Jordan University of Science and Technology

Autosomal recessive spinocerebellar ataxia 7 (SCAR7) is caused by variants in TPP1, the gene involved in classic late-infantile neuronal ceroid lipofuscinosis 2 disease (CLN2

Authors: Sun Y1, Almomani R, Breedveld GJ, Santen GW, Aten E, Lefeber DJ, &I

Abstract: Spinocerebellar ataxias are phenotypically, neuropathologically, and genetically heterogeneous. The locus of autosomal recessive spinocerebellar ataxia type 7 (SCAR7) was previously linked to chromosome band 11p15. We have identified TPP1 as the causative gene for SCAR7 by exome sequencing. A missense and a splice site variant in TPP1, cosegregating with the disease, were found in a previously described SCAR7 family and also in another patient with a SCAR7 phenotype. TPP1, encoding the tripeptidyl-peptidase 1 enzyme, is known as the causative gene for late infantile neuronal ceroid lipofuscinosis disease 2 (CLN2 disease). CLN2 disease is characterized by epilepsy, loss of vision, ataxia, and a rapidly progressive course, leading to early death. SCAR7 patients showed ataxia and low activity of tripeptidyl-peptidase 1, but no ophthalmologic abnormalities or epilepsy. Also, the slowly progressive evolution of the disease until old age and absence of ultra structural curvilinear profiles is different from the known CLN2 phenotypes. Our findings now expand the phenotypes related to TPP1-variants to SCAR7. In spite of the limited sample size and measurements, a putative genotype-phenotype correlation may be drawn: we hypothesize that loss of function variants abolishing TPP1 enzyme activity lead to CLN2 disease, whereas variants that diminish TPP1 enzyme activity lead to SCAR7.