Fast and slow strains of misfolded superoxide dismutase 1 in amyotrophic lateral sclerosis

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Mutations in superoxide dismutase 1 (SOD1) are one of the causes of familial amyotrophic lateral sclerosis (fALS). Most individuals with SOD1 ALS show a typical clinical course that lasts 2 to 5 years but more rarely, patients can exhibit a much more slowly progressing illness. For example, patients with the A4V or G85R mutations exhibit short durations of <3 years whereas patients inheriting the G37R or H46R mutations exbibit long disease durations of >15 years. An explanation for these very distinct clinical features of SOD1 fALS has not emerged thus far. A large body of evidence indicates that disease-causing mutations in SOD1 cause its misfolding and aggregation, and that this misfolded form of the protein mediates neurodegeneration. Misfolded mutant SOD1 exhibits prion properties including the ability to template disease-associated conformations to naïve mutant SOD1 to propagate and induce paralysis in SOD1 transgenic mice. Here, we show that fALS mutations in SOD1 produce discrete clinical strains of misfolded SOD1 that exhibit distinct incubation periods upon transmission. Mutations associated with rapidly progressing ALS produce strains that exhibit shorter incubation periods than mutations associated with slowly progressing disease. Our findings suggest that the characteristic clinical presentations of different SOD1 mutations in ALS are linked to prion attributes of misfolded SOD1 that dictate the rate at which toxic conformations of misfolded SOD1 accumulate and cause motor neuron degeneration.

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