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# Balancing selection in the extended MHC region maintains a subset of alleles with opposite risk profile for different autoimmune diseases

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## Background

Several susceptibility genetic variants for autoimmune diseases have been identified through genome-wide association studies (GWAS). Recent evidences have indicated that a subset of these polymorphisms (mostly located in the extended major histocompatibility complex region, xMHC) displays an opposite risk profile in different autoimmune conditions, with one allele predisposing to one disease while being protective for another. These observations open interesting questions on the evolutionary forces shaping the frequency of these alleles in human populations.

## Methods and results

Our aim was to analyze the selective processes acting on variants with an opposite effect on two or more diseases and to test the hypothesis whereby balancing selection has shaped the frequency of these alleles. Since balancing selection signatures are expected to extend over short genomic portions, we restricted our analyses to 10 regions carrying putative functional polymorphisms that might represent the disease variants (and the selection targets). Resequencing of 20 HapMap subjects with European ancestry (CEU) revealed no exceptional nucleotide diversity for *ZSCAN23, HLA-DMB, VARS2, PTPN22, BAT3,* and *C6orf47;* summary statistics were consistent with evolutionary neutrality for these gene regions. Conversely, the regions we analysed in *CDSN/PSORSC1, TRIM10/TRIM40, BTNL2,* and *TAP2* showed extremely high nucleotide diversity and most tests rejected neutrality, suggesting the action of balancing selection. The possibility that the signatures we observed at TAP2 and BTNL2 are secondary to linkage disequilibrium with HLA class II genes was ruled out. We extended population genetic analyses to Yoruba and East Asians and verified that balancing selection has been acting in most populations on CDSN/PSORSC1, TRIM10/TRIM40, BTNL2, and TAP2. These data were also confirmed by the application of multi-locus HKA tests that revealed a significant excess of polymorphism compared to divergence. Consistently, estimation of the time to the most recent common ancestor yielded deeper coalescent times than expected under neutrality.

## Conclusions

In summary, our data indicate that a portion of alleles with an opposite risk profile for different autoimmune diseases have evolved under a regime of long-standing balancing selection. Also, results herein indicate that balancing selection has operated on several non-HLA genes located in the xMHC. In addition to their involvement in autoimmunity, variants in *TAP2* and *TRIM10* influence the susceptibility to some viral infections, while *CDSN,* encoding corenodesmosin, is pivotal in maintaining the epidermal integrity, which serves as a barrier against invading pathogens. Therefore, we suggest that infectious diseases represent the selective pressure underlying the signatures we observed and contributed to shaping the genetic predisposition to autoimmunity in modern populations.

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