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Unveiling the genetic variation of severe continuous/mixedtype ossification of the posterior longitudinal ligament by whole-exome sequencing and bioinformatic analysis

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Background: Ossification of the posterior longitudinal ligament (OPLL) in thecervical spine is known as a rare, complex genetic disease, its complexity being partly because OPLL is diagnosed by radiological findings regardless of clinical or genetic evaluations. Although many genes associated with susceptibility have been reported, the exact causative genes are still unknown. We performed an analysis using next-generation sequencing and including only patients with a clear involved phenotype.

Method: We consecutively included 74 patients with severe OPLL patients with continuous-/ mixed-type and anoccupying ratio of ≥ 40%and 26 healthy controls, and performed whole-exome sequencing (WES) and bioinformatic analysis.Then, a validation test was performed for candidate variations. Participants were divided into 4 groups(rapidly-growing OPLL, growing rate ≥ 2.5%/y; slow-growing, < 2.5%/y; uncertain; and control).

Results: WES was performed on samples from 74 patients with OPLL (rapidly-growing, 33 patients; slow-growing, 37; and uncertain, 4) with 26 healthy controls. Analysis of 100 participants identified a newly implicated single-nucleotide variant (SNV) and 4 candidate genes based on GVB. The gene-wise variant burden (GVB) of CYP4B1 showed a more deleterious score in the OPLL than the control group. Comparison between the rapidlygrowing OPLL and control groups revealed seven newly identified SNVs. We found significant association for 2 rare missense variants; rs121502220 (odds ratio [OR] = infinite; minor allele frequency [MAF] = 0.034) in NLRP1 and rs13980628 (OR= infinite; MAF = 0.032) in SSH2. The 3genes are associated with inflammation control and arthritis, and SSH2 and NLRP1 are also relatedto vitamin D modulation.

Discussion: Identification of unique variants in novel genes such as CYP4B1 gene may induce the development of OPLL. In subgroup analysis, NLRP1 and SSH2 genes coding inflammationmolecules may related with rapidly-growing OPLL.