Rare missense and synonymous variants in UBE1 are associated with X-linked infantile spinal muscular atrophy.

X-linked infantile spinal muscular atrophy (XL-SMA) is an X-linked disorder presenting with the clinical features hypotonia, areflexia, and multiple congenital contractures (arthrogryposis) associated with loss of anterior horn cells and infantile death. To identify the XL-SMA disease gene, we performed large-scale mutation analysis in genes located between markers DXS8080 and DXS7132 (Xp11.3-Xq11.1). This resulted in detection of three rare novel variants in exon 15 of UBE1 that segregate with disease: two missense mutations (c.1617 G-->T, p.Met539Ile; c.1639 A-->G, p.Ser547Gly) present each in one XL-SMA family, and one synonymous C-->T substitution (c.1731 C-->T, p.Asn577Asn) identified in another three unrelated families. Absence of the missense mutations was demonstrated for 3550 and absence of the synonymous mutation was shown in 7914 control X chromosomes; therefore, these results yielded statistical significant evidence for the association of the synonymous substitution and the two missense mutations with XL-SMA (p = 2.416 x 10^-10, p = 0.001815). We also demonstrated that the synonymous C-->T substitution leads to significant reduction of UBE1 expression and alters the methylation pattern of exon 15, implying a plausible role of this DNA element in developmental UBE1.
expression in humans. Our observations indicate first that XL-SMA is part of a growing list of
neurodegenerative disorders associated with defects in the ubiquitin-proteasome pathway and
second that synonymous C-->T transitions might have the potential to affect gene expression.

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