Further neuroimaging and pathologic studies are necessary to confirm key brainstem structures generating RSWA and DEB in RBD.

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CATHEPSIN D DEFICIENCY CAUSES JUVENILE-ONSET ATAXIA AND DISTINCTIVE MUSCLE PATHOLOGY

The neuronal ceroid lipofuscinoses (NCLs) are a heterogeneous group of neurodegenerative disorders with the most common phenotype consisting of early-onset progressive motor deterioration, cognitive decline, visual failure, epilepsy, cerebellar ataxia, and premature death.¹

Mutations in the lysosomal protein cathepsin D (CatD/*CTSD*) underlie one subtype of NCL (CLN10) and were initially associated with a severe, congenital form resulting in early death,² with a single juvenile-onset CLN10 disease subsequently reported.³ We report additional novel mutations in *cathepsin D* in 2 consanguineous pedigrees, both with a juvenile onset of NCL and associated with characteristic muscle pathology.

Methods. Ethical approval to undertake this study was given by the National Hospital for Neurology and Neurosurgery/Institute of Neurology ethics

committees and informed consent was obtained from all participating family members.

Exome sequencing and homozygosity mapping were carried out in a large recessive consanguineous pedigree with complex ataxia and retinitis pigmentosa, which identified a homozygous missense mutation in *CTSD* in the index case of family A. We subsequently screened a cohort of complex ataxia cases all with associated retinitis pigmentosa and found a further homozygous missense mutation in *CTSD* in a second family. To support the pathogenicity of these variants, we carried out a kinetic assay of CatD activity in patient fibroblasts and performed detailed pathologic examination of patient muscle biopsies. See appendix e-1 on the *Neurology*® Web site at Neurology.org for additional details on the above methods.

Results. A summary of the clinical features of both pedigrees is shown in the table and pedigrees are shown in figure e-1.

Supplemental data
at Neurology.org

Table Clinical, genetic, and neuropathologic features of all reported CLN10 cases												
Family	Patient	Country of origin	CTSD mutation	CTSD activity, % of control	Phenotype	Age at onset	Age at death	Clinical features	Cerebellar atrophy	Neurophysiology	Histopathology	Reference
A	A:3	Somalia	p.Gly149Val-hom	—	Juvenile NCL	~15 y	33 y	Ataxia, RP, cognitive decline	Yes	Normal	Muscle: granulovacuolar material in angular atrophic fibers, GROD	This study
	A:4	Somalia	p.Gly149Val-hom	—	Juvenile NCL	~15 y	34 y	Ataxia, RP, cognitive decline, cardiomyopathy	Yes	Normal	—	This study
	A:5	Somalia	p.Gly149Val-hom	—	Juvenile NCL	~15 y	—	Ataxia, RP, cognitive decline	Yes	Sensory axonal neuropathy	—	This study
	A:8	Somalia	p.Gly149Val-hom	11	Juvenile NCL	~15 y	—	Ataxia, RP, cognitive decline	Yes	Normal	—	This study
B	B:3	Somalia	p.Arg399His-hom	11	Juvenile NCL	~8 y	—	Ataxia, RP, cognitive decline	Yes	Sensory axonal neuropathy	Muscle: granulovacuolar material in angular atrophic fibers, GROD; fibroblasts: membrane-bound vacuoles	This study
	C	—	Germany	p.Phe229Ile; p.Trp383Cys	14	Juvenile NCL	Early school-age	—	Ataxia, RP, cognitive decline	Yes	Skin: GROD, myelin-like lamellar structures	3
D	—	USA	p.Ser100Phe-hom	~0	Congenital NCL	Birth	2 d	Microcephaly, hypertonia	Yes	—	Brain: hypercellular cortex, autofluorescent storage material in neurons, astrocytes, and macrophages	7
E	—	Pakistan	p.Tyr255X-hom	~0	Congenital NCL	—	1 d	Microcephaly, hypertonia, seizures	Yes	—	Brain: extensive neuronal loss and glial activation, autofluorescent storage material in all cell types	8

Abbreviations: NCL = neuronal ceroid lipofuscinosis; RP = retinitis pigmentosa; GROD = granular osmiophilic deposits.

Exome sequencing identified a homozygous missense mutation (p.G149V in exon 4 of *CTSD*) in the index case of family A (A:5), which segregated with the affected cases in the family. The phenotype was of a juvenile onset of cerebellar ataxia and retinitis pigmentosa at around 15 years, which progressed to significant motor impairment and cognitive decline. Neurophysiologic studies showed a sensory axonal neuropathy. Two out of 4 family members remain alive, both with significant disability.

Sanger sequencing of a cohort of patients with complex ataxia with associated retinitis pigmentosa identified a further homozygous missense mutation in one individual (B:3) from a second consanguineous pedigree (p.Arg399His in exon 9 of *CTSD*). The clinical phenotype was similar to family A with an earlier age at onset of 8 years. This patient was also noted to have a sensory axonal neuropathy on neurophysiologic studies.

Muscle biopsies in patients A:3 and B:3 both exhibited distinctive pathologic features characterized by granulovacuolar material in angular atrophic fibers in addition to the granular osmiophilic deposits that are diagnostic for neuronal ceroid lipofuscinosis (figure e-2). Neither patient was reported to have a clinical myopathy, but patient A:4 was known to have a cardiomyopathy.

Both identified mutations were highly conserved throughout species (figure e-3) and predicted to be pathogenic through in silico analyses. Fluorometric kinetic analysis of CatD activity in cultured fibroblasts from patients A:3 and B:3 showed a significant reduction in enzyme activity compared to controls, confirming the pathogenicity of the mutations (figure e-4).

Discussion. The phenotype of all the patients in this study is of a complex recessive ataxia with associated pigmentary retinopathy and cognitive decline. There had been difficulty in establishing a diagnosis in these patients, which was unsurprising given the phenotypic overlap with other disorders including mitochondrial disorders, complex hereditary spastic parapareses, neurodegeneration with brain iron accumulation, and disorders of peroxisomal and lipid metabolism.

The abnormal muscle biopsies from patients A:3 and B:3 were particularly interesting findings. These showed a pattern of muscle pathology that may be sufficiently distinctive to permit a provisional diagnosis in future cases on the basis of the muscle biopsy. Although not used diagnostically, skeletal muscle is frequently involved in other NCL subtypes, with ultrastructural characteristics of NCL often seen on muscle biopsy.⁴ Dilated cardiomyopathy has been reported at autopsy in a Japanese CLN3 case.⁵

Recently it has been demonstrated in a zebrafish model that knockdown of CatD in fertilized embryos resulted in a congenital myopathy.⁶

Although many of the NCLs share some characteristic phenotypes, genetic and phenotypic heterogeneity often results in difficulty establishing a genetic diagnosis. Currently enzyme analysis for NCL is only routinely performed for *TPP1* (CLN2) and *PPT1* (CLN1). However, *CTSD* mutations remain a rare cause of NCL and next-generation approaches such as exome sequencing and targeted gene sequencing are increasingly useful in establishing diagnoses for these rare neurodegenerative conditions. Furthermore, the characteristic muscle pathology seen in *CTSD* mutations may help to guide clinical assessment, aid molecular diagnosis in patients with NCL, and help support or confirm pathogenicity of novel *CTSD* mutations.

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