Genome-wide studies and molecular targeting therapy for neurological diseases

Tatsushi Toda MD, PhD
Division of Neurology/Molecular Brain Science, Kobe University Graduate School of Medicine, Kobe, Japan

We aim to elucidate molecular mechanism and develop therapies for neurological disorders. Parkinson's disease (PD), one of the most common neurodegenerative diseases, is caused by multiple genetic and environmental factors. To identify PD-susceptibility variants, we performed a GWAS and two replication studies in a total of 2,011 PD cases and 18,381 controls from Japan. We identified a novel and strong PD-susceptibility locus on 1q32 and designated this as *PARK16*. *BST1* also showed a novel and strong association with PD. We detected a strong disease association at *SNCA* and *LRRK2* on 12q12, both causative genes for autosomal dominant parkinsonism. By comparing data with a Caucasian GWAS, we identified *PARK16*, *SNCA*, and *LRRK2* as population-common susceptibility genes for PD and *BST1* and *MAPT* as ones showing population difference. Our data show two novel PD-susceptibility loci, involvement of causal genes of autosomal dominant parkinsonism in typical PD, and the possibility that population differences underlie genetic heterogeneity in PD.

Fukuyama muscular dystrophy (FCMD), one of the most common autosomal recessive disorders in Japan, was the first human disease found to result from ancestral insertion of a SINE-VNTR-*Alu* (SVA) retrotransposon into a causative gene. In FCMD, the SVA insertion occurs in the 3' untranslated region (UTR) of the *fukutin* gene. Here we show that aberrant mRNA splicing, induced by SVA exon-trapping, underlies the molecular pathogenesis of FCMD. Introduction of antisense oligonucleotides (AONs) targeting the splice acceptor, the predicted exonic splicing enhancer and the intronic splicing enhancer prevented pathogenic exon-trapping by SVA in cells of patients with FCMD and model mice, rescuing normal *fukutin* mRNA expression and protein production. AON treatment also restored fukutin functions, including *O*-glycosylation of □-dystroglycan (□-DG) and laminin binding by □-DG. Moreover, we observe exon-trapping in other SVA insertions associated with disease (hypercholesterolemia, neutral lipid storage disease) and human-specific SVA insertion in a novel gene. Thus, we have discovered in human disease a role for SVA-mediated exon-trapping and demonstrated the promise of splicing modulation therapy as the first radical clinical treatment for FCMD and other SVA-mediated diseases.