



Mutation analysis of four Chinese families with pure hereditary spastic paraplegia: pseudo-X-linked dominant inheritance and male lethality due to a novel *ATL1* mutation

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Genet. Mol. Res. 14 (4): 14690-14697 (2015)

Received July 6, 2015

Accepted September 29, 2015

Published November 18, 2015

DOI <http://dx.doi.org/10.4238/2015.November.18.33>

ABSTRACT. We studied four Chinese families with pure hereditary spastic paraplegia (HSP) to investigate the clinical features and associated genetic mutations. Linkage analysis was performed for all families to map the disease locus onto autosomal chromosomes, and related loci involved in HSP on the X chromosome were also examined. Polymerase chain reaction (PCR) sequencing was used to detect gene mutations. To confirm the influence of a splice-site mutation on mRNA, we used reverse transcription-PCR and direct sequencing. Linkage analysis and *ATL1* gene sequencing of amniocytes were performed for prenatal genetic diagnosis. One missense variant (c.1517T>A) and a splice-site mutation (c.1245+1G>A) in *SPAST*, and two missense variants (c.715C>T, c.1204T>G) in *ATL1* were identified. The c.1245+1G>A mutation caused a deletion of exon 9 in the *SPAST* gene.

Prenatal genetic diagnosis showed that fetus did not carry the *ATLI* c.1204T>G mutation. Follow-up was maintained for 5 years, and the negative result was confirmed by evidence of a healthy growing boy. We identified two novel mutations and two previously reported mutations in *SPAST* and *ATLI*, respectively. The family with the *ATLI* c.1204T>G mutation exhibited male-lethality, female infancy-onset, and pseudo-X-linked dominant transmission, which had never been previously reported for HSP. Characteristic facial features were also noticed. The boy on whom prenatal gene diagnosis was performed is healthy and without unusual facies, suggesting that the c.1204T>G mutation might be related to these features. The results extend the genetic spectrum of HSP and suggest that linkage analysis remains a powerful tool in gene discovery studies.

Key words: *SPAST*; *ATLI*; Mutation; X-linked dominant; Hereditary spastic paraplegia