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Identification of a novel primary torsion dystonia locus (DYT13) on chromosome 1p36 in an Italian family with cranial-cervical or upper limb onset

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Abstract Primary torsion dystonia (PTD) is a clinically and genetically heterogeneous group of movement disorders, usually inherited in an autosomal dominant fashion. Three PTD loci (DYT1, DYT6 and DYT7) have been identified to date. However, in several PTD families linkage to the known loci has been excluded. We identified an Italian PTD family with 11 definitely affected members. Phenotype was characterised by juvenile or early-adult onset, prominent cranial-cervical and upper limb involvement, mild course and occasional generalisation. A genome-wide search performed in the family identified a novel PTD locus (DYT13) within a 22-cM interval on the short arm of chromosome 1, with a maximum lod score of 3.44 ($\theta = 0$) between the disease and marker D1S2667.

Primary torsion dystonia (PTD) is a movement disorder in which dystonia is the primary and indeed sole abnormality directly attributable to the condition [1]. PTD has a wide clinical spectrum and may be generalised, segmental or focal, its severity being largely determined by the age at onset. Patients with onset in childhood tend to develop severe generalised dystonia, while onset in adult life (commonly in cranial or cervical muscles) is less frequently associated with spreading to other body districts and to generalisation. PTD is often inherited in an autosomal dominant pattern with reduced penetrance (30%-40%) [1]. Three PTD loci have been identified. The gene responsible for early limb-onset generalised dystonia (DYT1) maps to chromosome 9q34 and codes for an ATP-binding protein termed torsinA. The only detected mutation is a 3-base pair (GAG) deletion, resulting in loss of a glutamic acid residue in a conserved region of the protein [2]. A form of adult-onset, focal PTD (DYT7) has been linked to chromosome 18p in a German family [3], while in two German-Mennonite families showing a mixed phenotype a novel locus (DYT6) has been mapped to chromosome 8 [4]. Linkage to known loci has been excluded in several PTD families, in which other genes are likely to be involved [5-8]. The identification of novel PTD genes is particularly difficult, as families with dystonia are often too small for linkage purposes and the heterogeneity of clinical presentation does not allow pooling of families.

We investigated a large Italian PTD family with 11 definitely affected members. The phenotype was characterised by focal or segmental dystonia with onset either in the cranial-cervical region or in the upper limbs, mild course and occasional generalisation (Table 1). The inheritance of PTD was clearly autosomal dominant, with affected individuals spanning 3 consecutive generations. After exclusion of linkage between the

Table 1 Clinical presentation of dystonia in definitely affected individuals (n=11)

		Onset		Latest examination	
Subject	Gender	Age (years)	Site	Age (years)	PTD distribution
1	F	5	Cranial-cervical	71	Upper face, larynx, neck, upper limbs (segmental)
2	M	10	Cervical	67	Upper face, neck, upper limbs (segmental)
3	F	26	Cranial-cervical	63	Upper face, larynx, pharynx, neck, upper limbs (segmental)
4	F	ND	Cervical	65	Neck (focal)
5	F	5	Upper limbs	61	Upper face, larynx, neck, trunk, limbs (generalised)
6	F	5	Cervical	59	Upper and lower face, neck, trunk (segmental)
7	M	20	Cervical	56	Lower face, neck, limbs (generalised)
8	F	ND	Cervical	58	Neck, right upper limb (segmental)
9	M	40	Right upper limb	45	Right upper limb (focal)
10	M	14	Cranial-cervical	32	Lower face, larynx, neck (segmental)
11	M	ND	Upper limbs	41	Upper limbs (segmental)

ND, not determined

disease and the already known PTD loci [6, 7], the family was considered suitable for a genome-wide analysis.

Four hundred highly polymorphic fluorescent microsatellite markers spanning the 22 autosomes were genotyped in all the available family members, to allow haplotype construction. Pairwise linkage analysis was performed using an assumption of autosomal dominant inheritance, reduced penetrance (0.40), a gene frequency of 0.0001 and equal allele frequencies for each marker. Most genotyped markers generated negative or non-significant lod scores at all tested recombination fractions (θ = 0-0.4), except for five markers on chromosomes 1, 5, 10, 12 and 15, which generated maximum lod scores between 1.0 and 1.8. The regions surrounding these 5 loci and all regions surrounding non-informative markers were then saturated with closely spaced microsatellite markers and haplotypes were constructed. The negative lod scores obtained and the detection of different haplotypes carried by the affected individuals in the family allowed the exclusion of all autosomes except for a region on the short arm of chromosome 1. All markers spanning this candidate interval produced positive lod scores, with a maximum lod score of 3.44 (θ = 0) between the disease and marker D1S2667. All affected individuals in the family shared a common haplotype between D1S2663 and D1S2697, allowing the identification of a 22-cM interval containing a novel PTD gene (DYT13).

Discussion

We have identified a fourth PTD locus, DYT13, on the short arm of chromosome 1 in a family from central Italy. The phenotype is characterised by prominent involvement of the cranial-cervical region and the upper limbs; age at onset is variable but usually in childhood or adolescence; progression is mild and disease course is relatively benign with occasional tendency to generalisation. Nineteen individuals partially or completely shared the haplotype segregating with the disease; 11 (58%) of them were affected by dystonia. This value of penetrance is slightly higher than the penetrance usually attributed to primary dystonia genes (30%-40%). However, it is worth noting that not all the unaffected members of the family were available for clinical examination and genotyping, and so the exact value of penetrance for the DYT13 gene remains to be defined.

The clinical picture is noticeably different from the DYT1 phenotype, where dystonia presents generally in a limb, rarely affects the cranial-cervical region, and has a higher tendency to generalise, producing a much more disabling disease [2]. The DYT6-associated phenotype is characterised by a wider distribution of body regions involved at onset and in the course of the disease, which has the tendency to be more severe and to generalise more frequently [4]. The phenotype in our family is also different from that described for the DYT7 gene, which is characterised by adult-onset pure focal cervical dystonia without tendency to spread to other body regions [3].

In several PTD families reported so far, linkage to the known PTD loci has been excluded; in some of these families the phenotype shares relevant clinical features with DYT13-linked dystonia. In two large non-Jewish families reported in 1994 and 1996 by Bressman and co-workers [6], the affected members presented with early or adult-onset dystonia confined to cervical and brachial regions. Two other PTD families, of Swedish and Italian origin, had a similar phenotypic presentation: variable age at onset (spanning from the second to the fifth decades), prominent cranial-cervical involvement, and upper limb tremor or occasional generalisation [6-8]. Some of these families may link to the DYT13 locus, as they are characterised by variable age at onset (juvenile or adult) and prominent cranial-cervical involvement.

A large number of genes map within the 22-cM candidate interval identified in our family, but none of them represents an obvious candidate for dystonia. The role of this novel dystonia locus remains to be tested in other PTD families. The identification of other families linked to DYT13 will help refine the locus position on the genetic map, which is an essential step towards the identification of the gene and its function.

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