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ORIGINAL COMMUNICATION

Systematic mutation analysis of seven dystonia genes in complex regional pain syndrome with fixed dystonia

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Abstract Complex regional pain syndrome type 1 (CRPS-1) is a chronic pain disorder that in some patients is associated with fixed dystonia. The pathogenesis of CRPS and its relation to dystonia remain poorly understood. Several genes (so-called DYT genes) identified in other causes of dystonia play a role in mechanisms that have been implicated in CRPS. Because different mutations in the same gene can result in diverse phenotypes, we sequenced all coding exons of the DYT1, DYT5a, DYT5b, DYT6, DYT11, DYT12, and DYT16 genes in 44 CRPS patients with fixed dystonia to investigate whether high-penetrant causal mutations play a role in CRPS. No such mutations were identified, indicating that these genes do not seem to play a major role in CRPS.

Keywords Complex regional pain syndrome · Fixed dystonia · DYT genes

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Introduction

Complex regional pain syndrome type 1 (CRPS-1) is a chronic pain condition that is commonly preceded by an injury to an arm or a leg, although spontaneous onset has been reported in 7% of the cases [13, 49]. Skin sensitivity, swelling, sweating and skin color and temperature changes are other features typical of the acute phase of the syndrome [34]. About 25% of CRPS patients also develop abnormal postures (fixed dystonia) of the affected extremity [22, 43]. Dystonia is a movement disorder in which twisting or repetitive movements or sustained postures are caused by involuntary, sustained muscle contractions [17].

The pathogenesis of CRPS and its relation to dystonia remain poorly understood. The identification of genes and signalling pathways that confer susceptibility to CRPS or dystonia in CRPS may therefore provide valuable insights on how host response mechanisms may turn aberrant in response to tissue injury. There is evidence to suggest that genetic factors may play a role in CRPS. The syndrome may cluster in families [1, 6, 11, 16, 19, 23, 49]. Although several genetic associations between CRPS and the HLA gene complex on the short arm of chromosome 6 (6p21.3) have been reported [12, 27, 33, 46, 48], to date no single causative gene has been identified. In contrast to CRPS, there have been many successes in identifying genes for primary dystonia (i.e. DYT1, DYT3), (for review see [36]) as well as genes involved in syndromes in which dystonia is part of a broader clinical spectrum (also referred to as dystonia plus syndromes) (i.e. DYT5a, DYT5b, DYT11, DYT12). Close to 20 chromosomal loci (so-called DYT loci) have been identified for primary dystonia and dystonia plus syndromes. For ten of them, the causative gene has been identified: DYT1 (*TorsinA* [39]), DYT3 (*TAF1* [26]),

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DYT5a (*GCH1* [25]), DYT5b (*TH* [31]), DYT6 (*THAP1* [18]), DYT8 (*MR1* [30, 41]), DYT11 (*SGCE* [52]), DYT12 (*ATP1A3* [10]), DYT16 (*PRKRA* [7]), and DYT18 (*SLC2A1* [50]).

Dystonia in CRPS may spread to other extremities, leaving some patients severely disabled [47]. There are reasons to suspect a higher genetic load in CRPS patients with fixed dystonia. The age at onset of CRPS patients with dystonia is, on average, 11 years younger than that of CRPS patients without dystonia [47], which suggests a larger role for genetic factors in this more affected subgroup of patients. Notably, two studies that found a positive association with the HLA complex investigated CRPS patients with fixed dystonia [12, 46]. We hypothesized that dystonia genes may confer susceptibility to CRPS or dystonia in CRPS. To increase our chances of finding gene mutations, we sequenced all coding exons of those DYT genes with a known role in biological pathways that may potentially express features of CRPS.

Patients and methods

Patients

Forty-four patients who visited our clinic with an early onset of CRPS-1 (<40 years) and dystonia in at least one extremity were considered for inclusion in the study (Table 1). CRPS was diagnosed according to the criteria of the International Association of the Study of Pain (IASP) [34]. Fixed dystonia was diagnosed by a neurologist with expertise in movement disorders (JJvH). Patient clinical characteristics are given in Supplementary Table 1. The study was approved by the Medical Ethical Committee of the Leiden University Medical Center. All patients gave written informed consent before participation.

Table 1 Characteristics of patients with complex regional pain syndrome (CRPS) with fixed dystonia

Number of patients	44	
Percentage (*N*) of females	96%	(42)
Mean (SD) age at onset of CRPS (years)	26.5	(9.1)
Mean (SD) age at onset of dystonia (years)	27.0	(8.8)
Mean disease duration (SD) (years)	14.2	(7.1)
Family history of CRPS—percentage (*N*)	27%	(12)
Preceding trauma—percentage (*N*)		
Fracture	11%	(5)
Surgery	23%	(10)
Soft tissue	43%	(19)
Non-trauma	23%	(10)
Extremities affected by CRPS—percentage (*N*)		
1	11%	(5)
2	32%	(14)
3	18%	(8)
4	39%	(17)
Extremities affected by dystonia—percentage (*N*)		
1	23%	(10)
2	41%	(18)
3	14%	(6)
4	14%	(6)
First affected extremity—percentage (*N*)		
Arm	52%	(23)
Leg	45%	(20)
Both	2%	(1)

Some patients had already received treatment before the start of the current study, therefore it was possible that at the time of evaluation the dystonia in these patient was no longer observed ($N = 4$)

N number, *SD* standard deviation

DYT gene selection

To increase the chance of finding gene mutations, we investigated DYT genes with a role in biological pathways involved in disease mechanisms that are considered to play a role in CRPS, or disease mechanisms that potentially may express one or more features encountered in CRPS. Of course, additional scientific information on CRPS pathology and/or DYT gene function may become available in the future, in which case additional DYT genes should be selected for investigation.

Currently, multiple mechanisms, including increased oxidative stress [15, 45], aberrant inflammation [4, 24], apoptosis [37] and aberrant neuroplasticity [14, 32, 37], have been suggested as being involved in the pathogenesis of CRPS-I. Additionally, DYT genes that potentially may play a role in expressing phenotypic characteristics, such as pain and susceptibility to external triggers in initiating the phenotype, were included in this study. Hence, seven out of ten DYT genes (i.e., DYT1, DYT5a, DYT5b, DYT6, DYT11, DYT12, and DYT16) were selected for this study.

Our rationale for this selection was as follows:

- Mutations in *Torsin A* (DYT1) cause early-onset torsion, the most common and severe form of hereditary primary torsion dystonia [39]. Its gene product is implicated in the response of neurons to enhanced oxidative stress [28] and perhaps plasticity changes [20].
- *GCH1* (DYT5a), which codes for GTP cyclohydrolase 1, the rate-limiting enzyme in the biosynthesis of tetrahydrobiopterin (BH4) is a critical factor in neuropathic and inflammatory pain [44]. BH4 is also able to reduce the inflammatory response and oxidative stress [2]. Notably, a polymorphism in *GCH1* is associated with pain sensitivity [44].

- *TH* (DYT5b), which codes for tyrosine hydroxylase, the rate-limiting enzyme in the synthesis of the neurotransmitter dopamine [21], which is involved in modulation of pain perception. Not only do decreased levels of dopamine contribute to painful symptoms [51], but dopamine may also inhibit upregulation of cytokines and induce the production of anti-inflammatory mediators [3]. Finally, dopamine has a prolonged effect on neuroplasticity [29].
- Mutations in *THAP1* (DYT6), a member of a family of cellular factors responsible for regulation of endothelial cell proliferation [8], acting also as a proapoptotic factor [42], have been recently linked to primary forms of dystonia [18].
- *SGCE* (DYT11) gene encodes ε-sarcoglycan, a protein in dopaminergic neurons in the substantia nigra and ventral tegmental area [9, 38] that seems to play a role in the synaptic function of the central nervous system [38].
- Mutations in *ATP1A3* (DYT12), which encodes the Na^+/K^+-ATPase α3 subunit can cause an increased cortical motor excitability and disruption of basal ganglia inhibitory control, leading to abrupt onset dystonia after physical or emotional trauma [5].
- *PRKRA* (DYT16), which codes for the protein kinase interferon-inducible double stranded RNA-dependent activator and plays an important role in response to extracellular stress and inflammatory cytokines interferon-γ and TNF-α [7, 40].

We could not find a clear rationale for selecting the remaining three DYT genes (i.e., DYT3, DYT8, and DYT18).

Mutation analysis in selected DYT genes

For the genetic analysis, genomic DNA was isolated from peripheral blood cells according to a standard salting-out method [35]. All coding exons and directly adjacent intronic sequences of the *TorsinA*, *CGH1*, *TH*, *THAP1*, *SGCE*, *ATP1A3*, and *PRKRA* genes were analyzed for mutations using direct sequencing analysis. Exons were amplified by PCR using exon-specific primers sets (Supplementary Table 2). Reactions were performed in a 25-μL reaction volume, containing 10 pmol of each primer, 1× PCR buffer (3 mM Tris–HCl, 75 mM $NH4_2SO4$, 7.5 mM $MgCl_2$ with pH 8.5) (Invitrogen, Breda, The Netherlands), 3 mM dNTPs, 0.25 U AmpliTaq DNA polymerase (Applied Biosystems, Nieuwerkerk aan den IJssel, The Netherlands), and 50 ng of genomic DNA. PCR conditions were as follows: 3 min at 94°C, followed by 33 cycles of 30 s at 94°C, 30 s at 60°C, and 1 min at 72°C, and an additional extension step of 10 min at 72°C. Unincorporated dNTPs and primers were removed by incubation at 37°C for 2 h with shrimp alkaline phosphatase (SAP) (USB Corporation, Cleveland, OH, USA) and exonuclease I (ExoI) (USB Corporation, Cleveland, OH, USA), followed by a deactivation step of 95°C for 15 min. For dideoxy sequencing, purified PCR product (15–25 ng) was used with 6 pmol forward or reverse primer in a final volume of 12 μL. Sequencing reactions were run on an automated sequencer (ABI3730, Applied Biosystems, Nieuwerkerk aan den IJssel, The Netherlands). Sequence analysis was performed using ContigExpress software (a component of vector NTI Suite V9.0.0; Invitrogen, Leek, The Netherlands).

Results

Here we sequenced all coding exons and directly adjacent intronic sequences of the DYT1, DYT5a, DYT5b, DYT6, DYT11, DYT12, and DYT16 genes in 44 CRPS patients with fixed dystonia and an early-onset of disease (Table 1). The mean age at onset of CRPS in patients was 26.5 [standard deviation (SD) 9.1]. The mean age at onset of dystonia in patients was 27.0 (SD 8.8). In 23% ($N = 10$) of patients, CRPS and dystonia developed without an initiating traumatic event. Some 89% ($N = 39$) had two or more extremities with CRPS symptoms, whereas 77% ($N = 34$) had two or more extremities with dystonia. In 27% ($N = 12$) of the patients a positive family history of CRPS was present. No causal mutations were identified in any of the patients with CRPS and fixed dystonia.

Discussion

The pathogenesis of complex regional pain syndrome type 1 (CRPS-1) is poorly understood. Evidence for genetic factors, especially the involvement of the HLA complex on chromosome 6, in CRPS is increasing [12, 27, 33, 46, 48]. Despite these achievements, no single genetic factor has been identified in CRPS.

About 25% of CRPS patients develop movement disorders, of which dystonia is the most common one [22, 43, 49]. We hypothesized that those DYT genes that are responsible for monogenic forms of dystonias, could play a role conferring susceptibility to develop fixed dystonia in CRPS patients, and perhaps also CRPS itself.

Seven primary dystonia and dystonia plus syndromes genes (namely DYT1, DYT5a, DYT5b, DYT6, DYT11, DYT12, and DYT16) were selected because of their role in biological pathways (i.e., an abnormal response to oxidative stress, involvement in inflammation, apoptosis, and/or neuroplasticity) that also have been suggested to be involved in CRPS or in the expression of clinical

characteristics typical of the syndrome (e.g., pain, a triggering event). No disease-causing mutations were found in any of these genes tested in a fairly large group of CRPS patients with fixed dystonia and an early onset of the disease.

Although we did not find any evidence for the involvement of these DYT genes in CRPS with fixed dystonia, we cannot exclude the possibility that certain mutations were missed by our direct sequencing approach. Moreover, as we a priori cannot predict whether causal mutations in CRPS with fixed dystonia are loss- or gain-of-function mutations, the problem of missing mutations may particularly be true in the case in which causal mutations would be of the former category. Loss-of-function mutations that are located in the promoter region, or in other regulatory sequences affecting gene expression levels, would remain undetected with our mutation analysis approach. The same is true for causal deletions or insertions that interfere with any of the primer binding sites. Finally, the possibility that low-penetrant variants in DYT genes confer an increased risk for CRPS with fixed dystonia was not tested. In this respect, it is worth mentioning again that a polymorphism in *GCH1* has been associated with pain sensitivity [44]. Our current patient sample is too small to perform meaningful association studies aimed at identifying such low-penetrant gene variants.

A definite conclusion that can be drawn from the present study is that exonic mutations that cause dystonia in the DYT phenotypes belonging to the seven genes that were investigated are *not* present in CRPS with fixed dystonia. In that sense, we can conclude that the pathogenesis in the 'DYT types' of dystonia differs from that in CRPS or dystonia in CRPS. As some of the DYT genes have only recently been identified (i.e., *SCL2A1* in DYT18) and heavily studied, it still is not entirely clear whether these genes do not play a role in relevant pathways of CRPS with fixed dystonia. Therefore, as knowledge of CRPS and of the biology of DYT genes is increasing, other DYT genes may become a target for a study like the one performed here. There remains the possibility, of course, that none of the DYT genes play a role in CRPS with fixed dystonia.

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Conflict of interest statement The authors declare that they have no conflict of interest.

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