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A novel splice-site mutation of *ALMS1* caused Alstrom syndrome in Yamane Jewish family

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Aim: To describe a novel mutation in splicing area of *ALM1* gene in a child clinically diagnosed for Alstrom syndrome. Setting: Whole-exome sequencing (WES).

Methods: Review of the clinical data since the child presentation on 2008, including neurological examination, brain magnetic resonance imaging and review of the family history were performed. Complete eye exam and further evaluation using fundus photography, optical coherence tomography (OCT) and electro-retinography were conducted. Genetic evaluation was performed by whole exome sequencing and bioinformatics analysis using the Burrows-Wheeler Aligner (BWA) and the Genome Analysis Tool Kit (GATK) software. Splice site prediction was done using SplicePort and Neural Networks tools. *In vitro* splicing assay was used to evaluate the effect of the identified mutation on splicing.

Results: The proband presented at age six with impaired vision, nystagmus and hyperopia with color blindness and was diagnosed as leber congenital amaurosis (LCA). The eye exams of the patient's family (parents and brothers) were unremarkable except for keratoconus of the father. During follow up period, he developed bilateral posterior sub-capsular cataract, disc pallor, degenerative retinal changes, and severe attenuation of the retinal vessels. Genetic evaluation was negative for LCA and WES revealed no relevant compound heterozygosity or recessive mutations. Targeted analysis of the *ALMS1* gene revealed recessive inversion of A-T at +3 positions at the end of exon 16 suggesting a novel splicing mutation causing Alstrom syndrome. cDNA analysis, involving fragment analysis and cloning, indicated that the c.11544+3A>T mutation eliminated the splice donor site, which led to a insertion of 72 nucleotides in the end of exon 16.

Conclusions: Here we describe a patient with systemic and ocular findings that were negative genetically for LCA but revealed a novel splice mutation of ALM1 suggesting Alstrom disease. The child diagnosis was confirmed by segregation study with the family.

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