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Review article

Hereditary spastic paraplegias with autosomal dominant, recessive, X-linked, or maternal trait of inheritance

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ABSTRACT

Hereditary spastic paraplegia (SPG) is a clinically and genetically heterogeneous group of neurodegenerative disorders that are clinically characterised by progressive spasticity and weakness of the lower-limbs (pure SPG) and, majoritorian, additional more extensive neurological or non-neurological manifestations (complex or complicated SPG). Pure SPG is characterised by progressive spasticity and weakness of the lower-limbs, and occasionally sensory disturbances or bladder dysfunction. Complex SPGs additionally include cognitive impairment, dementia, epilepsy, extrapyramidal disturbances, cerebellar involvement, retinopathy, optic atrophy, deafness, polyneuropathy, or skin lesions in the absence of coexisting disorders. Nineteen SPGs follow an autosomal-dominant (AD-SPG), 27 an autosomal-recessive (AR-SPG), 5 X-linked (XL-SPG), and one a maternal trait of inheritance. SPGs are due to mutations in genes encoding for proteins involved in the maintenance of corticospinal tract neurons. Among the AD-SPGs, 40–45% of patients carry mutations in the SPAST-gene (SPG4) and 10% in the ATL1-gene (SPG3), while the other 9 genes are more rarely involved (NIPA1 (SPG6), KIAA0196 (SPG8), KIF5A (SPG10), RNT2 (SPG12), SPGD1 (SPG13), BSCL2 (SPG17), REEP1 (SPG31), ZFYVE27 (SPG33, debated), and SLC33A1 (SPG42, debated)). Among the AR-SPGs, ~20% of the patients carry mutations in the KIAA1840 (SPG11) gene whereas the 15 other genes are rarely mutated and account for SPGs in single families yet (CYP7B1 (SPG5), SPG7 (SPG7), ZFYVE26 (SPG15), ERLIN2 (SPG18), SPG20 (SPG20), ACP33 (SPG21), KIF1A (SPG30), FA2H (SPG35), NTE (SPG39), GJA12/GJC2 (SPG44), KIAA0415 (SPG48) and 4 genes encoding for the AP4-complex (SPG47)). Among the XL-SPGs, 3 causative genes have been identified (L1CAM (SPG1), PLP1 (SPG2), and SLC16A2 (SPG22)). The diagnosis of SPGs is based on clinical, instrumental and genetic investigations. Treatment is exclusively symptomatic.

Contents

Abbreviations: ACP33, Maspardin gene; AD, Autosomal dominant; ALS, Amyotrophic lateral sclerosis; AP, Adaptor Protein complex; AR, Autosomal recessive; ATL1, Atlastin-1 gene; BMP, Bone morphogenic protein; BSCL2, Berardinelli-Seip congenital lipodystrophy gene; CYP7B1, Oxysterol 7-alpha-hydroxylase 1 gene; ER, Endoplasmic reticulum; ERLIN2, ER lipid raft associated 2 gene; GJA12/GJC2, Gap junction protein 12; HSN1, Hereditary sensory neuropathy type 1; HSP, Hereditary spastic paraplegia; HSPD1, Heat shock 60 kDa protein 1; KIAA0196, Strumpellin gene; KIAA0415, Putative helicase gene; KIAA1840, Spatacsin gene; KIF1A, Kinesin 3; KIF5A, Kinesin heavy chain isoform 5A; LICAM, L1-cell adhesion molecule; MASA, Mental retardation, aphasia, shuffling gait, and adducted thumbs; NBIA, Neurodegeneration with brain iron accumulation; NCAM, Neural cell adhesion molecule; NGS, Next-generation sequencing; NIPA1, Non-imprinted in Prader–Willi/Angelman syndrome 1 gene; NTE, Neuropathy Target Esterase; PLP1, Pproteolipid protein 1 gene; PNP, Polyneuropathy; REEP1, Receptor expression enhancing protein 1; RTN2, Reticulon 2; SLC16A2, Solute carrier family 16, member 2; SLC33A1, Solute carrier family 33; SPAST, Spastin gene; SPG, Spastic paraplegia gene; TCC, Thin corpus callosum; WMLs, White matter lesions; XL, X-linked; ZFYVE26, Zinc finger, FYVE domain containing 26; ZFYVE27, Zinc finger, FYVE domain containing 27.

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