THE HLA GENETIC RELATIONSHIP BETWEEN A WELL DEFINED SLOVENIAN POPULATION SAMPLE AND THE NATIONAL HAEMATOPOIETIC STEM CELL DONOR REGISTRY

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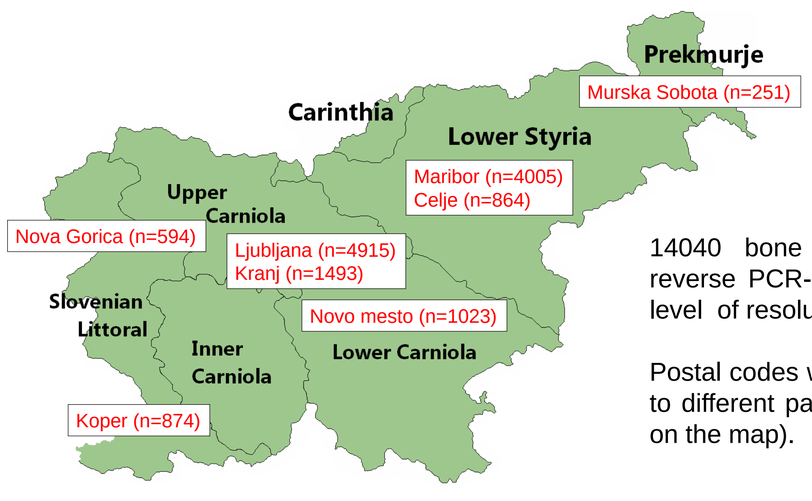
A population can be defined as a set of individuals who have been sharing a common mating history for a long time. Most often they are inhabitants of a given geographical area and speak the same language. A very important distinction to make is between the source population and different samples taken from it. The outcome of the statistical analyses and the inferences made on the population largely depends on the sample composition and size. The aim of our study was to compare the HLA polymorphism in a small sample of a (anthropologically) well-defined Slovenian population (wdp) and a large random sample of the (a priori more heterogeneous) Slovenian HSC donor registry, in order to determine whether the registry could be considered as representative of the population.

The well-defined population sample and registry data from Slovenia



14040 bone marrow donors typed using reverse PCR-SSO and PCR-SSP at 1st-field level of resolution for HLA-A, -B and -DRB1.

Postal codes were used to allocate the donors to different parts of Slovenia (indicated in red on the map).

As part of the AHPD project of the 16th IHW, a sample of 143 randomly chosen Slovenian individuals (all of whom had parents that have declared themselves as Slovenians), representing all parts of the country, was collected using the HLA-NET questionnaire for population studies.

The HLA-A, B, C, DR, DQ high resolution types were obtained with SBT. All null alleles and ambiguities within exons 2+3 (for class I) and exon 2 (for class II) were resolved using SSP.

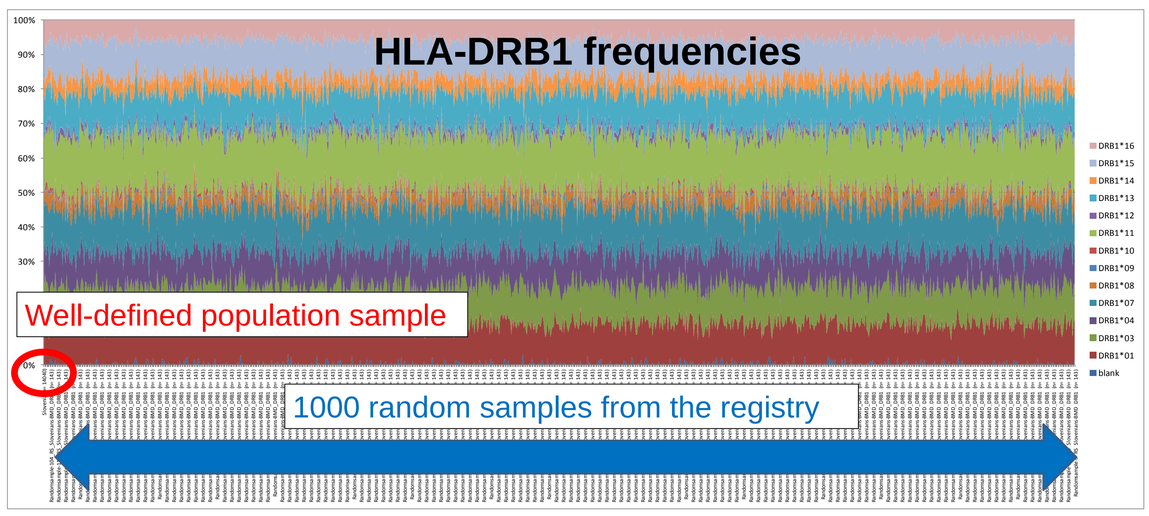
Tests of Hardy-Weinberg equilibrium

	Sample size (n)	HWE p-values HLA-A	HLA-B	HLA-DRB1
Well-defined population sample	143	0.96	1	1
Registry	14040	0.979	0.350	1
Ljubljana	4915	0.981	0.426	1
Maribor	4005	1	1	1
Celje	864	0.950	1	0.789
Kranj	1493	1	0.868	1
Nova Gorica	594	1	0.995	0.566
Koper	874	1	0.994	0.764
Novo mesto	1023	1	1	1
Murska Sobota	251	0.992	1	0.956

A powerful approach to test for Hardy-Weinberg equilibrium (HWE) in complex HLA data was used (http://geneva.unige.ch/generate/, Nunes et al. Tissue Antigens 2010).

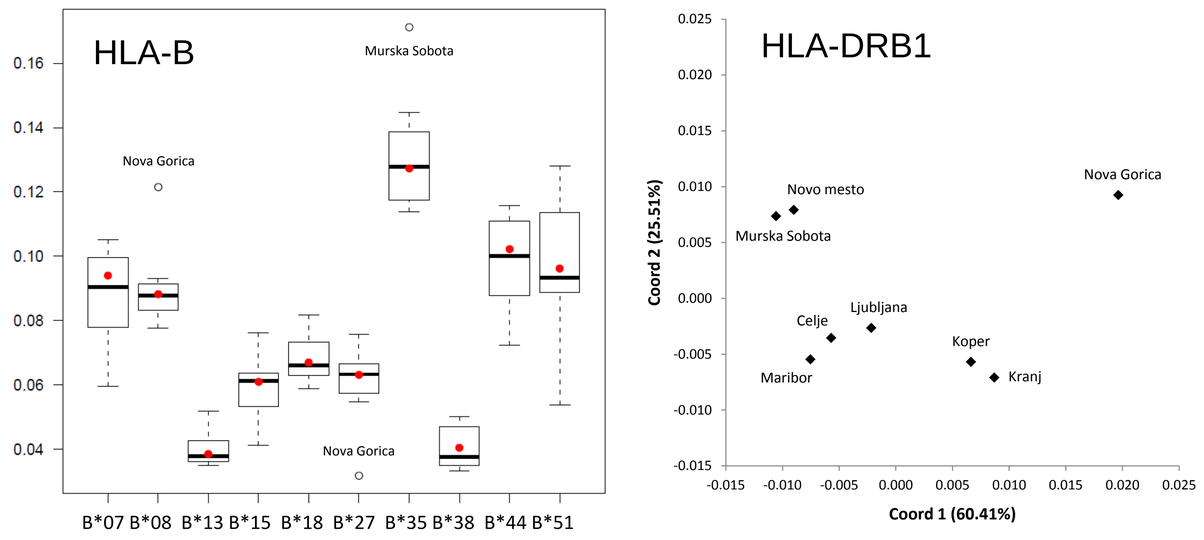
HWE is not rejected (P>0.05) both for the wdp sample (also for HLA-C and -DQB1, results not shown) and the BMD registry (either pooled together or for regions taken individually).

Comparing the registry and the well-defined population sample by re-sampling



A large number of samples of 143 donors were randomly drawn from the HSCT dataset and their HLA-A, -B and -DRB1 frequencies systematically compared to the frequencies observed in the well-defined population and the total registry. The assumption of Hardy-Weinberg equilibrium (HWE) was not rejected in any of the random samples. The frequencies estimated for these samples were never significantly different from the ones observed in both the wdp and the registry, as shown by tests of population differentiation and FST analyses.

Regional analysis of the Slovenian registry



HLA-A, -B and -DRB1 frequencies are very homogeneous among Slovenian regions, with almost no outliers detected (as illustrated on the top left graph for HLA-B), excepted for 2 regions (i.e. Nova Gorica and Murska Sobota). These regions located near the border with Italy and Hungary and inhabited by minorities from these 2 countries, respectively, harbor higher or lower frequencies for a few of the most frequent alleles, but are notwithstanding very similar to the other regions.

This is illustrated by the PCoA plot for HLA-DRB1 genetic distances (top right graph), with Nova Gorica, Novo Mesto and Murska Sobota showing slightly but not significant divergent genetic profiles to the other Slovenian regions.

Finally, the genetic diversity among Slovenian regions is significant (p<0.0001) but very low (F_{ST} of 0.07%, 0.09% and 0.06% for HLA-A, -B and -DRB1, respectively).

Conclusions

This study shows that the Slovenian HSC donor registry can be considered as representative of a well-defined Slovenian population. Complementary approaches have always found agreement between the estimates obtained from the wdp sample (recoded at 1st-field level of resolution) and those of the registry. Under these conditions, the HLA frequency profiles of the registry are those of the population, with the advantage, over the wdp sample, of having much higher precision because of a much larger sample size. The methodology presented is also suitable to obtain estimates for high resolution typings, when their proportion (3:1) is sufficient enough to ensure statistically reliable estimates (see Poster P154 for details).

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