A Mild PUM1 Mutation Is Associated with Adult-Onset Ataxia, whereas Haploinsufficiency Causes Developmental Delay and Seizures

Highlights

- The brain is sensitive to levels of PUM1 and some of its targets
- PUM1 haploinsufficiency causes developmental delay, ataxia, and other problems
- Mutations that reduce PUM1 levels by 25% are associated with adult-onset ataxia
- Regulators of disease-driving proteins are a pool of new candidate disease genes

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In Brief

Different dosages of an RNA-binding protein result in human neurological diseases of corresponding severities.

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A Mild *PUM1* Mutation Is Associated with Adult-Onset Ataxia, whereas Haploinsufficiency Causes Developmental Delay and Seizures

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SUMMARY

Certain mutations can cause proteins to accumulate in neurons, leading to neurodegeneration. We recently showed, however, that upregulation of a wild-type protein, Ataxin1, caused by haploinsufficiency of its repressor, the RNA-binding protein *Pumilio1* (*PUM1*), also causes neurodegeneration in mice. We therefore searched for human patients with *PUM1* mutations. We identified eleven individuals with either *PUM1* deletions or de novo missense variants who suffer a developmental syndrome (*Pumilio1*-related cerebellar ataxia, PRCA). Studies in patient-derived cells revealed that the missense mutations reduced *PUM1* protein levels by ~25% in the adult-onset cases and by ~50% in the infantile-onset cases; levels of known *PUM1* targets increased accordingly. Changes in protein levels thus track with phenotypic severity, and identifying posttranscriptional modulators of protein expression should identify new candidate disease genes.

INTRODUCTION

Decades of human and mouse genetic studies have taught us that neurons are intolerant of significant alterations in protein abundance. Doubling a protein’s levels, as in the case of chromosomal duplications, or halving it, as in the case of
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