The type 1 diabetes susceptible MHC-II β56H/57S polymorphisms positively regulate the orchestrators of rheumatoid arthritis

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Abstract:

The mouse major histocompatibility complex class II (MHC-II), which is analogous to the human leukocyte antigen (HLA), serves as a molecule for presenting peptides and plays a crucial role in T cell tolerance during thymocyte development. Variations in MHC-II are the primary genetic contributions to susceptibility to autoimmune diabetes in both nonobese diabetic (NOD) mice and humans. In previous studies, the substitution of the 56th and 57th amino acids from histidine (H) and serine (S) to proline (P) and aspartic acid (D), respectively, on the β chain of the unique NOD MHC-II I-Ag7 allele conferred resistance against autoimmune diabetes in a transgenic NOD.PD mouse model. The K/BxN mouse model exhibits many features common to human RA and spontaneously develops arthritis due to the expression of the transgenic T cell receptor (TCR), which can be specifically activated by the antigen glucose-6-phosphate isomerase (GPI282-294) peptides presented by the diabetogenic mouse MHC-II molecule I-Ag7. Here we aim to investigate the role of the T1D-susceptible MHC-II β56H/57S polymorphism in the pathogenesis of RA,

Generation of I-A$^{g7.PD}$ K/BxN mice

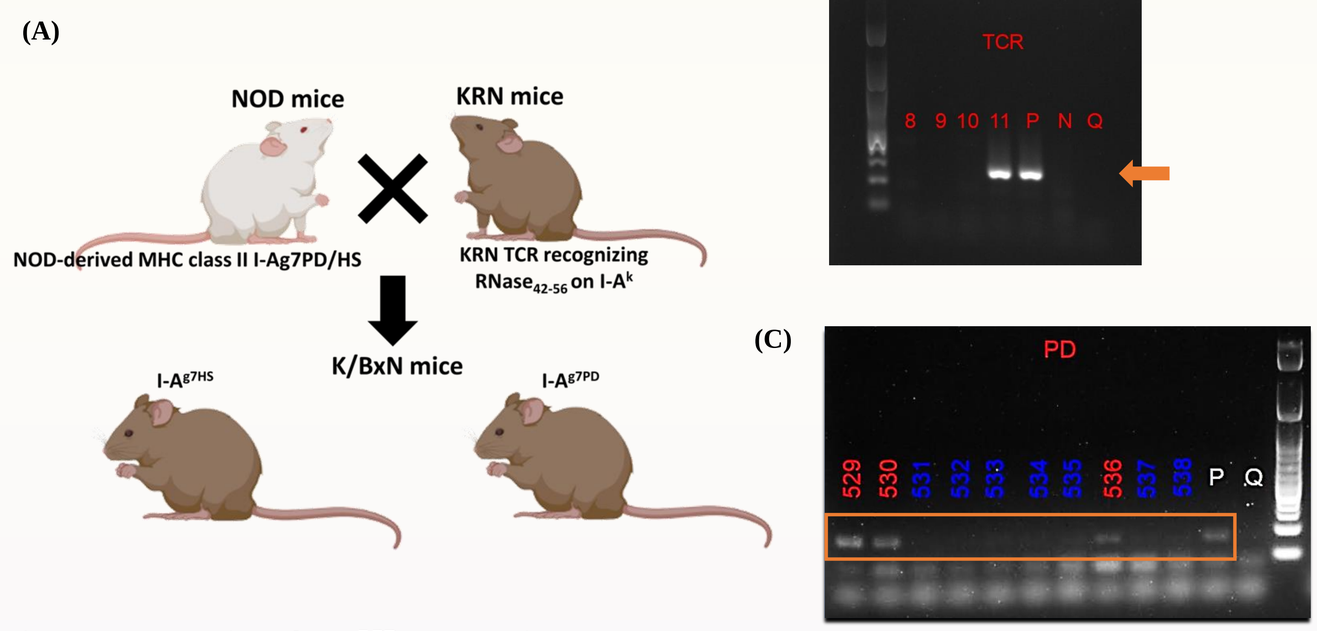


Figure 1. Generation of I-A$^{g7.PD}$ K/BxN mice.
(A) Crossing KRN-C57BL/6 and NOD-I-A$^{g7PD/HS}$ mice to generate I-A^{g7PD}K/BxN mice and I-A^{g7HS}K/BxN mice.
(B) Genotyping of TCR transgene mice. PCR detection of transgenic TCRβ in genomic DNA extracted from KRN mice.
(C) Genotyping of I-A^{g7PD}K/BxN mice. PCR detection of I-A^{g7PD}in genomic DNA extracted from K/BxN mice.

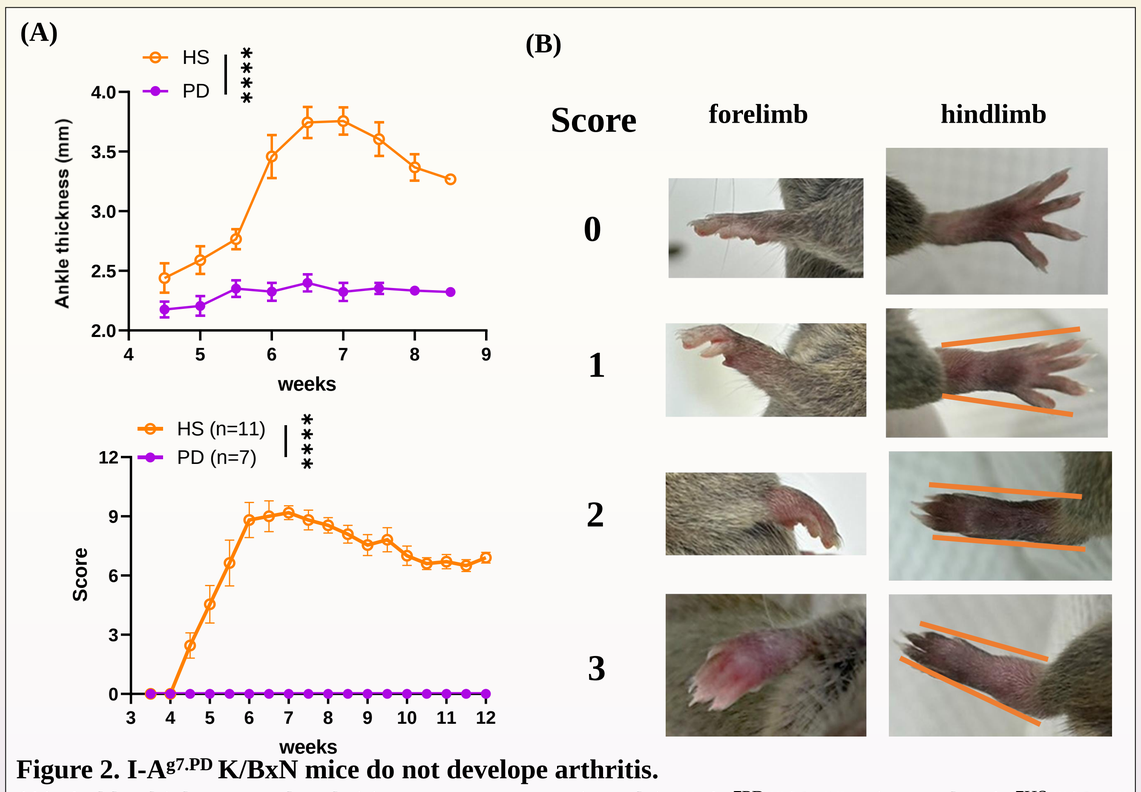
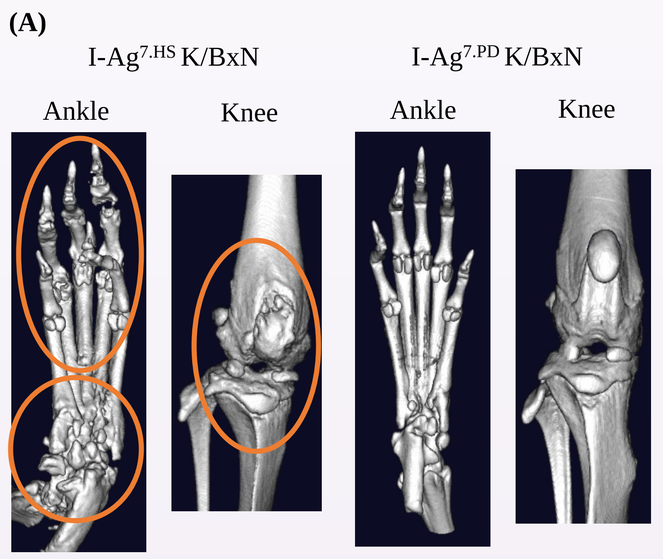


Figure 2. I-A$^{g7.PD}$ K/BxN mice do not develope arthritis.
(A) Ankle thickness and arthritis score were monitored in I-A^{g7PD}K/BxN mice and I-A^{g7HS}K/BxN mice from 3 weeks old to 12weeks old. . (B) Definition of arthritis score in K/BxN mice.



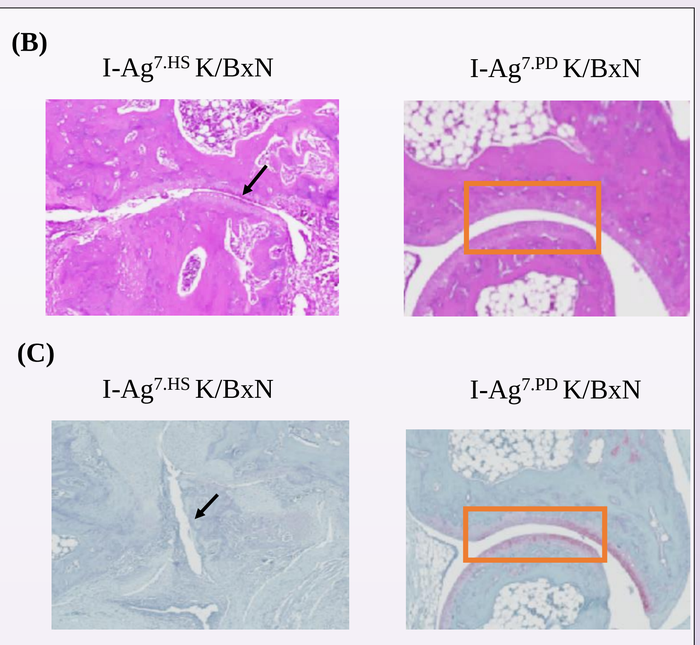


Figure 3. Joint inflammation of I-A$^{g7.PD}$ K/BxN mice
The ankles and knees of I-A^{g7PD}K/BxN mice and I-A^{g7HS}K/BxN mice at 12 weeks of age were analyzed by μCT (A), H&E staining (B) and Safranin O staining (C)

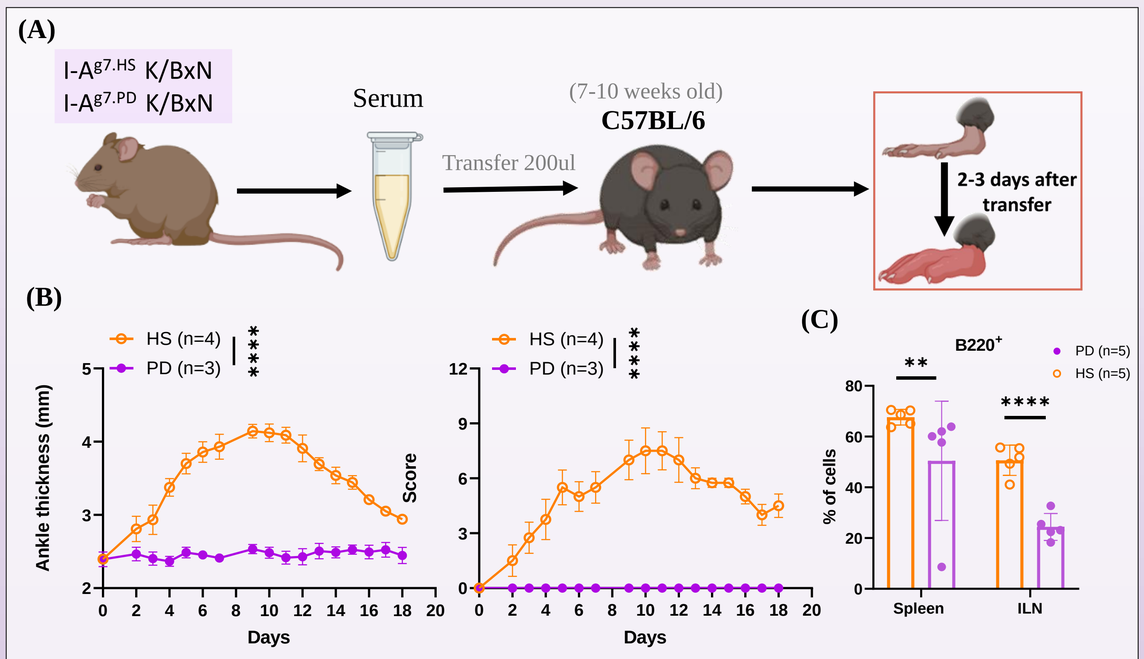


Figure 4.Serum transfer from I-A$^{g7.PD}$ K/BxN mice can not induce arthritis.
(A) Serum from 12 weeks old I-A^{g7PD}K/BxN mice and I-A^{g7HS}K/BxN mice was intraperitoneally injected into 7-10 weeks old wild type C57BL/6 mice and were monitored from day0 to day18.
(B) Ankle thickness and arthritis score were monitored in I-A^{g7PD}K/BxN-B6 mice and I-A^{g7HS}K/BxN-B6 mice.

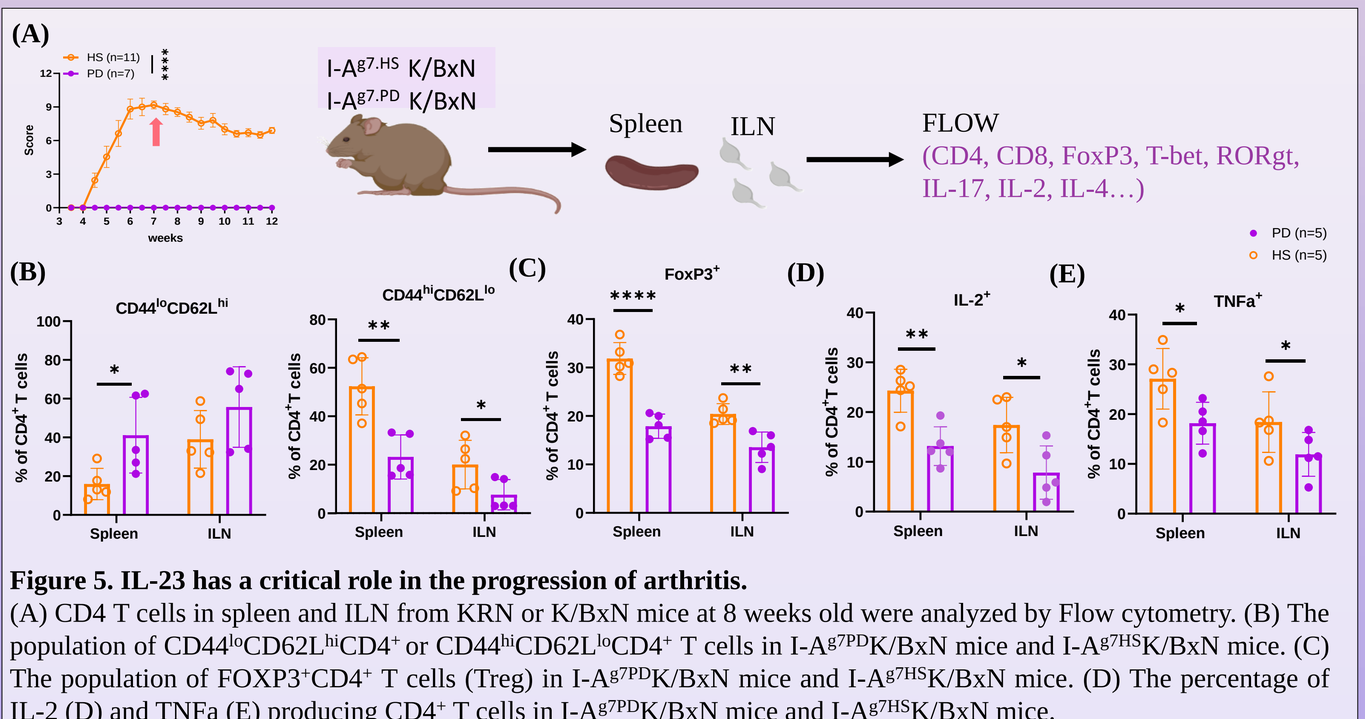


Figure 5. IL-23 has a critical role in the progression of arthritis.
(A) CD4 T cells in spleen and ILN from KRN or K/BxN mice at 8 weeks old were analyzed by Flow cytometry. (B) The population of CD44^{lo}CD62L^{hi}CD4^{+} or CD44^{hi}CD62L^{lo}CD4^{+} T cells in I-A^{g7PD}K/BxN mice and I-A^{g7HS}K/BxN mice. (C) The population of FOXP3^{+}CD4^{+} T cells (Treg) in I-A^{g7PD}K/BxN mice and I-A^{g7HS}K/BxN mice. (D) The percentage of IL-2 (D) and TNFa (E) producing CD4^{+} T cells in I-A^{g7PD}K/BxN mice and I-A^{g7HS}K/BxN mice.

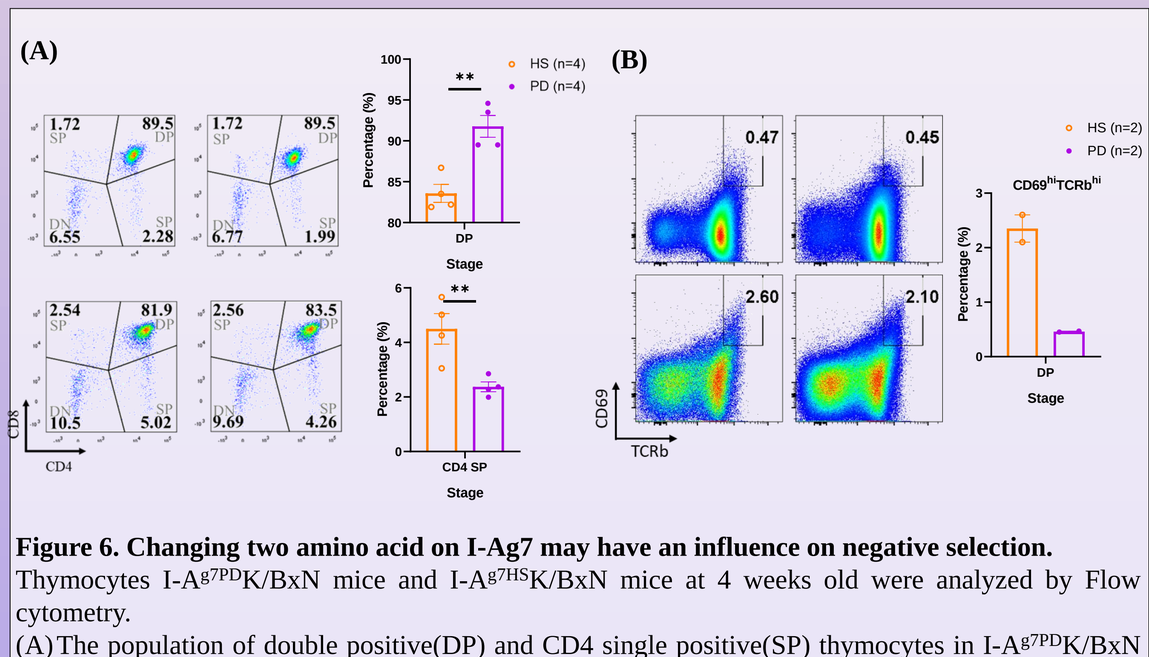


Figure 6. Changing two amino acid on I-Ag7 may have an influence on negative selection.
Thymocytes I-A^{g7PD}K/BxN mice and I-A^{g7HS}K/BxN mice at 4 weeks old were analyzed by Flow cytometry.
(A) The population of double positive(DP) and CD4 single positive(SP) thymocytes in I-A^{g7PD}K/BxN mice and I-A^{g7HS}K/BxN mice.
(B) The population of CD69^{+}TCRβ^{+} DP thymocytes in I-A^{g7PD}K/BxN mice and I-A^{g7HS}K/BxN mice.

Conclusion:

Taken together, the substitution of the 56th and 57th amino acids from HS to PD on the β chain of the I-A^{g7} allele is speculated to reduce the occurrence of RA.