Polygenic Risk Score for Prediction of Ossification of the Posterior Longitudinal Ligament

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INTRODUCTION: Ossification of the posterior longitudinal ligament (OPLL) is a multifactorial disease influenced by both genetic and environmental factors. It often progresses asymptomatically, and even minor trauma can sometimes lead to severe paralysis. Thus, identifying individuals at high risk is clinically important, as it enables early interventions such as imaging surveillance and lifestyle guidance to improve clinical outcomes. Our previous genome-wide association study (GWAS) demonstrated that OPLL is highly heritable [1], supporting the use of genetic information in risk prediction. The polygenic risk score (PRS), which aggregates the effects of many common variants identified through GWAS, reflects the cumulative genetic contribution to complex diseases like OPLL. PRS has been increasingly applied to predict disease risk, stratify populations, and advance personalized medicine. However, no study has yet evaluated prediction models for OPLL that incorporate genetic data. Here, we aimed to develop a genetic risk prediction model for OPLL using the PRS.

METHODS: Genotyping data from 74,462 individuals (36,789 males and 37,673 females), including 2,402 OPLL patients, were obtained using genotyping arrays and analyzed. The data consisted of four datasets (datasets 1–4). For all datasets, stringent single nucleotide polymorphism (SNP) and sample quality control procedures were applied, followed by SNP imputation. For imputation, we used a high-resolution reference panel constructed from the 1000 Genomes Project Phase 3 [1KGP3 (May 2013, n = 2,504)] together with 3,256 in-house Japanese whole-genome sequences (JEWEL 3K). We constructed polygenic risk scores (PRSs) using the pruning and thresholding method. We applied 20 different cutoffs for the GWAS P value thresholds and nine cutoffs for the r^2 thresholds, representing the strength of linkage disequilibrium between SNPs. The datasets were divided into (i) a discovery & validation set (datasets 1 and 4) and (ii) a test set (datasets 2 and 3). The discovery & validation set was further partitioned into five subsets, and PRSs were generated from GWAS in the discovery set and evaluated in the validation set using five-fold cross-validation, from which the optimal parameters were determined. Using these parameters, we calculated PRS in the test set based on GWAS results from the discovery & validation set (Fog. 1). We then performed receiver operating characteristic (ROC) analysis to compute the area under the curve (AUC).

RESULTS: OPLL patients exhibited significantly higher PRS values compared with controls ($P < 5 \times 10^{-50}$), confirming a strong genetic contribution to disease susceptibility. ROC analysis demonstrated that the predictive performance of the PRS alone yielded an AUC of 0.657 (95% CI: 0.639–0.675) (Fig. 2). To further assess risk stratification, individuals were divided into deciles according to their PRS values, and the incidence of OPLL was compared across these strata. A clear gradient of increasing disease risk was observed, with higher PRS deciles showing progressively elevated risk of OPLL. Using the 40–50% PRS group (5th decile) as the reference, individuals in the top 10% of the PRS distribution had a substantially increased risk, with an odds ratio of 3.04 (95% CI: 2.32–4.02) (Fig. 3).

DISCUSSION: Our findings demonstrate that prediction of OPLL is feasible using genetic information alone, although the predictive performance of the PRS by itself was modest. Individuals in the top 10% of the PRS carried a significantly higher risk for OPLL, underscoring the clinical importance of genetic risk stratification. To our knowledge, this is the first study to apply the PRS to OPLL, highlighting the potential utility of genetic profiling in a disease long recognized as highly heritable. Compared with previous approaches relying primarily on clinical information, our results suggest that incorporating genetic data provides an additional and independent dimension of risk assessment. The clear gradient in disease risk across PRS deciles supports its value for stratifying individuals by genetic susceptibility. Combining the PRS with established clinical risk factors is expected to improve prediction accuracy and may contribute to earlier identification and preventive strategies for individuals at high risk. Limitations of this study include potential population-specific effects, as our analysis was based on Japanese cohorts, and further validation in other ethnic groups will be required. Nevertheless, these findings provide important evidence for the role of genetic information in OPLL risk prediction and highlight the future potential of integrating the PRS into precision medicine approaches for spinal disorders.

SIGNIFICANCE/CLINICAL RELEVANCE: This study provides the first evidence that PRS can predict OPLL susceptibility, suggesting its potential for future clinical application.

REFERENCES: [1] Koike Y, et al. Genetic insights into ossification of the posterior longitudinal ligament of the spine. Elife 2023;12:e86514.

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IMAGES:

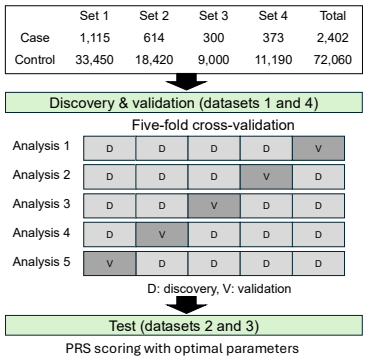

Fig.1 PRS analysis workflow

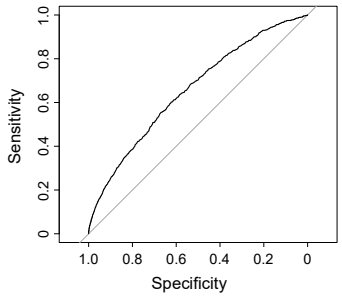

Fig.2 ROC analysis result

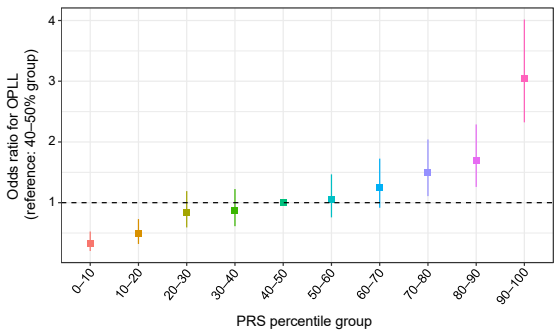

Fig.3 PRS stratification analysis result