Docket #: S15-430

Method to completely characterize the highly polymorphic KIR genomic region

Stanford researcher Paul Norman has developed an integrated capture/next-gen sequencing/ bioinformatics method to completely characterize the structure and sequence of the highly polymorphic killer cell immunoglobulin-like receptor (KIR) genes to aid in donor matching for clinical transplantations. KIRs are a family of proteins expressed by natural killer (NK) cells that, upon binding with HLA class I molecules, allow NK cells to discriminate healthy cells from infected or diseased cells. The genomic region containing KIR is unusually diverse, both in the number of genes and their alleles. The region is structurally complex and highly polymorphic. In addition, the genomic region is also strongly associated with a wide spectrum of diseases. It would be beneficial to understand KIR diversity, but methods to do so are limited by the complexity of the region.

Stanford is making available for licensing the copyrighted list of 4,000 oligonucleotide probes that cover the KIR genes and can be used to enrich KIR regions to prepare DNA libraries for next-gen sequencing. The bioinformatics pipeline that automatically analyzes KIR specific reads is open-source and will be made freely available – it attributes sequencing reads to specific KIR genes, determines copy number by read depth, and calls high-resolution genotypes for each of the KIR genes. This technology will facilitate donor matching for bone marrow transplants and allow determination of a complete description of KIR in the human population and its influence on physiology, disease, and immunotherapy.

Stage of research

The method was validated using DNA from well-characterized cell lines, by comparison with established methods of KIR genotyping and by determining KIR genotypes from the 1000 Genomes Project sequence data.

Applications

- Genotyping for:
  - Bone marrow transplantation- identification of matched donors
  - Study of population genetics and disease association

Advantages

- Unmet need- this is a single method that enables a focused and extensive characterization of KIR variation
- Well suited for genotyping large cohorts
- Improves understanding of disease association
- Bioinformatic pipeline is designed for use with any highly polymorphic gene system, thus the methods can be applied to other diverse genes and gene families

Publications

- Paul J. Norman, Jill A. Hollenbach, Neda Nemat-Gorgani, Steven J. Norberg, Wesley M. Marin, Elham Ashouri, Jyothi Jayaraman, Emily E. Wroblewski, John Trowsdale, Raja Rajalingam, Jorge R. Oksenberg, Lisbeth A. Guethlein, James A. Traherne, Mostafa Ronaghi and Peter Parham, Defining KIR and HLA Class I Genotypes at Highest Resolution via High-Throughput Sequencing, American Journal of Human Genetics, 2016 Aug 4;99(2):375-91. doi: 10.1016/j.ajhg.2016.06.023.
- Alicata C, Pende D, Meazza R, Canevali P, Loiacono F, Bertaina A, Locatelli F, Nemat-Gorgani N, Guethlein LA, Parham P, Moretta L, Moretta A, Bottino C, Norman PJ, Falco M. Hematopoietic stem cell transplantation: Improving alloreactive Bw4 donor selection by genotyping codon 86 of KIR3DL1/S1, Eur J Immunol. 46(6):1511-1517, 2016.
- Alicata C, Bottino C, Guethlein LA, Parham P, Norman PJ. Description of the novel KIR2DL4*035 allele identified using high-throughput sequencing. HLA. 2016 Mar;87(3):191-3.

Innovators

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