Definition of the HLA population diversity boundaries for clinical histocompatibility practice.

The catalogue of HLA alleles must distinguish well-documented alleles comprising the polymorphic HLA universe, to the extent that can be done with the current state of knowledge. The catalogue is an attempt to catalogue all HLA alleles recognized by ABO cross-matching and the World Health Organization Histocompatibility Nomenclature Committee at the end of 2019. This is an essential part of the adequate management of the international HLA nomenclature. The current version of the catalogue is a work in progress that will be updated regularly. The current version of the catalogue is available online at https://hla.alleles.org, and the official HLA nomenclature at https://www.eurofeatures.org.

Catalogue of well-documented alleles:
The number of HLA alleles in the official catalogue increases at a regular rate. At the present time, only about 15% of the alleles in the expression loci (A, B, C) and 30% in the low-expression loci (DRB1, DQB1, DPB1) are truly relevant in clinical typing. The number of official alleles still keeps growing, but the number of significant and relevant HLA alleles remain the same.

The chance of an individual having an allele from what we have called the nebulous set of sporadic alleles is as low or even lower that the chance of having a totally new allele never reported before and absent in the official nomenclature. In fact, in our laboratory, we find on average of two or three new alleles every month, a higher number than the rare alleles we identify.

Many of the alleles in the nebulous set are poorly documented, they have only been typed once and have no confirmation. They may very well have errors. Some alleles are known not to belong to the official list and one cannot help but wondering how many such alleles are in a similar situation.

In order for the official HLA nomenclature to be definite, each new allele sequence must be independently confirmed. In addition, the complete haplotype where the new allele has been identified must fully characterized.

In spite of the fear only a few years ago that the ever-growing list of HLA alleles will present an unsurmountable barrier in finding eligible donors for bone-marrow transplantation, the difficulty does not lie in the high mutation rate of the HLA system producing endless numbers of alleles, but in the recombination rate in the HLA region. The enemy of the transplant coordinator is not the rare allele, but the rare association between HLA-B and HLA-C. It is the rare haplotype. From this point of view, more emphasis should be given to the study of HLA haplotypes and their distribution in various populations.