0.0039; MAD = 0.0034) only for the large reward (P_{adj} = 0.002). In contrast, no significant differences were reported for the small (P_{adj} = 0.481) and medium (P_{adj} = 0.282) reward sizes between the two groups (Fig. 1). No further significant results are reported (see the Supporting Information).

Discussion

A recent work\(^1\) has proposed that excessive discounting of delayed reward is a transdiagnostic process in psychiatric disorders, in line with the evidence of steep DRD in several syndromes. This includes neurological disorders affected by impulse dyscontrol such as Parkinson’s disease.\(^4\) We further corroborate this suggestion by providing the evidence of altered (steep) DRD in TS. Our results have important implications for the current knowledge of the neurocognitive profile of TS, given that we provide evidence of dysfunctional reward-related decision making in this clinical population. This is in line with neuroimaging research on TS (see an earlier work\(^3\) for an overview) documenting structural and functional dysfunctions in brain regions relevant for reward processing and decision making. Furthermore, our results open new avenues to drug-free therapy for TS, suggesting the potential relevance of treatments that target cognitive processes related to DRD, in order to improve their dysfunctional social behavior.\(^4\) This hypothesis comes from the evidence that a steep DRD is associated with several socially dysfunctional conduct disorders, including disinhibitory and/or antisocial behavior.\(^5\)

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Supporting Data

Additional Supporting Information may be found in the online version of this article at the publisher’s web-site.

Novel Biallelic CTSD Gene Variants Cause Late-Onset Ataxia and Retinitis Pigmentosa

Case Report

A 45-year-old male patient presented with a 2-year history of progressive gait impairment. On neurological examination, he exhibited a cerebellar syndrome with saccadic ocular pursuit, intention tremor, dysarthria, and gait ataxia. MRI revealed cerebellar atrophy (Fig. 1A and Supporting Information Fig. S1A). The patient’s visual function had rapidly deteriorated from the age of 32. Ophthalmological examination showed a retinitis pigmentosa-like phenotype with central involvement (Fig. 1B and Supporting Information Fig. S1B).

Based upon the ataxia/retinitis pigmentosa complex, exome sequencing prioritized two previously unreported compound heterozygous variants in CTSD: The c.57_63del variant predicts a frameshift and premature stop codon in exon 1 (p.A20Sfs*25; class 4 according to American College of Medical Genetics and Genomics guidelines). The c.1064C > T missense variant leads to a p.T355M amino acid change (class 3).

Autosomal-recessive mutations in CTSD cause neuronal ceroid lipofuscinosis type 10 (NCL10).\(^1\) Whereas congenital NCL10 causes severe neurological deficits and early death, late infantile and juvenile NCL10 manifest with ataxia, retinitis pigmentosa, and cognitive decline, with the latest onset reported at 15 years of age.\(^5\) In light of the adult-onset phenotype, we aimed to characterize the functional impact of the missense variant in vitro.

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Clinical findings and experimental validation of pathogenicity of the c.1064C>T CTSD variant. (A) Sagittal T2-weighted MRI showing severe cerebellar atrophy. (B) Fundus photography depicts bone spicules characteristic for retinitis pigmentosa (arrows) and stippled fundus autofluorescence attributable to atrophy of the retinal pigment epithelium (right, from boxed area). (C) Pedigree showing mutational status in the patient and his mother. (D) Immunocytochemistry for Cathepsin D preprotein (upper line) and cleaved, active Cathepsin D (lower line). (E) Western blot of cell lysates using the identical antibodies as in (D) and a β-actin loading control. (F) Western blot analysis of autophagic flux in response to treatment with 20 nM of Bafilomycin A1. (G) Statistical analysis of baseline p62 levels (n = 9; *P < 0.01, analysis of variance followed by Bonferroni’s post-hoc test), p62 induction (n = 9; no significant differences), and LC3-II induction (n = 9; *P < 0.05; **P < 0.01). Scale bars, 12.5 μm. Baf, Bafilomycin A1; DAPI, 4',6-diamidino-2-phenylindole.
Experimental Validation

In patient-derived fibroblasts, Cathepsin D enzymatic activity was significantly reduced to 29% of the lower regular limit. This is notably higher than in congenital or juvenile NCL10, where enzymatic activity is either severely diminished or completely lost.\(^3\) Both immunocytochemistry and western blot showed severely reduced levels of active Cathepsin D, whereas levels of the pro-proenzyme were unchanged (Fig. 1D,E). Given that Cathepsin D activity is crucial for lysosomal degradation, we analyzed autophagic functions. Patient fibroblasts showed higher basal levels of the autophagy receptor protein, p62, as compared to control cells (Fig. 1F,G). Furthermore, accumulation of the autophagosome membrane protein, light chain 3/phosphatidylethanolamine conjugate (LC3-II), in response to the lysosomal degradation inhibitor, Bafilomycin A1, was attenuated in patient cells as compared to control fibroblasts, suggesting that autophagic flux is compromised.

Discussion

We here report and validate two novel pathogenic CTSD variants in a patient with an exceptionally late onset of NCL10 presenting with retinitis pigmentosa at 32 years, followed by ataxia at 43 years, however without cognitive impairment during follow-up until age 47. Whereas the c.57_63del variant leads to a premature stop codon and thus slightly reduced enzymatic activity of Cathepsin D even in the unaffected mother (data not shown), the additional presence of the c.1064C > T missense variant may explain the intermediate phenotype of the index patient. Our biochemical analyses indicate that mutant Cathepsin D is produced, but not efficiently processed into the mature form, linked to autophagic dysfunction.

An increased frequency of CTSD variants was observed in Parkinson’s and Alzheimer’s diseases.\(^4,5\) The identification of the mildly pathogenic missense variant supports the notion that minor changes in Cathepsin D activity may predispose for neurodegenerative diseases in late adulthood.

The late onset of this distinct phenotype caused by the variant reported herein prompts its analysis in cases of adult-onset ataxia and/or retinitis pigmentosa. Our findings implicate that enzymatic activity of Cathepsin D is inversely correlated to age at onset in NCL10.

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Supporting Data

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