LETTER: NEW OBSERVATION

A Novel *PRNP* Gene Mutation Associated with Gerstmann–Sträussler–Scheinker Syndrome

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Gerstmann–Sträussler–Scheinker syndrome (GSS) is a rare autosomal dominant prion disease and the most common genetic prion protein amyloidosis.[1] GSS typically manifests between the age of 35 and 55 years by a progressive cerebellar ataxia, cognitive decline, and associated pyramidal and extra-pyramidal signs. The clinical course is heterogeneous, varying with the underlying *PRNP* gene mutation.[2] We report the first documented Belgian case of GSS, associated with a novel *PRNP* mutation c.304C>T p.(Pro102Ser).

A 52-year-old man presented with balance disturbances 7 years before referral. He exhibited mild scanning speech, dysdiadochokinesia, kinetic tremor in upper limbs, postural instability, and ataxic gait (see also Supplemental Data). Oculomotor abnormalities included a gaze-evoked nystagmus, saccadic pursuit, and dysmetric saccades. Quantitative assessments by clinical rating scales scored as follows: Scale for Assessment and Rating of Ataxia (SARA) 10.5/40, Scale for Ocular motor Disorders in Ataxia (SODA) 5/24, Cerebellar Cognitive Affective Syndrome (CCAS)/Schmahmann Scale 80/120, Mini-Mental State Examination (MMSE) 28/30, and Montreal Cognitive Assessment (MoCA) 25/30 (errors in recall and language). Magnetic resonance imaging (MRI) revealed a pancerebellar atrophy.

Genetic testing for common dominant/recessive spinocerebellar ataxias and Friedreich's ataxia was negative. Whole exome sequencing identified a heterozygous *PRNP* variant: c.304C>T p.(Pro102Ser), paternally inherited. This variant, not found in the general population databases (GnomAD) and not previously described in the literature, affects the same amino acid residue as the Pro102Leu mutation, most frequently associated with GSS syndrome.[2] Pro102Leu, recognized as pathogenic in the ClinVar database, typically manifests clinically as a progressive cerebellar syndrome. This mutation affects a critical amino acid residue influencing the three-dimensional structure of the prion protein.[3] The variant c.304.C>T p.(Pro102Ser) in the *PRNP* gene results in a missense substitution at the same site. Following the American College of Medical Genetics and Genomics (ACMG) guidelines, this variant was classified as likely pathogenic (criteria PM2, PM5, PP1, PP3, PP4).[4]

The proline-to-serine substitution at position 102 likely affects the structure and function of the prion protein, contributing to GSS pathogenesis. The region surrounding residue 102 contains four lysine residues crucial for stability and function of the normal prion protein. Previous studies have suggested that the Pro102Leu mutation neutralizes lysine residues' function, promoting the conversion into the pathological form (PrPsc).[3] Our Pro102Ser mutation may similarly disrupt this lysine cluster, as indicated by in silico protein structure simulations. The human prion protein structure was predicted using AlphaFold based on the reference sequence NP_000302.1 (Fig. 1). The predicted secondary structure aligns with previous experimental reported by Würtrich et al., as described in the Protein Data Bank (PDB ID 1QLX and 1QLZ).[5] Our model suggests that the flexible N-terminal tail may be in proximity to α-helix in the globular domain (region 215–225). Pro102Ser mutation (ie, sequence KSSKPKTNMK) alters both conformation (cyclic to non-cyclic) and polarity (non-polar to polar) of the residue, potentially enabling hydrogen-bonding interactions with nearby α-helices in the mutated sequence (Fig. 1C). Further investigation is needed to elucidate the effects of this mutation on protein dynamics and aggregation propensity.

In conclusion, we report the first case of GSS associated with the c.304C>T; p.(Pro102Ser) mutation in the

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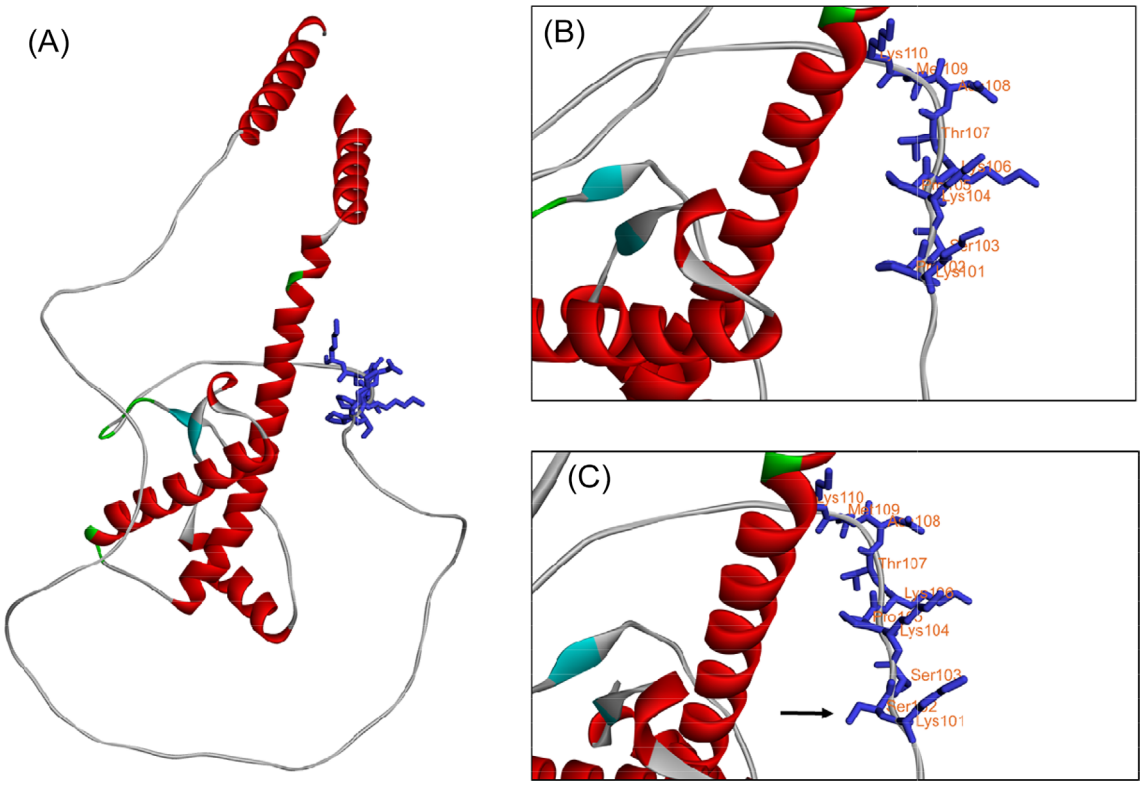

FIG. 1. (A) AlphaFold-predicted three-dimensional structure of the human prion protein. (B) View of the structure around the lysine cluster (blue sticks), region 101–110 of the normal sequence. (C) Same region with the proline to serine substitution at position 102. [Color figure can be viewed at wileyonlinelibrary.com]

PRNP gene. Our structural analysis highlights the potential impact of this mutation on protein conformation, particularly in the lysine cluster region.

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Data Availability Statement

Data are available on request.

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Supporting Data

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