



Improving biobank collection usability by computational HLA and KIR typing methods

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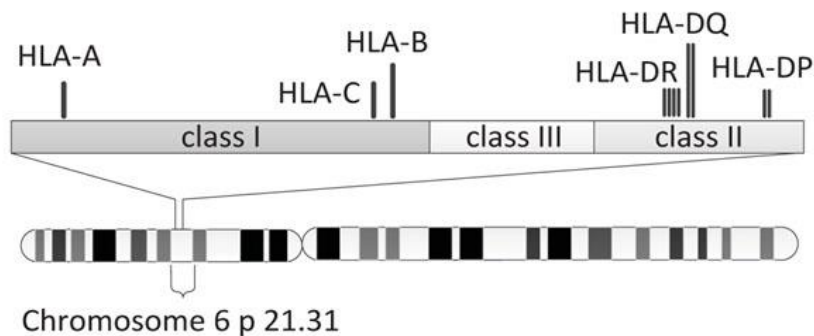
Nordic Biobank Conference 2022

Conflict of interest

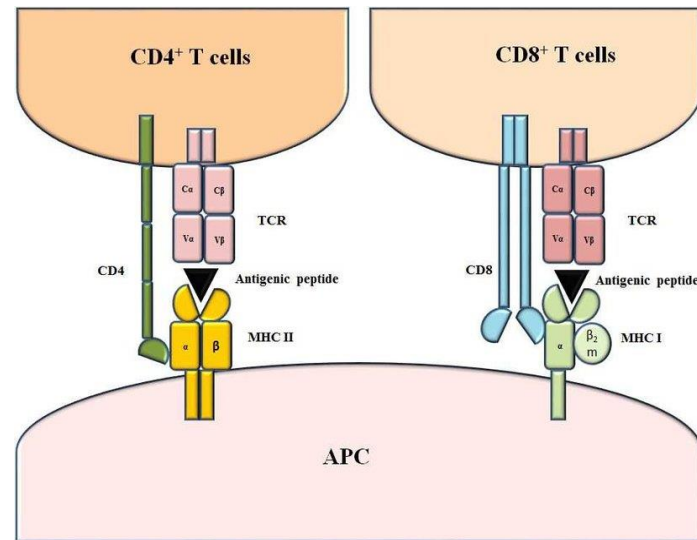
No conflict of interest to declare

Human leucocyte antigen HLA

- HLA region is the most polymorphic region in the human genome:
 - Number of HLA Class I Alleles 24 703
 - Number of HLA Class II Alleles 9 719
- Population specific polymorphism and LD pattern



Xie et al 2010



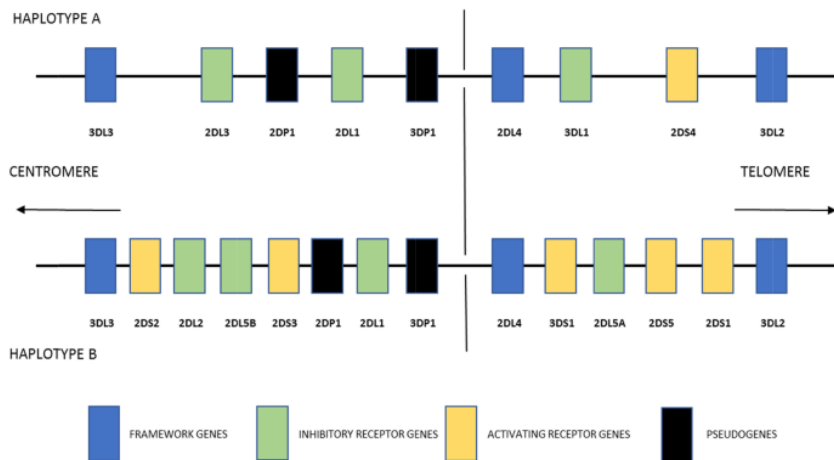
Majumdar et al 2018

HLA molecules encode for specialized glycoproteins that play a pivotal role in antigen presentation

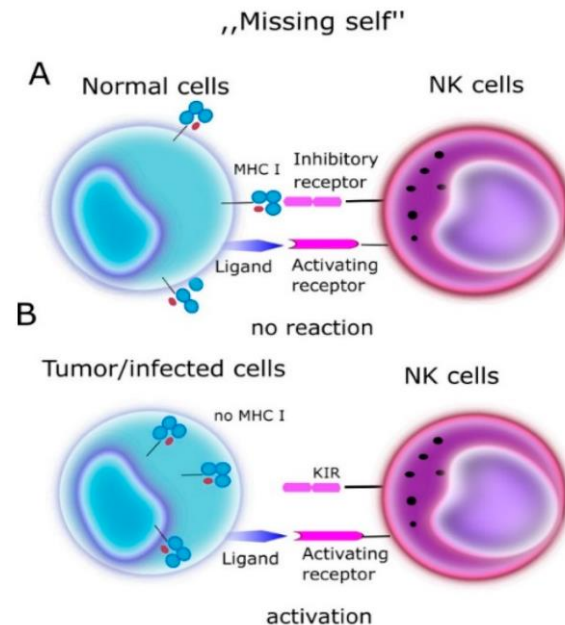
- Class I genes are expressed in most somatic cells
- Class II genes are expressed on antigen presenting cells

Killer-cell immunoglobulin-like receptor

- KIR gene region is located on 19q13.4 in leukocyte receptor complex (LRC)
- KIR genes are highly polymorphic in allelic and in haplotypic level
 - Inhibitory: Haplotype A
 - Activating: Haplotype B
 - ~55% of the haplotypes are a mixture of A and B haplotypes



Downing et al 2022



Debska-Zielkowska et al 2021

KIR receptors recognise KIR ligands (HLA class I epitopes) and regulate the killing of virus infected or malignant cells through NK cells

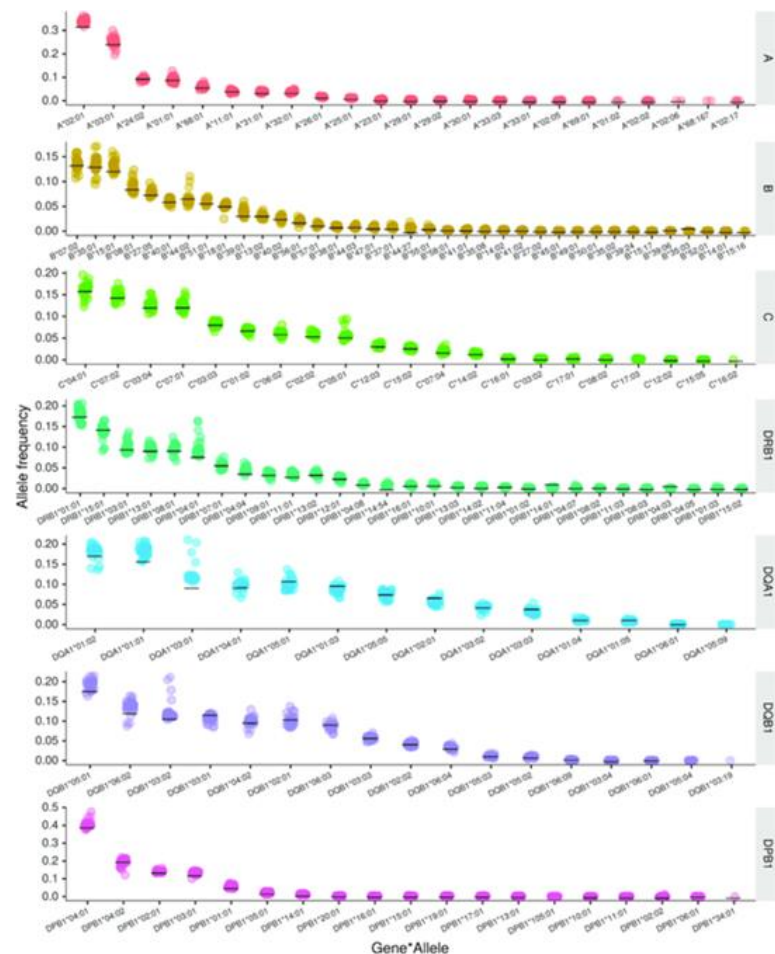
Improving the biobank genomic data

Biobank material

- The biobank samples, $n = 35\,400$, were collected along blood donation from donors who gave a written broad biobank consent
- The use of the samples and genotype data is in accordance with the biobank consent and meets the requirements of the Finnish Biobank Act 688/2012
- The samples had been previously genotyped by FinnGen ThermoFisher Axiom custom array v2

HLA imputation

- HLA typing for the seven classical class I and II genes was performed *in silico* with HIBAG algorithm (v1.14.0) and population specific reference panel
 - Low/high resolution level
- Imputation accuracy: the number of errors varied modestly between loci and remained within a median range of 0.2–3.9%

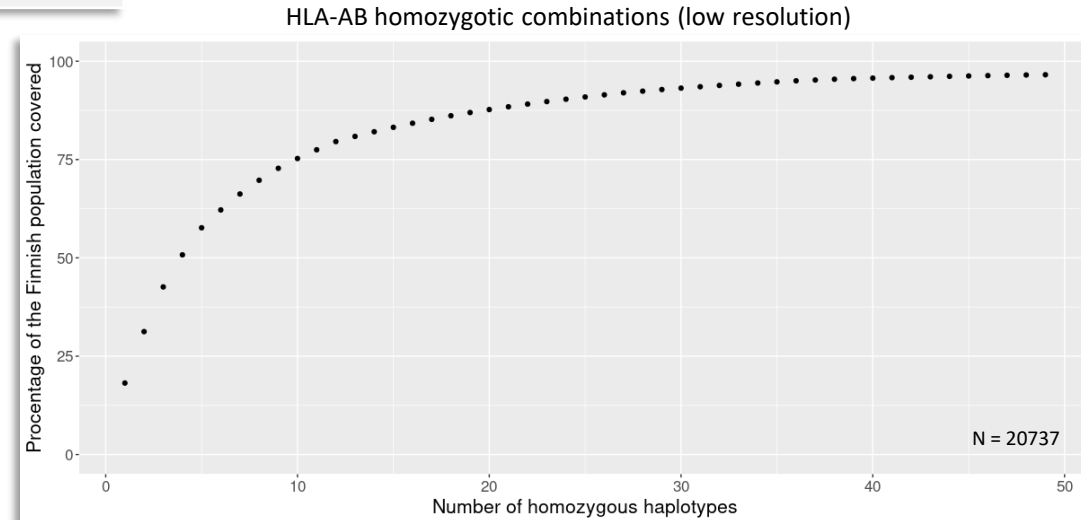


Important note: Imputed result does not replace clinical result. The imputed result must be confirmed by clinically approved methods.

Ritari et al 2020

Identified HLA homozygotes based on imputation results

	N
Biobank data	35 400
HLA-AB homozygous individuals	1219
Different HLA homozygotes	57



KIR imputation

- Identification of KIR gene content for the 12 non-framework genes was performed *in silico* by the random forest model
 - 2DL1, 2DL2, 2DL3, 2DL5, 2DP1, 2DS1, 2DS2, 2DS3, 2DS4, 2DS5, 3DL1, 3DS1
 - Presence/absence level
- Imputation accuracy: The mean overall accuracy of prediction was 0.985 (95% CI [0.970–0.992])



Ritari et al 2022

Important note: Imputed result does not replace clinical result. The imputed result must be confirmed by clinically approved methods.

Two examples of projects utilizing improved biobank data

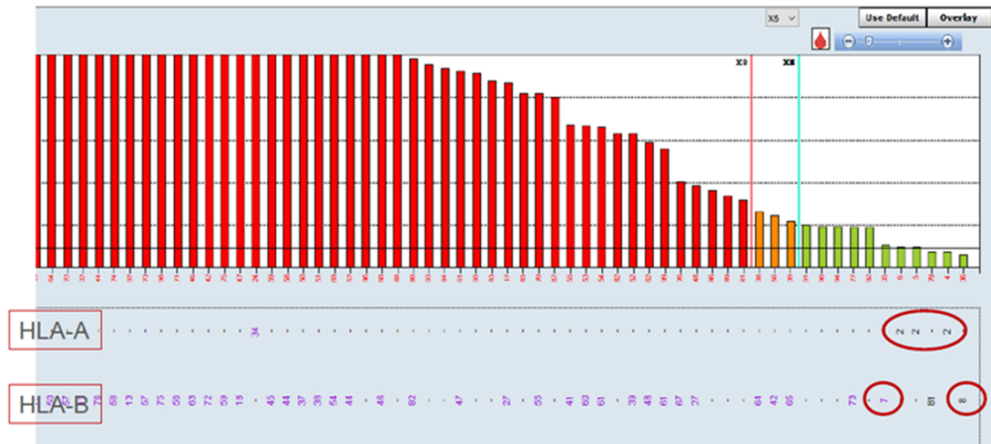
Example 1: Utilization of genome data in blood donors' HLA testing

Aim of the project is, based on the HLA imputation results, to:

1. target thrombocyte donation recruitment for optimal (HLA-AB homozygous) donors
2. expand the available donor pool

With sufficient donor pool that cover vast majority of the population, HLA matched thrombocytes may be provided for:

1. Extensively immunized patients
2. Patients with rare HLA type



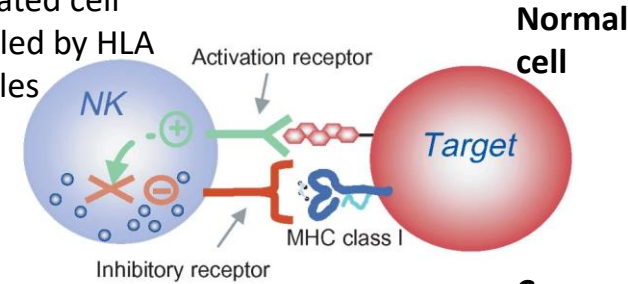
Example 2: The significance of genetic background for the function of Natural Killer cells

Aim of the project is to study how the genetic background of the donor, especially KIR genotype, affects NK cell efficiency to kill target cells *in vitro*

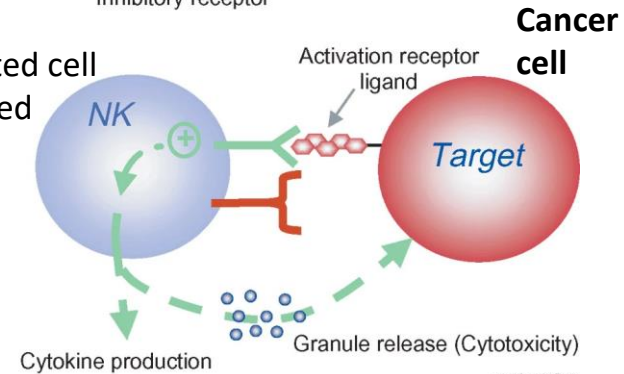
Biobank material utilization:

- Donors with KIR B haplotype content were recontacted and invited for sampling
- Donors participating in the project were asked for an informed consent

NK cell mediated cell lysis is controlled by HLA class I molecules



NK cell mediated cell lysis is activated



French et al 2003

Conclusions

- Large scale biobank genetic data sets and newly developed bioinformatic tools enable new possibilities in precision medicine based research
- Imputation is a rapid and cost effective typing tool on large scale genetic data sets
- By providing results for immunogenetically significant genomic regions, such as HLA and KIR regions, biobank material usability can be increased

Thank you!



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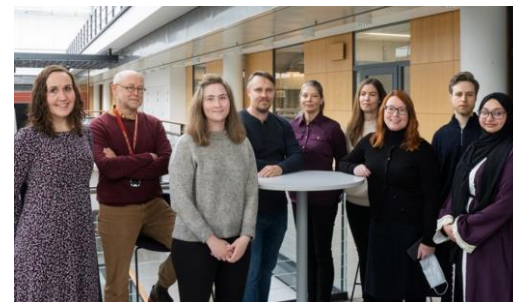


Finnish Red Cross
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