PEDIATRIC RHEUMATOLOGY

MEETING ABSTRACT Open Access

PW03-014 - TLR4 and MEFV variants are Behçet's risk factors

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Introduction

Genome-wide association studies (GWAS) are a powerful means for identifying genes with disease-associated common variants, but they are not well-suited to detect genes with disease-associated rare or low-frequency variants. It has long been debated whether the innate immune system is involved in the pathogenesis of Behçet's disease (BD) but genetic evidence to support this hypothesis is sparse.

Objectives

To determine whether rare and low frequency variants in genes involved in innate immunity are associated with BD.

Methods

In the current study, non-synonymous variants (NSVs) identified by deep exonic resequencing of 10 genes found by GWAS (*IL10*, *IL23R*, *CCR1*, *STAT4*, *KLRK1*, *KLRC1*, *KLRC2*, *KLRC3*, *KLRC4*, and *ERAP1*) and 11 genes selected for their role in innate immunity (*IL1B*, *IL1R1*, *IL1RN*, *NLRP3*, *MEFV*, *TNFRSF1A*, *PSTPIP1*, *CASP1*, *PYCARD*, *NOD2*, and *TLR4*) were evaluated for BD association in Japanese and Turkish populations. A differential distribution of the rare and low frequency NSVs of each gene in 2461 BD cases compared with 2458 controls was evaluated by three different burden tests.

Results

By stringent criteria requiring at least one burden test with study-wide significance ($p < 0.0024$) and a corroborating test with at least nominal significance ($p < 0.05$), rare and low frequency NSVs in one GWAS-identified gene, *IL23R* ($p = 6.9 \times 10^{-5}$), and one gene involved in innate immunity, *TLR4* ($p = 8.0 \times 10^{-4}$), were associated with BD. In addition, damaging or rare damaging *NOD2* variants were nominally significant across all three burden tests applied ($p = 0.0063$ to 0.045). Furthermore, carriage of *MEFV*-M694V, but not other *MEFV* mutations known to cause recessively inherited familial Mediterranean fever, conferred BD risk in the Turkish population (OR = 2.65, $p = 1.8 \times 10^{-12}$).

Conclusion

Rare and low frequency NSVs of two novel BD-associated genes, *MEFV* and *TLR4*, implicate innate immune and bacterial sensing mechanisms in BD pathogenesis. Furthermore, disease-associated *IL23R* rare and low frequency NSVs add to the common variant GWAS evidence implicating this locus.

Disclosure of interest

None declared.

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