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Hereditary spastic paraplegias phenotype constitute part of broader rare genetic Mendelian inherited disorders

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Hereditary Spastic Paraplegias (HSPs) are a group of rare neurological diseases of remarkable clinical and genetic heterogeneity. Cardinal features involve lower limbs spasticity, abnormal gait and difficult walking that eventually ends, in most of the cases, in being a wheel chair bound. Interestingly, presentation in patients with HSPs, particularly the autosomal recessive forms is much more than lower limbs spasticity and difficult walking. The variable association with developmental delay, psychomotor retardation, learning disabilities or even mental retardation, retinopathy, skin changes, distinctive brain malformation, ataxia, or extrapyramidal involvements brings up AR-HSPs as rare syndromes of broad clinical spectrum rather than just neurodegenerative spastic movement disorders. The axonal transport machinery, altered in HSP, comprises elaborate components of motor proteins, microtubules, shaping and distribution of subcellular organelles and enzymes involved in nucleotides or lipid metabolism. Families of different ethnic background; Qatari and other ethnicities, with a unified clinical feature of variably progressive lower limbs spasticity and walking difficulty were ascertained. Families either with only these standard features or in association with variable presentations of ataxia, pain insensitivity, remarkable vertebral destruction, regression in mental abilities, severe psychomotor retardation, and notable neuro-radiological abnormalities were enrolled in the study. Whole Genome Sequencing (WGS) was applied to identify candidate genes in the recruited families. Clinical findings are presented in addition to demographic and age groups' distribution, complex HSP rare phenotypes with interesting extraneural presentations, of which, features of marked pain insensitivity, skin changes and cerebellar atrophy were seen in independent families. WGS revealed involvements of rarely encountered HSPs genes, of which genes deriving purines and fatty acid metabolism and mitochondrial proteins. A family with double pathogenic mutations in Parkin gene and a known HSP gene was identified. Identification of causative genes of rare Mendelian diseases in a research setting promotes the opportunity to diagnostics molecular genetics, improved genetic counseling qualities and primary prevention.

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