HLA-OLI: A new MHC class I pseudogene and HLA-Y are located on a 60 kb indel in the human MHC between HLA-W and HLA-J

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Key Highlights

- Identification of a new HLA Class I locus, HLA-OLI, with similarities to HLA-P
- Identification of the location of HLA-Y. An HLA Class I pseudogene identified in 2003 but its location has remained elusive until now
- HLA-OLI and HLA-Y are present on a 60kb DNA insertion between HLA-A and HLA-W which is found in some people but not others. Including individuals with the same HLA-A type

Background

The best donor for a patient needing a bone marrow/hematopoietic cell transplant (HCT) is a sibling shown to have inherited the same HLA genes from each parent. The next best donor is an HLA-matched unrelated individual (Matched unrelated donor or MUD). However, despite equivalent matching for what are considered the critical transplant genes there is a higher risk of poorer outcomes, including graft v host disease and transplant related mortality, for patients receiving a transplant from a MUD.

The reasons for the disparity in outcomes is unclear but the clue may lie in the fact that matched siblings are fully matched for the entire content of the MHC, not just HLA genes, whereas MUDs may be mismatched at many additional MHC loci and non-conventionally typed HLA or other genes may contribute to outcomes.

MHC diversity, structure and modes of inheritance are currently poorly understood, particularly at the population level. The release of population whole genome sequencing into the public databases and the development of ThermoFisher/One Lambda's Typestream Visual software for accurate genotyping HLA and other loci from whole genome sequence is beginning to unravel our knowledge about the MHC.

As a first step to research MHC diversity, we directly compared MHC sequence from samples of PanGenome project with the human genome reference and identified many of the pangenome sequences to have a 60kb relative to the reference. Annotation of this 60kb sequence revealed HLA-Y and HLA-OLI. A subsequent analysis of whole genome sequence data from the thousand genomes project demonstrated that some individuals with the same HLA type either had, or didn't have the 60kb indel. The implications of transplanting when mismatching for the insertion/deletion are not known.

Conclusion

The identification of a new locus in the MHC, the first in 20 years, demonstrates that much is to be learned about MHC diversity and how this may impact HCT outcomes. Our work to understand MHC structure and diversity is ongoing with a longer-term view to develop the best matching strategies (products) for optimum outcomes in HCT, including typing of potential unrelated donors onto the international unrelated HCT registry. Our work also has broader implications for the study of MHC evolution and the role of the MHC in diseases where the MHC is implicated as a disease risk locus.