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Report from the Killer-cell Immunoglobulin-like Receptors (KIR) component of the 17th International HLA and Immunogenetics Workshop

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Abstract

The goals of the *KIR* component of the 17th International HLA and Immunogenetics Workshop (IHIW) were to encourage and educate researchers to begin analyzing *KIR* at allelic resolution, and to survey the nature and extent of *KIR* allelic diversity across human populations. To represent worldwide diversity, we analyzed 1269 individuals from ten populations, focusing on the most polymorphic *KIR* genes, which express receptors having three immunoglobulin (Ig)-like domains (*KIR3DL1/S1, KIR3DL2* and *KIR3DL3*). We identified 13 novel alleles of *KIR3DL1/S1*, 13 of *KIR3DL2* and 18 of *KIR3DL3*. Previously identified alleles, corresponding to 33 alleles of *KIR3DL1/S1*, 38 of *KIR3DL2*, and 43 of *KIR3DL3,* represented over 90% of the observed allele frequencies for these genes. In total we observed 37 KIR3DL1/S1 allotypes, 40 for KIR3DL2 and 44 for KIR3DL3. As KIR allotype diversity can affect NK cell function, this demonstrates potential for high functional diversity worldwide. Allelic variation further diversifies *KIR* haplotypes. We determined *KIR3DL3~KIR3DL1/S1~KIR3DL2* haplotypes from five of the studied populations, and observed multiple population-specific haplotypes in each. This included 234 distinct haplotypes in European Americans, 191 in Ugandans, 35 in Papuans, 95 in Egyptians and 86 in Spanish populations. For another 35 populations, encompassing 642,105 individuals we focused on *KIR3DL2* and identified another 375 novel alleles, with approximately half of them observed in more than one individual. The *KIR* allelic level data gathered from this project represents the most comprehensive summary of global *KIR* allelic diversity to date, and continued analysis will improve understanding of *KIR* allelic polymorphism in global populations. Further, the wealth of new data gathered in the course of this workshop component highlights the value of collaborative, community-based efforts in immunogenetics research, exemplified by the IHIW.

Keywords

KIR3DL1/S1; KIR3DL2; KIR3DL3

Introduction

The *Killer-cell Immunoglobulin-like Receptor* (*KIR*) region is located on human chromosome 19q13.4 [1–4]. KIR molecules are primarily expressed on natural killer (NK) cells [5] and a small percentage of T-cells [6]. KIR interact with specific amino acid motifs expressed by some human leukocyte antigen (HLA) class I molecules [5], and function to modulate the cytolysis of infected and/or otherwise altered cells, such as neoplastic cells. The *KIR* gene complex is characterized by structural variation that creates multiple gene-content haplotypes. In addition, each of the *KIR* genes exhibits allelic variability [7], which generates considerable intra- and inter-population diversity [8]. This diversity can influence immune responses against pathogens, which has the potential to alter the fitness of individuals [9, 10]. Specific combinations of KIR with their cognate HLA ligands are associated with autoimmunity [3, 11, 12], infectious diseases [13, 14], cancer [15, 16], pregnancy outcomes [17, 18], are crucial in determining clinical outcomes of hematopoietic stem cell transplantation (HCT), and solid organ transplants [19–22].

The allelefrequencies.net database (AFND) has collected *KIR* datasets from 245 populations across the globe [23]. A similar resource was recently developed called the KIR and Disease Database (KDDB), which gathered KIR associations from 204 published articles, and indicates a growing interest in *KIR* in epidemiological studies. These associations consisted of 32 autoimmune diseases, 19 infectious diseases, 16 cancer, eight chronic inflammatory diseases, three related to pregnancy, and one psychiatric disease. [24]. The complex polymorphism observed in this gene family, when combined with the high sequence similarity among *KIR* genes [25, 26], imposes technical difficulties for sequencing and genotyping to full allelic resolution. Thus, despite the fact that *KIR* gene content polymorphism has been extensively studied, *KIR* allelic diversity has been characterized in only a handful of well-defined populations [27–32].

KIR gene content variation was examined during previous International HLA and Immunogenetics Workshop (IHIW) studies. In the 15th and 16th IHIW, the *KIR* anthropology component (Population Global Distribution of KIR and Ligand) aimed to accumulate and examine the *KIR* and *HLA* frequencies in individuals recruited from distinct populations worldwide [33, 34], in order to replicate the earlier findings of coevolution of *KIR* and *HLA* [30, 33, 35, 36]. The preliminary studies conducted by Hiby et al. (2004) while investigating the role of maternal KIR and fetal HLA-C in preeclampsia, first raised the question whether KIR and HLA class I coevolution is related to reproductive fitness [17]. Single et al. (2007) demonstrated evidence of *KIR-HLA* coevolution, by showing a negative correlation of the frequency of *KIR3DS1* with *HLA-Bw4* [35], followed by several other studies corroborating the coevolution of *KIR* with *HLA* [30, 33, 36]. Further evidence of *KIR-HLA* coevolution was demonstrated in the 16th IHIW, in which 105 populations were examined and a strong positive correlation of KIR2DL3 and its ligand HLA-C1 was observed [34].

The goal of the 17th IHIW *KIR* component was to collect *KIR* allelic data to characterize the nature and extent of allelic diversity across human populations using primarily next generation sequencing (NGS) technology. As NGS for *KIR* has not yet been implemented in

several laboratories that study *KIR*, Sanger sequencing was also welcomed [30, 37]. All the participants performing *KIR* genotyping were required to validate their method by genotyping a control panel, however, the reference laboratories performed most genotyping. Many investigators participated in the *KIR* component by providing DNA specimens sequenced by one of the reference laboratories. Here, we present a summary of the *KIR* component of the 17th IHIW working group meeting, and the *KIR* allelic data generated from the 45 worldwide populations that were analyzed. Our preliminary analysis focused on the *KIR* genes that encode three Ig domain receptors because they have been most extensively characterized to the allelic level and their diversity has been shaped by natural selection [38].

Materials and methods

Participants from eleven laboratories submitted *KIR* allelic genotyping data from a total of 45 populations. Five populations were analyzed through the entire coding sequence for *KIR3DL1/S1*, *KIR3DL2* and *KIR3DL3* polymorphism, four for *KIR3DL2* and one for *KIR3DL1/S1*. Exons 4 and 5 from *KIR3DL2* were analyzed in the remaining 35 populations. The participants either used NGS platforms or Sanger sequencing to generate *KIR* allelic data locally, or contributed DNA samples to be sequenced at the workshop reference laboratory at Stanford University. The list of all populations, including sample size, *KIR* genes, sequencing method, sample contributor and the location where sequencing was performed is given in Table 1. Additionally, Single molecule real-time (SMRT) *KIR* gene sequencing was performed for 19 IHIW cell lines from populations including European, black southern African, Warao Amerindian and Chinese.

NGS genotyping of *KIR* genes containing three Ig-like domains

To determine the sequences of *KIR* genes containing three Ig-like domains, a previously described capture/enrichment method, followed by NGS [39] was applied. DNA isolated from healthy unrelated blood donors from the following populations was used: Ugandan (n = 174); Egyptian (n = 136); European American (USA) (n = 376); Papuan (n = 185); and Spanish (n = 153). The Ugandan, Egyptian and Spanish populations have been previously examined for *KIR* gene content [40–42]. Similarly, the European American sample was described in a recent *HLA* study [43]. The Papuan sample consists of individuals from both the highland and lowland regions, as described [44].

Sanger sequencing for genotyping *KIR3DL1/S1* and *KIR3DL2*

KIR3DL2 was genotyped using sequence-based typing in samples from Brazil, which included Euro-descendants from Curitiba (n = 42), non-mixed Brazilians with Japanese ancestry (n = 22) and Amerindians from the Kaingang (n = 30) and Guarani (n = 49) populations. The Brazilian populations have been previously described for *KIR* gene-content [45–47]. Exons 3, 4, 5, 7–9 were amplified with gene-specific primers and the products were sequenced with Big Dye terminator kit (Applied Biosystems) according to the manufacturer's instructions. Specific PCR-SSP primers were designed to resolve two common ambiguities; where it was otherwise not possible to distinguish the genotype *KIR3DL2*002+*010* from *KIR3DL2*010+*015,* and the genotype *KIR3DL2*001+*007*

from *KIR3DL2*006+*010*. Primer sequences are available upon request. *KIR3DL1/S1* was genotyped using sequence-based typing as reported earlier [30] in unrelated healthy Mexican Mestizos (n = 59). The Mexican Mestizos population *KIR* gene-content variation was examined in an earlier report [37].

Large scale *KIR3DL2* sequencing

Sequence data for exons 4 and 5 of *KIR3DL2* was generated from a total of 642,105 individuals from 35 populations (Table 1). PCR amplicons were generated from these exons individually, and then sequenced using Illumina paired-end technology (HiSeq or MiSeq). Alleles were called using the neXtype algorithm [48] and IPD-KIR library version 2.7.0 (Release, 14th July 2017) as the reference [7].

SMRT *KIR* gene sequencing for IHIW cell lines

In addition to the populations described above, *KIR* allele sequences were also generated for a small panel of IHIW cell lines. Briefly, samples underwent PCR targeting individual *KIR* genes to amplify full-length alleles (5′ UTR to 3′ UTR). Amplicons of the same locus were pooled together and sequenced on Pacific Biosciences' RSII platform using a movie time of six hours to obtain maximum read depth. A combination of Pacific Biosciences' SMRTAnalysis and Anthony Nolan's AlleleTeaSet software (Anthony Nolan Research Institute, London, UK) were used to demultiplex and analyze the sequences. For the purposes of this study, the coding domain sequences were extracted from the phased, full-length sequence for further analysis.

Data analysis

All data analysis including allele counts, and frequency estimations were performed in the R environment for statistical computing and visualization [49]. The haplotype analysis was carried out using the R 'haplo.stats' package [50].

The *KIR* Component Meeting

The *KIR* component meeting of the 17th IHIW was held during two breakout sessions. Each participant presented the results of the population data submitted by their group. Additionally, updates on the state of *KIR* haplotype reference sequences, *KIR* in Allelefrequencies.net database, *KIR* nomenclature, and the IPD-KIR database were presented. Finally, there was an overview of PING (Pushing Immunogenetics to the Next Generation) software package [39], which is a bioinformatics pipeline for the analysis of next-generation sequencing *KIR* data. A supplementary file describes the schedule of the *KIR* component meeting, titles of the presentation and details of the presenters (Supplementary File S1).

Results

Allelic diversity of KIR3DL1/S1, KIR3DL2 and KIR3DL3

We analyzed *KIR3DL1/S1, KIR3DL2* and *KIR3DL3*, which encode receptors having three Ig domains. These genes have been the most extensively characterized to date, and their

allelic diversity has been shown to be shaped by natural selection [38]. We observed 33 previously identified alleles of *KIR3DL1/S1*, 38 of *KIR3DL2* and 43 of *KIR3DL3*. We also identified 13 novel alleles for *KIR3DL1/S1*, 13 for *KIR3DL2* and 18 for *KIR3DL3* genes. The validation of these novel alleles is underway. Thus, the total numbers of alleles identified in the workshop samples were 46 for *KIR3DL1/S1,* 51 for *KIR3DL2* and 61 for *KIR3DL3* (Table 2), and these encode 37, 40 and 44 distinct KIR allotypes respectively (Table 2). Considering the modest sample sizes analyzed compared with *HLA* (more than 30 million to date [51]), this suggests that there are many more alleles remaining to be discovered and that the extent of *KIR* polymorphism identified in human populations could ultimately equal or exceed the extent of *HLA* polymorphism.

The allele frequencies of KIR receptors having three immunoglobulin (Ig)-like domains namely; *KIR3DL1/S1*, *KIR3DL2*, and *KIR3DL3* as well as the duplication/deletion polymorphism of *KIR3DL1/S1* detected in the 10 populations analyzed are given in Figures 1 and 2, respectively. These frequencies are deposited in the allele frequency net database (AFND) database (http://www.allelefrequencies.net/default.asp). Data were examined at the polypeptide sequence resolution, which is equivalent to the first three digits in the allele name, as described in IPD/KIR Database (https://www.ebi.ac.uk/ipd/kir/). The frequencies range from 0.1% to 48.7% for the various alleles of *KIR3DL1/S1* (Figure 1A), 0.1% to 61.7% for *KIR3DL2* (Figure 1B) and 0.1% to 33% for *KIR3DL3* (Figure 1C) in total across all populations. The number of those alleles classified as rare (those with a frequency of <1% in any given population) was 31 for *KIR3DL1/S1* (67.4%), 38 for *KIR3DL2* (74.5%), and 38 for *KIR3DL3* (62.3%). Thus, both common and rare alleles contributed substantially to the rich worldwide diversity of *KIR*. In addition to allelic variation, deletions and duplications of the entire *KIR3DL1/S1* gene were also observed (Figure 2). The highest frequency of deletions and duplications were observed in the Papuan population (13.5% and 8.4%, respectively). Meanwhile, no deletions and/or duplications were observed for *KIR3DL2* (except for *KIR3DL1/2v*, a fusion gene derived from *KIR3DL1* and *KIR3DL2*) [52].

Haplotypic diversity of KIR3DL1/S1, KIR3DL2 and *KIR3DL3 genes*

Specific *KIR* alleles and haplotypes are associated with better education of NK cells and/or control of specific pathogens [14, 53]. Diversity in *KIR* haplotypes may therefore contribute to improved population survival. To estimate the extent of haplotype diversity we analyzed the five populations that were genotyped for *KIR3DL3, KIR3DL1/S1* and *KIR3DL2;* European American, Ugandan, Papuan, Egyptian and Spanish (Table 2)**.**ld> *KIR3DL3* is located in the segment of the *KIR* region oriented towards the centromere of chromosome 19, and *KIR3DL1/S1* and *KIR3DL2* in the telomere oriented segment [4]. Since, the centromeric and telomeric *KIR* genes are separated by a region that contain a recombination hotspot [54, 55], we analyzed both full and telomeric-only haplotypes. We observed 503 distinct population-specific *KIR3DL3~KIR3DL1/S1~KIR3DL2* haplotypes and 158 distinct population-specific *KIR3DL1/S1~KIR3DL2* haplotypes. Additionally, we found six shared haplotypes, five of which, *3DL1*001~3DL2*001, 3DL1*005~3DL2*010, 3DS1*013~3DL2*007, 3DL1*015~3DL2*002*, and *3DL3*003~3DS1*013~3DL2*007*

were present in all five populations (Table 3), and one (*3DL3*002~3DS1*013~3DL2*007)* was present in all except the Egyptian population (Table 3).

Our analysis of allelic variation in *KIR3DL3~KIR3DL1/S1~KIR3DL2* haplotypes revealed 234 distinct haplotypes in European Americans, 191 in Ugandans, 35 in Papua New Guineans, 95 in Egyptians, and 86 in the Spanish population (Table 2). The top ten most frequent *KIR3DL3~KIR3DL1/S1~KIR3DL2* haplotypes are listed in Table 2. Limiting to *KIR3DL1/S1~KIR3DL2* haplotypes, we identified 66 distinct haplotypes in European Americans, 81 in Ugandans, 16 in Papuans, 40 in Egyptians, and 24 in the Spanish population (Table 4). The top 10 most frequent *KIR3DL1/S1~KIR3DL2* haplotypes in each population are listed in Table 4.

KIR3DL2 single nucleotide variations in exons 4 and 5

To achieve a high-depth analysis in an extremely large sample size, we focused on exons 4 and 5 from *KIR3DL2*, which encode for the extracellular D1 and D2 domains of the KIR3DL2 molecule, which are most likely to contact the HLA ligand directly [56]. We targeted 642,105 individuals from 35 populations and examined single nucleotide variations. We observed SNP variation in 78.5% (467 of 595) of all nucleotides that comprise these two exons. Among the observed single nucleotide substitutions, 67.4% (315 of 467) are nonsynonymous, and the reminders encode for either synonymous (31.3%) or premature stop codons (1.3%) (Table 5). Almost half of these nucleotide variations were observed in more than one individual, and the remainder in a single individual each (singletons). As expected, the number of these singletons increases with sample size (Supplementary Figure S1). Out of 375 *KIR3DL2* allelic variants identified in this study, 275 were population-specific and 221 were found in the German population, which is the population with the largest sample size.

KIR diversity in IHIW cell lines

Data from a total of 19 IHIW cell lines from populations including European, black southern African, Warao Amerindian and Chinese were submitted for analysis. Different subsets of genes were investigated for each sample, resulting in the definition of 105 allele types in total, including 45 distinct alleles. The use of long read sequencing allowed the resolution of previous phase ambiguity over the large intron 5/6 (>5 Kbp) in *KIR3DL3*. In addition, novel *KIR3DL3* and *KIR2DL1* alleles were characterized in the cell lines AKIBA and SPO010, respectively, correcting previous allele typing [57]. Further characterization of a broader panel of IHIW cell lines using SMRT DNA sequencing is ongoing, helping to maintain the functionality of this valuable resource.

Future directions

The 17th IHIW *KIR* component has effectively applied the IHIW paradigm as a model for studying global *KIR* allelic diversity. Collaboration and multi-centric efforts were essential both to encourage the adoption of high-resolution *KIR* genotyping, and to generate *KIR* allelic data in an unprecedented scale from diverse ancestries. These data will be the basis of a more thorough examination of the *KIR* diversity in order to improve our understanding of KIR in human health and disease, as well as to provide a resource for immunogenetic

databases for future research. The *KIR* allelic data gathered in this project represents the most comprehensive summary of global *KIR3DL1/S1, KIR3DL3* and *KIR3DL2* allelic diversity to date and provides an increased understanding of *KIR* allelic polymorphism and *KIR* evolution. The intention of the organizers is to continue this work during the 18th IHIW that will be held in Amsterdam in 2021, with the hope that more laboratories will adopt *KIR* allelic genotyping approaches and that a greater number of populations will be analyzed for all *KIR* genes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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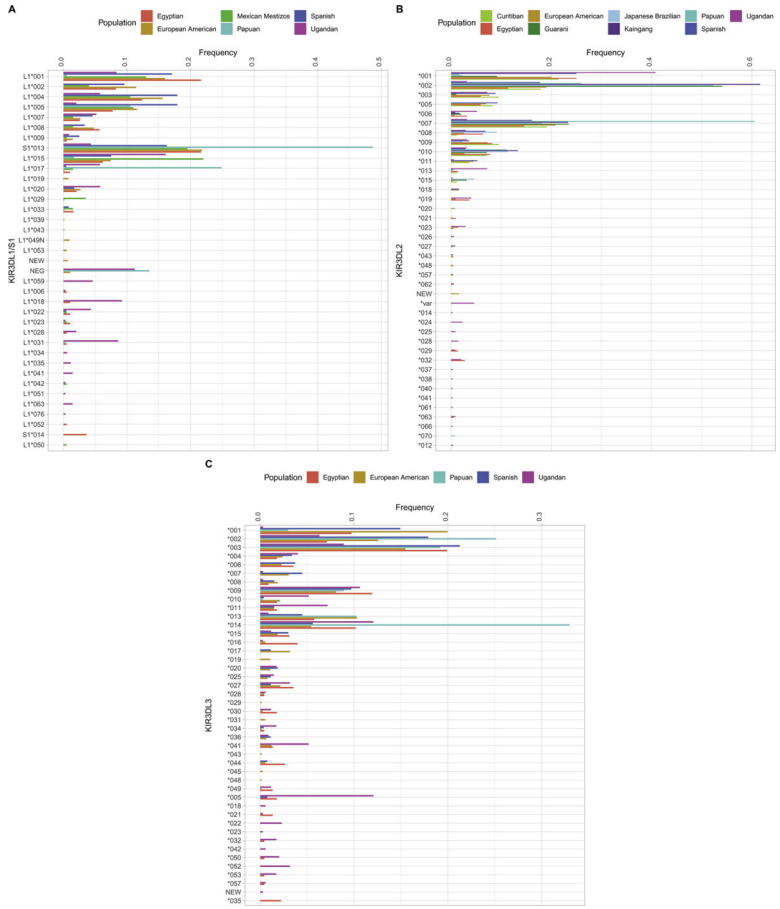

Figure 1: Allele frequency distribution in workshop populations for KIR receptors having three immunoglobulin (Ig)-like domains.

Figure 1A: *KIR3DL1/S1* allele frequency distribution in workshop populations. Figure 1B: *KIR3DL2* allele frequency distribution in workshop populations. Figure 1C: *KIR3DL3* allele frequency distribution in workshop populations.

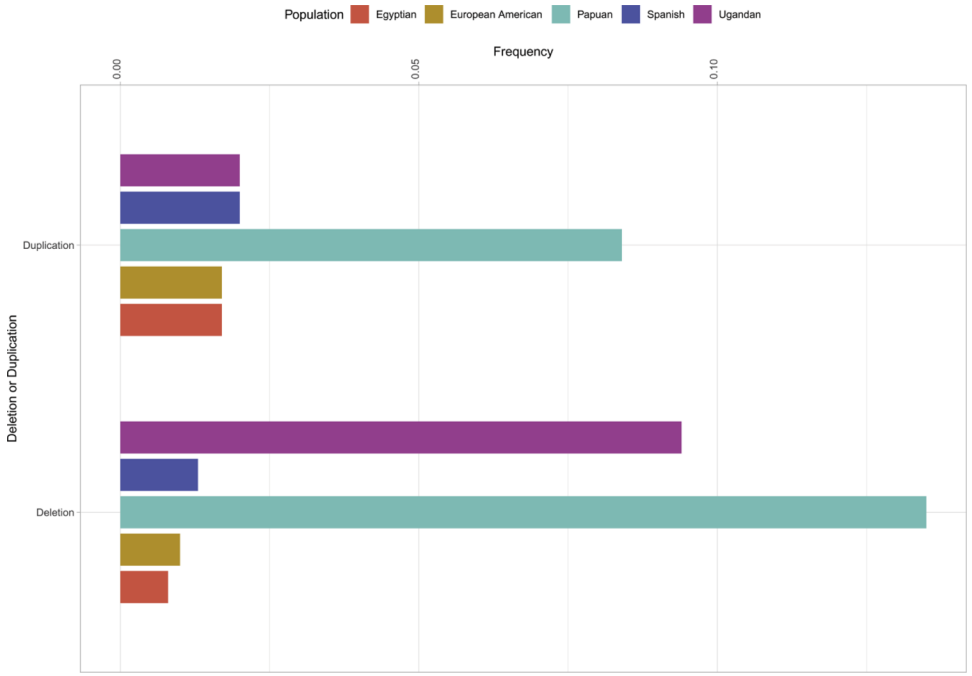

Figure 2:
KIR3DL1/S1 structural variations in workshop populations.

Table 1:

Details of *KIR* allele-level sequencing of workshop populations, including sample size, *KIR* genes, *KIR* typing method, sample contributor and sequencing location

Population	N	Genes	Method	Sample contributor	$Sequencing
Uganda	174	*KIR3DL1/S1, KIR3DL2* and *KIR3DL3*	NGS	Traherne/Moffett	Local
Egypt	136	*KIR3DL1/S1, KIR3DL2* and *KIR3DL3*	NGS	Elfishawi	Stanford
European American	378	*KIR3DL1/S1, KIR3DL2* and *KIR3DL3*	NGS	Hollenbach/Oksenberg	Stanford
Papua New Guinea	185	*KIR3DL1/S1, KIR3DL2* and *KIR3DL3*	NGS	Mentzer/Oppenheimer	Stanford
Spain	153	*KIR3DL1/S1, KIR3DL2* and *KIR3DL3*	NGS	GETHIT#	Stanford
Curitiba	42	KIR3DL2	Sanger	Augusto/Petzl-Erler	Local
Kaingang	30	KIR3DL2	Sanger	Augusto/Petzl-Erler	Local
Guarani	49	KIR3DL2	Sanger	Augusto/Petzl-Erler	Local
Japanese-Brazilian	22	KIR3DL2	Sanger	Augusto/Petzl-Erler	Local
Mexican Mestizos	100	KIR3DL1S1	Sanger	Gorodezky	Local
Germany	564253	KIR3DL2 exons 4 and 5	NGS	DKMS	Local
Poland	6509	KIR3DL2 exons 4 and 5	NGS	DKMS	Local
Kosovo	649	KIR3DL2 exons 4 and 5	NGS	DKMS	Local
Serbia	857	KIR3DL2 exons 4 and 5	NGS	DKMS	Local
Croatia	1947	KIR3DL2 exons 4 and 5	NGS	DKMS	Local
Brazil	381	KIR3DL2 exons 4 and 5	NGS	DKMS	Local
Syria	554	KIR3DL2 exons 4 and 5	NGS	DKMS	Local
Bosnia-Herzegovina	992	KIR3DL2 exons 4 and 5	NGS	DKMS	Local
Sri Lanka	1809	KIR3DL2 exons 4 and 5	NGS	DKMS	Local
Austria	1374	KIR3DL2 exons 4 and 5	NGS	DKMS	Local
Czech Republic	620	KIR3DL2 exons 4 and 5	NGS	DKMS	Local
Kazakhstan	1701	KIR3DL2 exons 4 and 5	NGS	DKMS	Local
Spain	1053	KIR3DL2 exons 4 and 5	NGS	DKMS	Local
France	865	KIR3DL2 exons 4 and 5	NGS	DKMS	Local
India	393	KIR3DL2 exons 4 and 5	NGS	DKMS	Local
USA	903	KIR3DL2 exons 4 and 5	NGS	DKMS	Local
Vietnam	546	KIR3DL2 exons 4 and 5	NGS	DKMS	Local
Greece	2695	KIR3DL2 exons 4 and 5	NGS	DKMS	Local
Hungary	833	KIR3DL2 exons 4 and 5	NGS	DKMS	Local
Romania	1425	KIR3DL2 exons 4 and 5	NGS	DKMS	Local
Afghanistan	541	KIR3DL2 exons 4 and 5	NGS	DKMS	Local
Great Britain	755	KIR3DL2 exons 4 and 5	NGS	DKMS	Local
Burundi	398	KIR3DL2 exons 4 and 5	NGS	DKMS	Local
Albania	469	KIR3DL2 exons 4 and 5	NGS	DKMS	Local
Lebanon	437	KIR3DL2 exons 4 and 5	NGS	DKMS	Local

Population	N	Genes	Method	Sample contributor	$Sequencing
Other	8326	KIR3DL2 exons 4 and 5	NGS	DKMS	Local
Russia	5288	KIR3DL2 exons 4 and 5	NGS	DKMS	Local
Switzerland	405	KIR3DL2 exons 4 and 5	NGS	DKMS	Local
Portugal	1450	KIR3DL2 exons 4 and 5	NGS	DKMS	Local
Turkey	26119	KIR3DL2 exons 4 and 5	NGS	DKMS	Local
Netherlands	981	KIR3DL2 exons 4 and 5	NGS	DKMS	Local
Iran	1059	KIR3DL2 exons 4 and 5	NGS	DKMS	Local
Italy	4416	KIR3DL2 exons 4 and 5	NGS	DKMS	Local
Morocco	449	KIR3DL2 exons 4 and 5	NGS	DKMS	Local
Ukraine	653	KIR3DL2 exons 4 and 5	NGS	DKMS	Local

#**GETHIT** means for Spanish Working Group in Histocompatibility and Transplant Immunology study;

$**Local sequencing** means *KIR* genotyping was performed by the participant's lab either using a NGS exome capture method [38] for *KIR* genes containing three Ig receptors (Traherne/Moffett lab) or Sanger sequencing for *KIR3DL1S1* (Gorodezky lab) and *KIR3DL2* (Augusto/Petzl-Erler) or an in-house developed NGS short amplicon approach for *KIR3DL2* (DKMS lab). For **Stanford Sequencing**,*KIR* genotyping was performed at Stanford using a NGS exome capture method [38].

Table 2:

Allelic variations of one centromeric (*KIR3DL3)* and two telomeric (*KIR3DL1/S1* and *KIR3DL2)* genes diversifies *KIR* haplotypes in European American, Ugandan, Papuan, Egyptian and Spanish populations

	Centromeric	Telomeric		
Population	***KIR3DL3***	***KIR3DL1/S1***	***KIR3DL2***	**Frequency**
European American[¥] (Total observed 234)	**003*	*S1*013*	**007*	0.051
	**001*	*S1*013*	**007*	0.043
	**001*	*L1*004*	**005*	0.035
	**001*	*L1*002*	**002*	0.028
	**002*	*L1*001*	**001*	0.028
	**002*	*L1*005*	**001*	0.027
	**003*	*L1*002*	**002*	0.026
	**013*	*L1*001*	**001*	0.020
	**013*	*S1*013*	**007*	0.020
	**001*	*L1*001*	**001*	0.018
Ugandan[¥] (Total observed 191)	**005*	*L1*001*	**001*	0.049
	**002*	*L1*015*	**001*	0.031
	**014*	*L1*031*	**001*	0.028
	**010*	*L1*017*	**023*	0.026
	**014*	*L1*018*	**001*	0.023
	**011*	*L1*018*	**001*	0.020
	**022*	*NEG*	**006*	0.020
	**009*	*L1*022*	**001*	0.019
	**004*	*L1*059*[a]	-	0.017
	**003*	*L1*007*	**008*	0.017
Papuan[¥] (Total observed 35)	**002*	*S1*013*	**007*	0.165
	**014*	*S1*013*	**007*	0.142
	**014*	*NEG*	**007*	0.100
	**003*	*S1*013*	**007*	0.100
	**014*	*L1*017*	**002*	0.075
	**002*	*L1*017*	**002*	0.066
	**003*	*L1*017*	**002*	0.060
	**009*	*S1*013*	**007*	0.051
	**013*	*L1*005*	**010*	0.047
	**013*	*L1*017*	**002*	0.028
Egyptian[¥] (Total observed 95)	**003*	*L1*001*	**001*	0.045
	**009*	*L1*001*	**001*	0.034
	**003*	*S1*013*	**007*	0.034
	**003*	*L1*002*	**002*	0.027

	Centromeric	Telomeric		
Population	***KIR3DL3***	***KIR3DL1/S1***	***KIR3DL2***	**Frequency**
	**003*	*L1*007*	**008*	0.027
	**001*	*L1*020*	**009*	0.027
	**014*	*S1*013*	**007*	0.027
	**013*	*L1*001*	**001*	0.020
	**027*	*L1*001*	**001*	0.020
	**015*	*L1*002*	**002*	0.020
Spanish[¥](Total observed 86)	**003*	*L1*002*	**002*	0.055
	**002*	*L1*005*	**001*	0.050
	**001*	*L1*001*	**001*	0.047
	**001*	*L1*004*	**005*	0.047
	**003*	*S1*013*	**007*	0.046
	**009*	*S1*013*	**007*	0.040
	**002*	*S1*013*	**007*	0.040
	**002*	*L1*004*	**003*	0.035
	**002*	*L1*001*	**001*	0.031
	**001*	*L1*015*	**002*	0.026
[#]Total Alleles	61	46	51	
[$]Total Allotypes	44	37	40	

[¥]The number of distinct haplotypes identified by analyzing one centromeric (*KIR3DL3)* and two telomeric (*KIR3DL1/S1* and *KIR3DL2)* genes;

[#]Number of distinct alleles (including novel alleles);

[$]Number of distinct allotypes (including novel allotypes);

[a]*L1*059* is an allele of *KIR3DL1/2v*, a fusion gene derived from *KIR3DL1* and *KIR3DL2*.

Table 3:

A summary of six haplotypes shared across five populations analyzed

A. Haplotypes of *KIR3DL3, KIR3DL1/S1* and *KIR3DL2*							
Centromeric	**Telomeric**		**Haplotype Frequency**				
KIR3DL3	***KIR3DL1/S1***	***KIR3DL2***	**European American**	**Spanish**	**Egyptian**	**Ugandan**	**Papuan**
**003*	*S1*013*	**007*	0.051	0.046	0.034	0.003	0.100
**002*	*S1*013*	**007*	0.016	0.040	-	0.003	0.165
B. Haplotypes of *KIR3DL1/S1* and *KIR3DL2*							
Telomeric			**Haplotype Frequency**				
KIR3DL1/S1	***KIR3DL2***		**European American**	**Spanish**	**Egyptian**	**Ugandan**	**Papuan**
*L1*001*	**001*		0.115	0.124	0.174	0.072	0.005
*L1*005*	**010*		0.017	0.019	0.050	0.011	0.100
*S1*013*	**007*		0.189	0.138	0.116	0.020	0.481
*L1*015*	**002*		0.071	0.071	0.012	0.011	0.014

Table 4:

The 10 most frequent *KIR3DL1/S1* and *KIR3DL2* haplotypes in European American, Ugandan, Papuan, Egyptian and Spanish populations

	Telomeric		
Population	***KIR3DL1/S1***	***KIR3DL2***	**Frequency**
European American[¥] (Total observed 66)	*S1*013*	**007*	0.189
	*L1*001*	**001*	0.115
	*L1*002*	**002*	0.112
	*L1*005*	**001*	0.079
	*L1*015*	**002*	0.071
	*L1*004*	**003*	0.071
	*L1*004*	**005*	0.063
	*L1*008*	**009*	0.040
	*L1*001*	**011*	0.028
	*L1*020*	**009*	0.027
Ugandan[¥] (Total observed 81)	*L1*015*	**001*	0.092
	*L1*031*	**001*	0.077
	*L1*001*	**001*	0.072
	*L1*004*	**003*	0.052
	*L1*059*[a]	-	0.046
	*L1*018*	**001*	0.041
	L1 NEG	**019*	0.040
	*L1*022*	**001*	0.036
	*L1*015*	**013*	0.033
	L1 NEG	**006*	0.032
Papuan[¥] (Total observed 16)	*S1*013*	**007*	0.481
	*L1*017*	**002*	0.243
	L1 NEG	**007*	0.124
	*L1*005*	**010*	0.100
	*L1*015*	**002*	0.014
	*L1*001*	**001*	0.005
	*L1*005*	**001*	0.005
	*S1*013*	**010*	0.005
	L1 NEG	**010*	0.005
	L1 NEG	**070*	0.005
Egyptian[¥] (Total observed 40)	*L1*001*	**001*	0.174
	*S1*013*	**007*	0.116
	*L1*002*	**002*	0.093
	*L1*004*	**005*	0.070

	Telomeric		
Population	***KIR3DL1/S1***	***KIR3DL2***	**Frequency**
	*L1*004*	**003*	0.052
	*L1*005*	**010*	0.050
	*L1*008*	**009*	0.047
	*S1*013*	**006*	0.041
	*L1*014*	**032*	0.035
	*L1*005*	**001*	0.031
Spanish[¥](Total observed 24)	*L1*005*	**001*	0.138
	*S1*013*	**007*	0.138
	*L1*001*	**001*	0.124
	*L1*002*	**002*	0.100
	*L1*004*	**005*	0.100
	*L1*004*	**003*	0.095
	*L1*015*	**002*	0.071
	*L1*007*	**008*	0.048
	*L1*001*	**011*	0.038
	*L1*009*	**011*	0.024

[¥]The number of distinct haplotypes identified by analyzing two telomeric genes (*KIR3DL1/S1* and *KIR3DL2)*;

[a]*L1*059* is an allele of *KIR3DL1/2v*, a fusion gene derived from *KIR3DL1* and *KIR3DL2*.

Table 5:

KIR3DL2 variation in exons 4 and 5 (D1 and D2 domains) among 642,105 individuals from 35 populations

***KIR3DL2* variation**	**Count**
Allelic variation	
1 nucleotide change	288
2 nucleotide changes	82
3 nucleotide changes	5
Sum of all allelic variants	**375**
Variant description	
Single nucleotide polymorphism	**467**
Synonymous substitutions	146
Non-synonymous substitutions	315
Premature stop codon	6
Total number of nucleotide sites	**595**
Number of Amino Acid changes	**Codon**
0	23
1	77
2	66
3	24
4	7
5	1
Polypeptide sites	**199**