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Abstracts

Articles appearing in the June 2019 issue

Oligogenic basis of sporadic ALS: The example of *SOD1* p.Ala90Val mutation

Objective To characterize the clinical and neuropathologic features of patients with amyotrophic lateral sclerosis (ALS) with the superoxide dismutase 1 (*SOD1*) p.Ala90Val mutation, as well as the mutation frequency and the role of oligogenic mechanisms in disease penetrance.

Methods An index patient with autopsy-proven ALS was discovered to have the *SOD1* p.Ala90Val mutation, which was screened in 2 Finnish ALS cohorts (n = 453). Additional contributing variants were analyzed from whole-genome or whole-exome sequencing data.

Results Seven screened patients (1.5%) were found to carry the *SOD1* heterozygous mutation. Allele-sharing analysis suggested a common founder haplotype. Common clinical features included limb-onset, long disease course, and sensory symptoms. No TDP43 pathology was observed. All cases were apparently sporadic, and pedigree analysis demonstrated that the mutation has reduced penetrance. Analysis of other contributing genes revealed a unique set of additional variants in each patient. These included previously described rare *ANG* and *SPG11* mutations. One patient was compound heterozygous for *SOD1* p.Ala90Val and p.Asp91Ala.

Conclusions Our data suggest that the penetrance of *SOD1* p.Ala90Val is modulated by other genes and indicates highly individual oligogenic basis of apparently sporadic ALS. Additional genetic variants likely contributing to disease penetrance were very heterogeneous, even among Finnish patients carrying the *SOD1* founder mutation.

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Novel pathogenic *XK* mutations in McLeod syndrome and interaction between XK protein and chorein

Objective To identify *XK* pathologic mutations in 6 patients with suspected McLeod syndrome (MLS) and a possible interaction between the chorea-acanthocytosis (ChAc)- and MLS-responsible proteins: chorein and XK protein.

Methods Erythrocyte membrane proteins from patients with suspected MLS and patients with ChAc, ChAc mutant carriers, and normal controls were analyzed by XK and chorein immunoblotting. We performed mutation analysis and XK immunoblotting to molecularly diagnose the patients with suspected MLS. Lysates of cultured cells were co-immunoprecipitated with anti-XK and anti-chorein antibodies.

Results All suspected MLS cases were molecularly diagnosed with MLS, and novel mutations were identified. The average onset age was 46.8 ± 8 years, which was older than that of the patients with ChAc. The immunoblot analysis revealed remarkably reduced chorein immunoreactivity in all patients with MLS. The immunoprecipitation analysis indicated a direct or indirect chorein-XK interaction.

Conclusions In this study, *XK* pathogenic mutations were identified in all 6 MLS cases, including novel mutations. Chorein immunoreactions were significantly reduced in MLS erythrocyte membranes. In addition, we demonstrated a possible interaction between the chorein and XK protein via molecular analysis. The reduction in chorein expression is similar to that between Kell antigens and XK protein, although the chorein-XK interaction is a possibly noncovalent binding unlike the covalent Kell-XK complex. Our results suggest that reduced chorein levels following lack of XK protein are possibly associated with molecular pathogenesis in MLS.

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Q. Niu, X. Wang, M. Shi, Q. Jin. 2015;1:e20. doi.org/10.1212/NXG.0000000000000017