symptomatic management of EDS, in addition to cognitive behavioral interventions for fatigue, which supports the conclusions of Castori et al.

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References

1. Voermans NC, van Alfen N, Pillen S, et al. Neuromuscular involvement in various types of Ehlers-Danlos syndrome. Ann Neurol 2009;65:687–697.
2. Voermans NC, Knoop H, van de KN, et al. Fatigue is a frequent and clinically relevant problem in Ehlers-Danlos syndrome. Semin Arthritis Rheum 2009 Oct 29 [Epub ahead of print].

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Myostatin Depletion: A Therapy for Ehlers-Danlos Syndrome?

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Voermans et al[1] demonstrated that the muscle weakness, myalgia, and easy fatigability reported by the majority of patients with Ehlers-Danlos syndrome (EDS) are due to direct muscle and peripheral nerve involvement, rather than to a secondary effect.

In EDS patients, physical therapy that improves muscle strength around lax joints leads to better joint stability, reducing joint hypermobility and the frequency of dislocations. Therefore, the neuromuscular pathology could also be responsible, at least in part, for the musculoskeletal complications that characterize these syndromes.

Recently, we reported on a patient whose medical and genetic assessment supports this assumption.[2] He was a male patient (presently 42 years old), with a complex phenotype, in which a 75kb resolution array comparative genomic hybridization disclosed a de novo deletion spanning about 13.7Mb in the 2q31.2q23.3 region, leading to hemizygosity of many known genes, among which were *COL3A1*, *COL5A2,* and *MSTN*. We subsequently confirmed with real-time polymerase chain reaction experiments the deletion of these 3 genes (data not shown).

Loss-of-function mutations of *COL3A1* and *COL5A2* genes are responsible for the dominantly inherited forms of EDS type I and IV.[3,4] Instead, *MSTN* encodes for myostatin, a negative regulator of muscle growth also known as growth and differentiation factor 8, which is expressed mainly in skeletal muscle cells. Loss-of-function mutations of one *MSTN* allele result in overgrowth of skeletal muscle in various mammals (including humans), and inhibition of myostatin activity increases muscle mass and strength in experimental models.[5]

According to the *MSTN* monosomy, the patient displayed an exceptional constitutional muscular mass (Fig 1), especially considering the absence of such favoring factors as competitive sports, hypoglycemia, and high levels of testosterone, growth hormone, and insulinlike growth factor-1. The EDS symptoms were limited to recurrent inguinal hernias and to a mild mitral valve prolapse. However, he had no muscle weakness, myalgia, or easy fatigability, and interestingly, he also had no generalized joint hypermobility or recurrent joint dislocation.

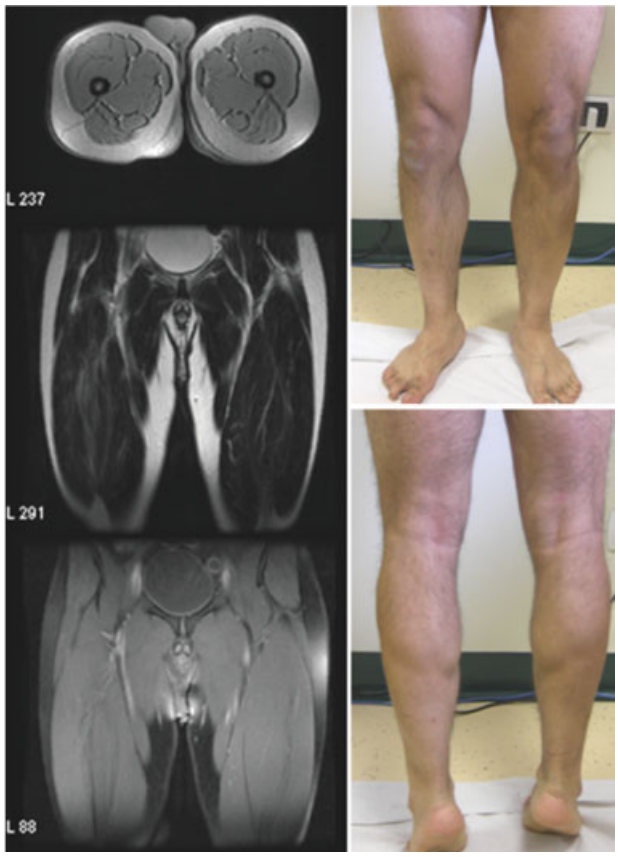

FIGURE 1: On the left, the magnetic resonance imaging of the legs shows no alteration of the muscular architecture, no fibrosis, no fat deposition, and very good trophism of quadriceps; on the right, pictures of the legs highlight the good muscular definition of quadriceps and gastrocnemius. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

We therefore hypothesize that haploinsufficiency of *MSTN* acts as a modifier allele that exerts a protective effect against EDS clinical manifestations in our patient.

In conclusion, these findings support the hypothesis of a direct involvement of muscle damage in the pathogenesis of neuromuscular as well as musculoskeletal defects, and suggest that: 1) EDS patients could benefit from more systematic medical care of muscular function; and 2) myostatin depletion could be employed as a possible pharmacological approach.

Further investigation on animal models could provide definitive support for our proposal.

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References

1. Voermans NC, Van Alfen N, Pillen S, et al. Neuromuscular involvement in various types of Ehlers-Danlos syndrome. Ann Neurol 2009;65:687–697.

2. Prontera P, Bernardini L, Stangoni G, et al. 2q31.2q32.3 deletion syndrome: report of an adult patient. Am J Med Genet A 2009; 149A:706–712.

3. Schwarze U, Schievink WI, Petty E, et al. Haploinsufficiency for one *COL3A1* allele of type III procollagen results in a phenotype similar to the vascular form of Ehlers-Danlos syndrome, Ehlers-Danlos syndrome type IV. Am J Hum Genet 2001;69:989–1001.

4. Mitchell AL, Schwarze U, Jennings JF, Byers PH. Molecular mechanisms of classical Ehlers-Danlos syndrome (EDS). Hum Mutat 2009;30:995–1002.

5. Joulia-Ekaza D, Cabello G. The myostatin gene: physiology and pharmacological relevance. Curr Opin Pharmacol 2007;7: 310–315.

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PLA2G6 Mutations and Parkinson's Disease

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Phospholipases A_2 (PLA_2s) are involved in reactions that result in the release of arachidonic acid and other fatty acids. *PLA2G6* is a calcium-independent PLA_2. Paisan-Ruiz and colleagues[1] recently reported *PLA2G6* mutations in two families who do not fit the typical phenotype of infantile neuroaxonal dystrophy. Affected individuals in these families with *PLA2G6* mutations have adult-onset, L-dopa–responsive, complicated parkinsonism without brain iron accumulation on magnetic resonance imaging.[1] These patients also share overlapping features with Kufor–Rakeb syndrome, which is caused by *ATP13A2* mutations.[2] These observations extend the phenotypic spectrum of *PLA2G6*-related neurodegeneration. Parkinson's disease (PD) is the prototype of adult-onset, L-dopa–responsive parkinsonism. Clinical signs of dystonia either at presentation (especially in young-onset cases) or as part of motor complication are commonly encountered in PD.

ATP13A2 mutations/variants have also been associated with young-onset typical PD patients.[2,3] Thus, to address the interesting question whether *PLA2G6* mutations are an important cause of PD with dystonia or a positive family history, we conducted a comprehensive analysis of the *PLA2G6* gene in a PD cohort.

Subjects diagnosed with PD based on the UK PD Brain Bank Criteria and healthy control subjects were initially recruited, with approval from the institution ethics committee and subjects' written informed consent. Sequencing of the coding exons and exon-intron boundary of the *PLA2G6* gene was performed in 96 PD patients with young age at onset/dystonia at presentation or during disease progression, or those with a positive family history. Further screening of any suspected mutations was conducted in 100 healthy control subjects. We detected five single-base substitutions, but only one resulted in an amino acid change (Table). This is a novel heterozygous C-to-G substitution in exon 17 resulting in a proline-to-arginine change. Proline is a nonpolar (hydrophobic) amino acid, whereas arginine has a positive charge (hydrophilic amino acid). The pK of ionizing side chain of proline is 7, and this increases to 12.48 with arginine. It is possible that the substitution could influence interaction of PLA2G6 with other proteins. The patient with this variant presented at age 69 years and had typical features of PD with dystonic spasms and L-dopa–responsive parkinsonism. Computed tomography of the brain did not show any abnormal hyperdense or hypodense lesions suggestive of calcium or iron deposition. The patient had a younger brother with PD, but because of the small family size, we were unable to conduct any meaningful segregation analysis. Although this functional variant was not present in 100 healthy control subjects, more studies are needed to determine whether it is a pathogenic mutation or a rare benign variant.

TABLE: PLA2G6 Variants in Patients with Parkinson's Disease

Exon	Position	Amino Acid Change	Number of Patients
2	87 G>A	Alanine > alanine	22
14	1959 T>A	Glycine > glycine	1
14	1983 G>A	Threonine > threonine	1
17	2355 C>T	Threonine > threonine	1
17	2417 C>G	Proline > arginine	1

Our data suggest that *PLA2G6* mutations are unlikely to be an important cause of the common garden variety of PD patients with dystonia or a positive family history (at least in our population). Thus, screening for new *PLA2G6* mutations in adult subjects would probably be more cost-effective if focus is directed at those with atypical akinetic rigid syndrome or L-dopa–responsive dystonia-parkinsonism associated with other neurological features.

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References

1. Paisan-Ruiz C, Bhatia KP, Li A, et al. Characterization of PLA2G6 as a locus for dystonia-parkinsonism. Ann Neurol (in press).

2. Di Fonzo A, Chien HF, Socal M, et al. ATP13A2 missense mutations in juvenile parkinsonism and young onset Parkinson disease. Neurology 2007;68:1557–1562.

3. Lin CH, Tan EK, Chen ML, et al. Novel ATP13A2 variant associated with Parkinson disease in Taiwan and Singapore. Neurology 2008;71:1727–1732.

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