus and ataxia without significant progressive dementia. The causative gene of this variant has been localized to the pericentromeric region of chromosome 12 [7].

Homozygosity mapping utilizing inbred families is a practical strategy for mapping rare autosomal recessive disorders [8]. The high prevalence of consanguinity among Jordanians makes it possible to identify inbred families with rare recessive disorders that are large enough to independently establish linkage [9]. In these families, individuals with the trait are likely to have inherited both copies of the mutated gene from a common ancestor and are thus identical by descent (IBD) not only at the trait locus but also at neighboring marker loci.

In this report, we describe a Jordanian family with four siblings with cerebellar ataxia, juvenile onset progressive action tremor and atonic seizures. The mode of inheritance is autosomal recessive and the responsible gene mapped to the pericentromeric region of chromosome 12 by homo-zygosity mapping and parametric linkage analysis. We discuss the similarities and differences between our family and the one described as a new form of ULD [7].

2. Subjects, materials and methods

2.1. Subjects

We identified a family from Jordan with four individuals affected with a distinct form of ataxia. The family has been followed by the same neurologist (A.S.D.) for the last 10 years and the evolution of symptoms and signs, especially in the two youngest subjects, have been carefully noted in their medical records. We obtained a detailed family history and constructed a three generation pedigree (Fig. 1). We reviewed the records and updated the clinical picture at every outpatient clinic visit over the last 6 years. Informed consent was provided by the participants and their legal guardians.

2.2. Genotyping

A genome-wide scan for linkage was performed with the ABI PRISM linkage mapping set of fluorescent micro-satellite DNA markers, version 2 (PE Biosystems, Foster City, CA) using only affected individuals. To refine the region of interest, 14 microsatellite markers were chosen for genotyping. Amplification of these markers was performed by PCR under standard conditions. The amplified products were analyzed on 6% denaturing polyacrylamide gel, and stained with silver nitrate according to standard protocols [10].

2.3. Statistical analysis

The LOD score analysis was performed using MLINK of the FASTLINK computer program package [11]. The genetic and physical map distances for the genome and fine mapping markers were obtained from the Rutgers combined linkage—physical map (Build 35) [12]. The data were checked for genotyping errors using PEDCHECK [13] to identify Mendelian inconsistencies while the MERLIN [14] program was used to detect potential genotyping errors that did not produce Mendelian inconsistencies. Multipoint linkage analysis was performed using ALLEGRO [15]. The parametric linkage analysis was carried out assuming autosomal recessive inheritance, full penetrance, no phenocopies, disease allele frequency of 0.001 and equal marker allele frequencies. Since false positive results may be obtained when analyzing the data using too low of a frequency for the marker allele segregating with the disease, we carried out a sensitivity analysis for the multipoint linkage analysis with frequency of the marker alleles ranging from 0.2 to 0.8. This was done in order to determine whether the multipoint LOD scores are robust to allele frequency misspecification. Haplotypes were constructed using the SIMWALK2 [16].

3. Results

3.1. Clinical picture

V-3: This currently 18-year-old girl was noted to have ataxia around the age of 15 months when she started to walk. Her parents recognized an unbalanced gait with side-to-side swaying and noted that she would hold onto furniture for support. She developed a fine hand tremor at the age of 4 years which progressed to a coarse jerky hand movement by the age of 10 years, particularly upon reaching for objects and persisting throughout the active movement. The tremor was not present at rest or when maintaining a posture without movement. The onset of the atonic seizures was around the age of 10 years, manifested by sudden drops to the floor mostly occurring on waking up in the morning but sporadically during the day as well. She has had no other types of seizures. She developed slurred speech and frequent choking attacks around the age of 10 years. During the early school years, she performed very well, but her scholastic achievement dropped significantly due to the jerky hand movements, the embarrassing frequent falls and the consequent development of an impaired mood. Her growth parameters and early development, other than the motor skills, were normal. On physical examination she had intact cranial nerve function without nystagmus, normal tone and muscle power with mild hyporeflexia and intact deep and superficial sensation. Coordination was abnormal with hypermetria on finger to nose test and disidiadochokinesia. She had a coarse action tremor, a wide-based ataxic gait and absent Romberg sign. There were no myoclonic jerks in the facial or limb muscles. Serum lactate,

CPK, hearing and vision were normal. The EEG showed generalized paroxysms of sharp/slow wave activity. An MRI at the age of 16 years was normal, specifically reporting no cerebellar hypoplasia. She received valproate with full control of the seizures and remarkable improvement in the tremor as evidenced by legible handwriting but without changing the course of the ataxia.

V-4: This currently 15-year-old girl had a similar course and is currently doing well, as she is seizure free and the tremor is markedly improved on valproate. An MRI was normal at age 13 years and the EEG pattern was similar to her sister's.

V-5: The clinical picture of this currently 12-year-old girl is exactly like her sisters. She responded to valproate with full seizure control and marked improvement in the tremor. Her MRI was normal at age 10 years and EEG findings were similar to both sisters.

V-6: This 8-year-old boy has ataxia, coarse action tremor and dysarthria and just started to have atonic seizures. He was just started on valproate and it is early to comment on the response. His MRI was normal at the age of 5 years. The EEG pattern was similar to his 3 older sisters.

Two maternal aunts and one maternal uncle are similarly affected by history. One aunt and the uncle died at the age of 17 years from complications of the disorder, as they were accident and infection prone. One untreated aunt is still alive at the age of 40 years, albeit she is unable to ambulate due to frequent falls and has a coarse action tremor. It is her wish that she does not participate in this study at this time.

The clinical picture of the four affected children is summarized in Table 1.

3.2. Linkage analysis

The genome-wide scan showed four regions of homo-zygosity; all but one were excluded by genotyping all family members for markers within the regions. The region of interest, around the centromere of chromosome 12, was refined using 14 microsatellite markers. Pair-wise linkage analysis produced a maximum LOD score of 2.2. The multipoint linkage analysis produced a maximum LOD score of 3.3, which did not change on the multipoint sensitivity analysis. The haplotypes for 14 different markers in the region of linkage were constructed for all the participating family members (Fig. 1). The minimal region of homozygosity in the affected individuals was 18.67 cM (23 Mb) between the microsatellite markers D12S1591 on the short arm of chromosome 12 and GATA137B11 on the long arm of chromosome 12 and contains about 85 genes (Fig. 2) [12].

4. Discussion

The clinical picture consists of early onset ataxia, dysarthria, progressive coarse action tremor and atonic seizures. Cognitive function is spared by clinical assessment, although no formal testing was carried out, and there are no non-neurologic symptoms. This form of ataxia appears to be distinct from other autosomal recessive ataxia syndromes [1]. There are similarities with the recently described form of ULD [7], in particular that both families are of Middle Eastern origin, but there are clear discrepancies as well. The presenting symptom

in all four of our subjects was the early onset ataxia which was noticed at the onset of walking. We assert that they have action process, worsens as the hand approaches the target and continues for few seconds after the target is reached. This was quite evident in our patients whose handwriting worsened as the coarseness of the tremor increased. In action myoclonus the jerky coarse movements are apparent with the onset of the symptom, occur with the initiation of movement but usually remit within seconds, even with sustained movement. It is possible that the tremor in our patients is composed of two components, the ataxic tremor and the action myoclonus and that the treatment with valproate both eliminated the action myoclonus and improved the tremor. In addition, the types of epileptic seizures are different as the subjects in our family only have atonic seizures with early morning peak, while nocturnal (no early morning peak) tonic-clonic or myoclonic seizures were present in all affected members of the reported family [7]. Even if the limb tremor has an action myoclonus component, this is not a myoclonic seizure. A comparison between affected individuals in both families is summarized in Table 2. However, it is to be noted that the age of our oldest patient at the most recent evaluation was similar to the age at the evaluation of the youngest patient in the other family. Evolution of the clinical picture in the affected individuals in our family into a PME is still plausible, but even so the emphasis on myoclonus, if not epilepsy, may be misplaced.

The syndrome in this family is autosomal recessive, since male and female siblings are affected and the parents are normal and consanguineous. The gene responsible for the syndrome in this family lies within the pericentromeric region of chromosome 12 by linkage analysis, assuming the autosomal recessive model. Although the pedigree structure is compatible with a mitochondrial DNA disorder, the clinical picture does not support this consideration. The recently described form of ULD is also linked to the pericentromeric region of chromosome 12 and the critical region is completely included in our critical region. Although this observation probably denotes a common genetic etiology for these two autosomal recessive disorders in both families with similar phenotype, genetic heterogeneity is still possible. This scenario has been found in an autosomal recessive immunologic disorder, Griscelli syndrome, where two distinct molecular types with similar phenotype, linked to the same region on chromosome 15, but were due to different mutations in two different genes [17,18].

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Fig. 1. Pedigree of the family showing the haplotypes for the markers in the pericentromeric region of chromosome 12. The horizontal lines indicate a crossover event and a recombinant chromosome.

Fig. 2.

Ideogram of chromosome 12 showing the critical region between D12S1591 and GATA137B11. Mb, Megabases; cM, centimorgan.

Table 1

Summary of the clinical features of the four affected individuals

Clinical feature	V-3	V-4	V-5	V-6
Age at examination	18 years	15 years	12 years	8 years
ATAXIA (Onset)	15 months	15 months	15 months	15 months
ATAXIA (Nature)	Unsteady gait, holding onto furniture for support			
ATAXIA (Dysarthria)	+	+	+	+
ATAXIA (Bulbar features)	+	+	+	–
ATAXIA (Eye movement)	–	–	–	–
TREMOR (Onset)	4 years	4 years	4 years	3 years
TREMOR (Type)	Starts fine and progresses to coarse over 4–5 years			
SEIZURES (Onset)	10 years	9 years	9 years	8 years
SEIZURES (Type)	Atonic (drop attacks), worse in the morning			
Investigations (EEG)	Generalized or paroxysmal sharp/slow-wave activity			
Investigations (MRI)	Normal, no evidence of cerebellar hypoplasia			
Treatment (Valproate)	+	+	+	+
Treatment (Response)	Full seizure control, tremor improved			

Table 2

Clinical features of affected individuals from the two reported families

Feature	El-shanti et al.	Berkovic et al. [7]
Age range	8–18 years	17–37 years
Age at onset of presenting symptom	15 months	5–10 years
Presenting symptom	Ataxia, unsteady gait	Seizures
Type of seizures	Atonic	Myoclonic or tonic-clonic
Onset of seizures	8–10 years	5–10 years
Timing of seizures	Early morning	Nocturnal
Type of movement disorder	Action tremor	Action myoclonus
Facial myoclonus	Absent	Present