GLOBAL DISTRIBUTION OF HLA-E ALLELES BASED ON NEXT-GENERATION SEQUENCING OF 1.8 MILLION INDIVIDUALS

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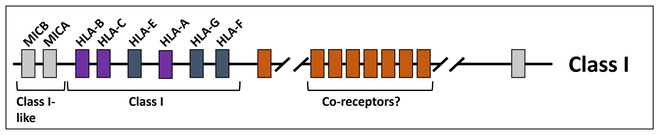
Introduction

Avoidance of HLA-E*01:03 homozygous donors has been reported to improve the outcome of hematopoietic stem cell transplantations (HSCT) in certain settings (C. Tsamadou et al., BBMT 2019).
Consequently, DKMS implemented a short amplicon based Next-Generation Sequencing (NGS) high-throughput workflow for HLA-E donor registry typing. Our approach provides resolution of the clinically relevant antigen recognition domain (ARD) level for all currently (IMGT/HLA version 3.36) known HLA-E alleles. In July 2017, DKMS added HLA-E to the default typing profile for newly enrolled potential donors for HSCT.
Since then, more than 1,800,000 samples have been typed for HLA-E at DKMS donor centers in Germany, Poland, the United Kingdom, the United States, Chile, and India.



Methods

HLA-E is typed by our well-establish high-throughput approach relying on an amplicon spanning exons 2 and 3. Amplicons are sequenced by Illumina MiSeq or HiSeq 2500 instruments without fragmentation, preserving phase information. Reads are analysed by our in-house typing software neXtype. Primary typing results comprise the high-resolved alleles HLA-E*01:01:02, 01:03:03, 01:04, 01:05, 01:07 and 01:08N and three G-groups: HLA-E*01:01:01G, 01:03:01G and 01:03:02G. For this analysis, typing results have been translated to their respective 2-field equivalent.
Upon enrollment with a DKMS donor center, potential stem cell donors provide information on their self-assessed ethnic background. Ethnic groups have been considered only, if typing results were available for at least 100 individuals.

Amplicon

	Allele	Exon 2	Exon 3	Exon 4	Exon 5	Exon 7
E*01:01:01G	01:01:01:01 (-10)	Seq 2A	Seq 3A	Seq 4A	Seq 5A	Seq 7A
	01:09	Seq 2A	Seq 3A	**Seq 4E**	Seq 5A	Seq 7A
	01:01:02	Seq 2B	Seq 3A			
E*01:03:01G	01:03:01:01 (-04)	Seq 2A	Seq 3B	Seq 4A	Seq 5A	Seq 7A
	01:03:05	Seq 2A	Seq 3B	Seq 4D		
	01:06	Seq 2A	Seq 3B	**Seq 4C**	Seq 5A	Seq 7A
	01:10	Seq 2A	Seq 3B	Seq 4A	**Seq 5B**	Seq 7A
E*01:03:02G	01:03:02:01 (-02)	Seq 2B	Seq 3B	Seq 4A	Seq 5A	Seq 7A
	01:03:04	Seq 2B	Seq 3B	**Seq 4B**	Seq 5A	Seq 7A
	01:03:03	Seq 2B	**Seq 3E**	Seq 4A	Seq 5A	**Seq 7B**
	01:04		**Seq 3D**			
	01:05	**Seq 2C**	Seq 3B			
	01:07	Seq 2A	**Seq 3C**			
	01:08N	**Seq 2D**	Seq 3B	Seq 4A	Seq 5A	Seq 7A

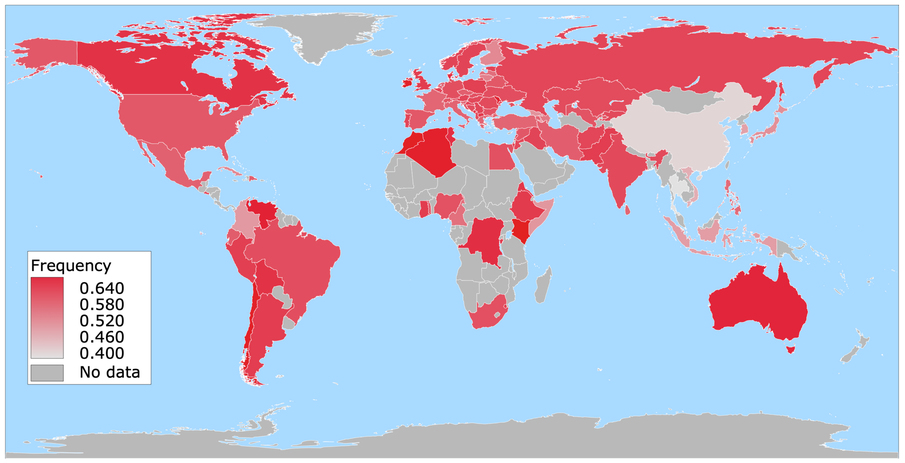
All HLA-E alleles are shown. Exon sequences (Seq) that are unique to one allele are highlighted in **bold**. Exons 1, 6 and 8 share the same exon sequence for all currently known HLA-E alleles.

Results

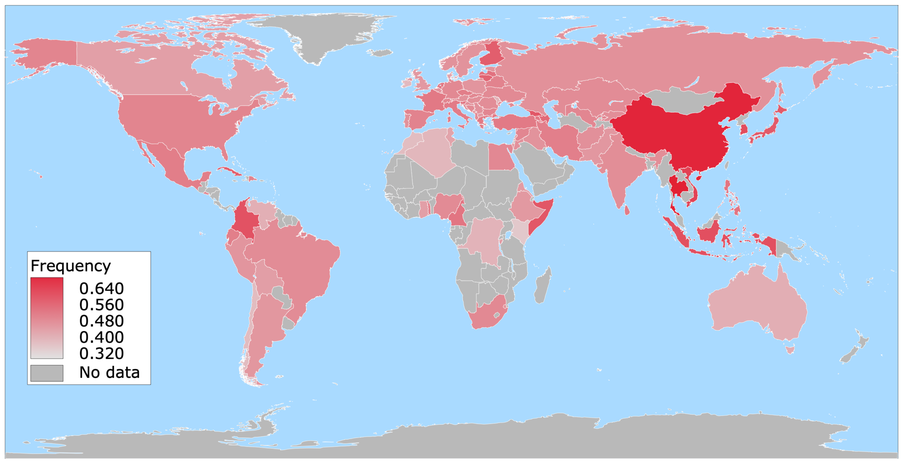
HLA-E is dominated by two allele groups, HLA-E*01:01 and HLA-E*01:03, rendering this locus almost bi-allelic.
For ethnic groups with sample sizes of at least 100 individuals, we observed frequencies for HLA-E*01:01g from f_{min}=40.1% (Thailand) to f_{max}=63.1% (Kenya). Accordingly, we observed a frequency range from f_{min}=35.6% (Kenya) to f_{max}=59.9% (Thailand) for HLA-E*01:03. While in most East Asian countries HLA-E*01:03 is dominant, in Kenya, Morocco, and Chile HLA-E*01:01 is the most frequent allele.
HLA-E*01:05 has been observed most frequently in individuals with an ethnic background from the Democratic Republic of Congo (f=2.5%), Kenya (f=1.4%), and Ghana (f= 1.0%).
Conclusions: We observed the highest deviation from bi-allelic behavior as reflected in the share of HLA-E*01:05 in samples from African countries. Also, a considerable shift between the two dominating allele groups was seen.
Alleles 01:04 und 01:08N are not observed in any sample.

Global Distribution

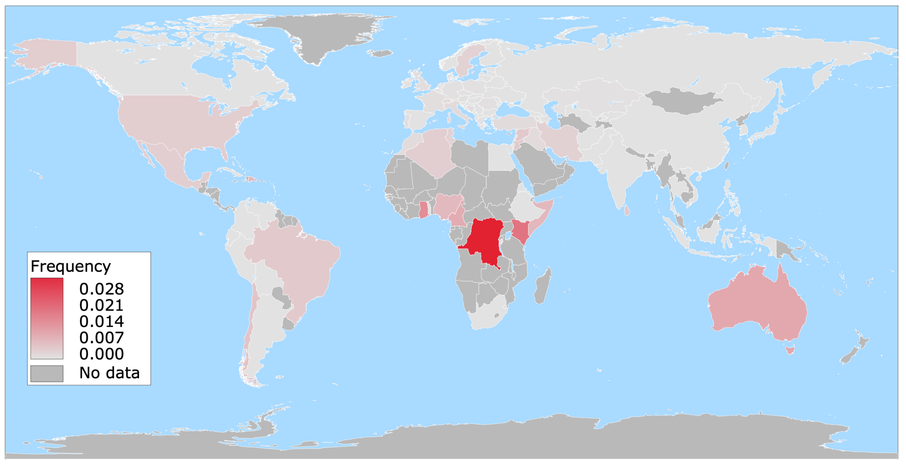
- HLA-E*01:01



- HLA-E*01:03



- HLA-E*01:05



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