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Some human *KIR* haplotypes contain two *KIR2DL5* genes: *KIR2DL5A* and *KIR2DL5B*

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Abstract Killer-cell immunoglobulin-like receptors (KIR) comprise a family of structurally diverse proteins encoded by a compact cluster of genes located in human Chromosome 19q13.4. The most recently described member of the KIR family, KIR2DL5, is represented in human populations by at least four gene variants, whose exons differ by two to eight nucleotides. We show here that these structurally similar variants are encoded by alleles of two different loci, *KIR2DL5A* and *KIR2DL5B*, which map to different regions of the *KIR*-gene cluster. Regarding *KIR2DL5*, four groups of *KIR* haplotypes can be distinguished: those having both *KIR2DL5A* and *KIR2DL5B*, those having either *KIR2DL5A* or *KIR2DL5B*, and those lacking *KIR2DL5*. Positive association between *KIR2DL5A* and *KIR2DL5B* was detected but did not reach statistical significance. These results are consistent with a model in which *KIR2DL5A* and *KIR2DL5B* are products of a gene duplication, which through the action of subsequent recombination have became separated on some haplotypes.

Keywords Gene duplication · Haplotypes · *KIR* genes · Natural killer cells · Polymorphism

Introduction

Killer-cell immunoglobulin-like receptors (KIR) regulate the response of human natural killer cells through recognition of HLA class I molecules, whose expression is frequently altered in tumors and cells infected by intracellular pathogens (Algarra et al. 2000; Brodsky et al. 1999; Colonna and Samaridis 1995; Tortorella et al. 2000; Wagtmann et al. 1995). KIR are encoded by a family of approximately 14 genes located in ~150 kb of the leukocyte receptor cluster (chromosome region 19q13.4), which also contains some *KIR* pseudogenes (Martin et al. 2000; Vilches et al. 2000c; Wende et al. 1999;Wilson et al. 2000). During the evolution of primates, *KIR* genes have undergone repeated duplications, followed by rapid diversification of the paralogues (Martin et al. 2000; Vilches and Parham 2002). As a result of multiple duplication and unequal crossing-over events, *KIR*-gene content varies greatly in the genomes of different individuals, the variation affecting both the number and the identity of genes. Certain combinations of *KIR* genes are found more frequently than others, defining multiple *KIR*-gene haplotypes (Norman et al. 2001, 2002; Rajalingam et al. 2002; Shilling et al. 2002; Uhrberg et al. 1997; Witt et al. 1999). The complexity of these haplotypes is further increased by sequence polymorphisms of the individual *KIR* genes that constitute them; as a result, the proportion of individuals expressing identical KIR is very low (Shilling et al. 2002).

KIR2DL5, the most recently described member of the KIR family (Vilches et al. 2000c), exemplifies both forms of variation: its gene is found in approximately 52–79% of individuals in several populations (Norman et al. 2002; Rajalingam et al. 2002; Vilches et al. 2000c), and it is represented by four sequence variants (Vilches et al. 2000a). The exons of the more common variants, *2DL5.1* and *2DL5.2*, have nucleotide sequences differing by 7 substitutions (~0.5%) (Vilches et al. 2000a). *KIR* with nucleotide sequences differing by less than 2% are generally considered alleles of the same locus (Steffens et al. 1998; Vilches and Parham 2002). However, previous analysis of the *KIR2DL5* sequence in several members of one family revealed a possible exception to this rule: one progenitor carrying both *2DL5.1* and *2DL5.2* had passed neither variant to her offspring (Vilches et al. 2000a).

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The latter finding was inconsistent with allelic relationship between *2DL5.1* and *2DL5.2* and pointed to these variants behaving as two different loci in the aforementioned family. However, this conclusion was confused by the presence of other *2DL5* variants in the same family and by the unavailability of some of its members: in particular, ones having inherited the haplotype supposedly bearing both *2DL5.1* and *2DL5.2* (Vilches et al. 2000a). To address the questions raised by these findings, we investigated the inheritance and distribution of *KIR2DL5* variants with the goal of determining their genetic relationship.

Materials and methods

Genomic DNA was obtained from the peripheral blood of voluntary donors using a modified salting-out method (Miller et al. 1988). The donors belonged to 56 families from which both progenitors and one or more siblings were available. Typing of *KIR* genes and *KIR2DL5* variants was performed by PCR-SSP as described elsewhere (Gómez-Lozano and Vilches 2002; Uhrberg et al. 1997; Vilches et al. 2000a, b). Six possibly informative families, according to the *KIR2DL5* types of the progenitors (see results), were selected for further analysis. The *KIR2DL5* variants and the *KIR* genes present in all members of these six families were determined. HLA typing was performed using standard techniques, in order to rule out possible errors in identification of the samples, and to confirm the relationships between the members of these families (not shown).

Phenotypic frequencies (pf) of *2DL5* variants were determined by direct counting. Genotypic (gf) and haplotype (hf) frequencies were calculated with the formula $gf=1-\sqrt{(1-pf)}$. Linkage disequilibrium (Δ) between *2DL5A*001* and *2DL5B*002* was calculated with the expression $\Delta=hf-gf_A \times gf_B$, and the relative linkage disequilibrium was determined with the relation $\Delta_{rel}=\Delta/(gf_B \times (1-gf_A))$.

To determine the phylogenetic relationships among *KIR2DL5* variants of humans and common chimpanzees (*Pan troglodytes*) (Khakoo et al. 2000), a distance tree was constructed by a neighbor-joining method (Saitou and Nei 1987) using the Pileup and PAUPsearch applications of the Wisconsin package (Genetics Computer Group) and represented using TreeView 1.6.5 (by R.D.M. Page, http://taxonomy.zoology.gla.ac.uk/rod/rod.html). Confidence of groupings was estimated by 500 bootstrap replicates (Felsenstein 1985). The exons of the following nucleotide sequences were analyzed (GenBank accession numbers are given in parentheses): *Homo sapiens 2DL5A*001* (AF204903), *2DL5B*002* (AF217486), *2DL5B*003* (AF217487), *2DL5B*004* (AF260138–AF260141); *Pan troglodytes 2DL5.1* (AF258805) and *2DL5.2* (AF274005) (Khakoo et al. 2000; Rajalingam et al. 2001). See footnote 1 for nomenclature of human *KIR2DL5*.

Results

KIR haplotypes can have two, one or no *KIR2DL5* genes

To assess for the existence of *KIR* haplotypes containing two *2DL5* loci and to determine the extent of this trait, we sought families in which one parent had two *2DL5* variants and the other parent had none. To identify such families, we analyzed the distribution of the *2DL5* gene and its four published variants in both parents of 56 families. Six parental couples fulfilled the required characteristics and *2DL5* was subtyped in their children to determine the inheritance of the gene variants (Fig. 1).

Table 1 Distribution of *KIR2DL5* variants in 112 unrelated individuals discloses a positive, non-statistically significant, association between *KIR2DL5A*001* and *KIR2DL5B*002*. (hf=0.0551; $\Delta=0.0250$ ($\chi^2_{yates}=0.014$; n.s.); $\Delta_{rel}=0.1846$)

*2DL5A*001*	*2DL5B*002*	Number	Percent
+	+	12	10.71
+	–	25	22.32
–	+	22	19.64
–	–	53	47.32
gf_{001}= 0.1817	gf_{002}= 0.1655	112	100.00

One or more siblings from each of three families (H29, H90 and H42) inherited two *2DL5* variants from one parent, demonstrating that these two variants correspond to different *2DL5* loci. Moreover, two other siblings of family H29 lacked the *2DL5* gene, further supporting the interpretation that their father had one haplotype carrying two copies of the *2DL5* gene and one haplotype lacking *2DL5*. The two *KIR2DL5* loci have been assigned the designations *KIR2DL5A* and *KIR2DL5B* by the Gene Nomenclature Committee of the Human Genome Organization (http://www.gene.ucl.ac.uk/nomenclature/genefamily/kir.html)[1]. Accordingly, the *2DL5.1* variant will be named henceforth *2DL5A*001* and the *2DL5.2* variant, *2DL5B*002*, following nomenclature guidelines suggested previously (Gardiner et al. 2001).

All *KIR* genes that appear to be present in the haplotypes containing both *2DL5A*001* and *2DL5B*002* (see below) were found also in haplotypes EM46-*b* and EM6-*b*, which might also contain both *2DL5* loci. However, this possibility could not be verified, since those haplotypes were not transmitted to the progeny. By contrast, haplotypes containing either *2DL5A*001* or *2DL5B*002*, but not both, were inherited by siblings 4 and 5 of family H42 and all available descendants of families EM46, EM6 and H182. These results demonstrate that *2DL5A*001* and *2DL5B*002* are not invariably linked in *KIR* haplotypes, but are also found separate of each other.

The two *KIR2DL5* loci are only weakly associated

The results from *KIR2DL5* subtyping of the parents in 56 families provided assessment of the distribution of the *2DL5* gene and its variants in 112 unrelated individuals (Table 1). Fifty-nine individuals (52.68%) had a *2DL5* gene, a frequency similar to those found in other

[1] The HGNC also establishes *KIR3DL3* for the gene represented by sequences *KIRCI*, *KIR44* and *KIR3DL7*, whereas *KIR2DP1* refers to the pseudogene previously known as *KIR15*, *KIRZ* or *KIRY*, and the term *KIR3DP1*, to the gene fragment previously known as *KIR48*, *KIRX* or *KIR2DS6* (Andre et al. 2001; Barten et al. 2001; Martin et al. 2000; Torkar et al. 1998; Vilches and Parham 2002; Vilches et al. 2000c; Wilson et al. 2000). *3DP1-ex2+* and *3DP1-ex2–* are unofficial names for two structural forms of the *KIR3DP1* pseudogene, containing or lacking, respectively, exon 2 and its flanking introns (Gómez-Lozano and Vilches 2002).

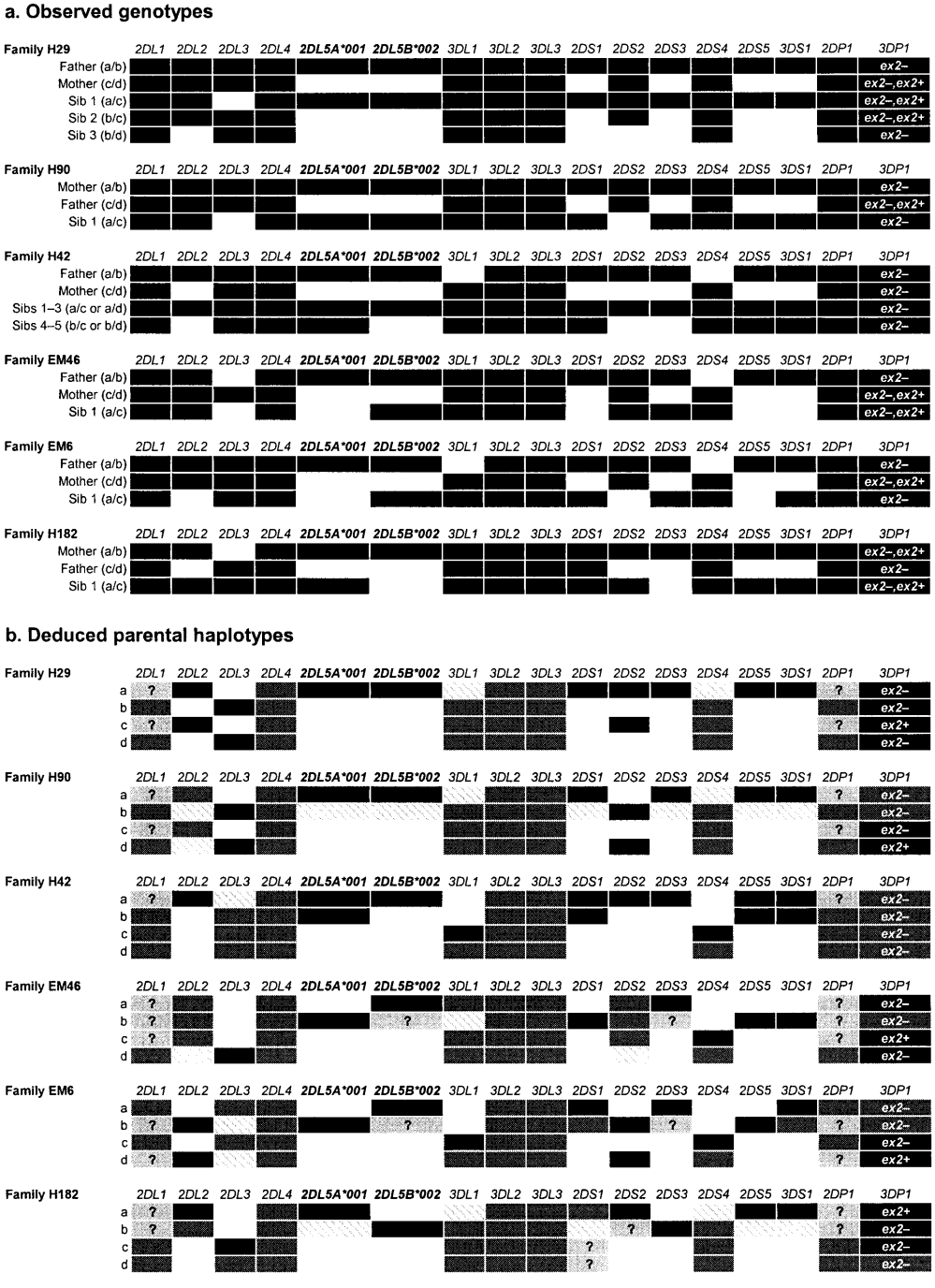

Fig. 1 *KIR* haplotypes contain 0–2 copies of the *KIR2DL5* gene. **a** *KIR* genotypes of all available members of six informative families in which one parent has two *KIR2DL5* variants and the other parent has none. **b** Deduced parental *KIR*-gene haplotypes. Confirmed presence or absence of a gene in a haplotype, as demonstrated by family segregation, are represented by *filled* and *blank* boxes, respectively. In addition, variable intensities of shading denote different degrees of uncertainty: *dark gray* indicates the probable presence of a gene as inferred from both family analysis and previous knowledge of the genetic relationships between *KIR* genes (e.g., positive or negative associations between *KIR* genes or operational allelisms, such as those of *3DL1* and *3DS1*, or *2DL2* and *2DL3*; Crum et al. 2000; Norman et al. 2001, 2002; Shilling et al. 2002; Toneva et al. 2001; Uhrberg et al. 1997; Witt et al. 1999); *oblique stripes in a white box*, probable absence of the gene; *light gray and a question mark*, genes whose presence in a haplotype is uncertain. See footnote 1 for nomenclature of recently described genes and pseudogenes

studies (Vilches et al. 2000c). Variants *2DL5A*001* and *2DL5B*002* were detected in 37 (33.04%) and 34 individuals (30.36%), respectively, whereas no examples of *2DL5B*003* or *2DL5B*004* were identified. Therefore, a possible consequence of the duplication of the *2DL5* gene, the existence of individuals having more than two *2DL5* variants, was not observed in this study.

*2DL5A*001* and *2DL5B*002* were found together in 12 out of the 112 donors (10.71%, Table 1). A positive, yet non-statistically significant, linkage disequilibrium value was deduced from this frequency (relative linkage disequilibrium: 18.46%). This positive value is consistent with *2DL5A*001* and *2DL5B*002* being encoded at two different loci, since a negative linkage disequilibrium would be expected should these variants be alleles of the same locus.

Variability of haplotypes containing or lacking the *KIR2DL5* gene

We determined the *KIR* genes present in the genome of each member of the six informative families (Fig. 1a). The segregation of these genes was then analyzed to deduce the haplotypes in which they had been inherited

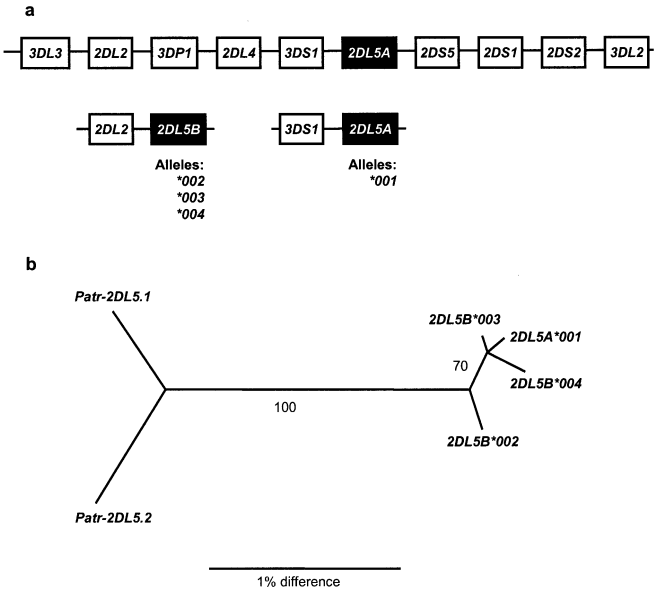

Fig. 2 **a** Location of *KIR2DL5A* and *KIR2DL5B* in the *KIR*-gene cluster. The relative positions of the *KIR2DL5A* and *KIR2DL5B* loci, as assessed by physical linkage analysis (Vilches et al. 2000a), are shown with respect to a completely sequenced *KIR*-gene haplotype that contains just one of the *KIR2DL5* genes (Wilson et al. 2000). **b** The duplication and diversification of the human *KIR2DL5* gene postdates the divergence of humans and chimpanzees. A distance tree, built using a neighbor-joining method, depicts the phylogenetic relationships among *KIR2DL5* variants of humans and common chimpanzees (*Pan troglodytes*). Confidence of groupings was estimated by 500 bootstrap replicates; only clusters observed in 70% or more replicates are represented (bootstrap values shown beside each branch)

(Fig. 1b). The genes encoding 2DL1, 2DL4, 3DL2 and 3DL3, and the *2DP1* pseudogene were found in all individuals; therefore their inheritance could not be ascertained.

In addition, the inheritance of some genes could not always be demonstrated directly due to the distribution of those genes in certain families. In those cases, the genes were either left unassigned or were assigned to particular haplotypes based on previous knowledge of the genetic relationships between *KIR* genes (see legend to Fig. 1). A color code was used to denote the different degrees of certainty in each gene assignment.

The three haplotypes carrying both *2DL5A*001* and *2DL5B*002* (*a*-haplotypes of families H29, H90, H42) were characterized by having *2DL2*, *2DS1*, *2DS3*, *2DS5*, *3DS1* and *3DP1-ex2–*; and by lacking *2DL3*, *2DS4* and *3DL1*. They differed in the presence of *2DS2*, identified in only two of the three haplotypes. Similar or identical haplotypes were deduced in two other families (EM6-*b* and EM46-*b*), and they could also bear a duplicated *2DL5* gene but, as previously mentioned, this could not be demonstrated since those haplotypes were not inherited by any of the offspring studied.

Two haplotypes containing *2DL5A*001*, but not *2DL5B*002*, were identified (H42-*b* and H182-*a*). These haplotypes had *3DS1*, *2DS1* and *2DS5*, lacked *2DS4* and *3DL1*, and differed in the presence or absence of the *2DL2*, *2DL3*, *2DS2* and *2DS3* genes and in their *3DP1* alleles. Conversely, *2DL5B*002* appeared without *2DL5A*001* in two haplotypes (EM46-*a* and EM6-*a*) and these were most divergent, since they shared only *2DS3*, aside from the "framework" genes found in most if not all haplotypes. The *2DS3* gene was also shared by haplotype H182-*b*, which might also contain *2DL5B*002* without *2DL5A*001*. These results are consistent with previously reported physical linkages of *2DL5A*001* with *3DS1*, and of *2DL5B*002* with *2DL2* (Vilches et al. 2000a; Wilson et al. 2000; Fig. 2a). However, identification of *2DL5B*002* in the absence of *2DL2* in haplotype EM6-*a* reveals that these physical associations are not invariable.

Thirteen or 14 haplotypes lacked a *KIR2DL5* gene; those included H29-*b*, possibly H90-*b* and, by definition, both haplotypes of the six progenitors selected for this feature (*c* and *d* of each family). The presence and the absence of the *KIR2DL5* gene have been previously found to correlate with the "B'' and "A'' subgroups of *KIR*-haplotypes, respectively (Vilches et al. 2000c). However, only six or seven of the 13 *2DL5*-negative haplotypes defined in this study appear to belong to the "A'' subgroup, as defined by the combination of *2DL1*, *2DL3*, *2DL4*, *3DL1*, *3DL2* and *2DS4* (haplotypes H29-*b* and -*d*, H42-*c* and -*d*, EM46-*d*, EM6-*c* and, possibly, H182-*c* or -*d*). The remaining *2DL5*-negative haplotypes had typical features of the "B" subset: genes for other non-inhibitory KIR (*2DS1* in H182-*c* or -*d*; *2DS2* in H90-*d* and, possibly, -*b*); *2DL2* instead of *2DL3* (H90-*c*); or both traits at the same time (haplotypes H29-*c*, EM46-*c* and EM6-*d*). The three latter haplotypes were characterized by having the exon-2-positive form of the *KIR3DP1* pseudogene (Gómez-Lozano and Vilches 2002; Wilson et al. 2000); this feature is shared by only two other haplotypes defined in this study, which also had *2DS2* (H90-*d* and H182-*a*).

Discussion

Previous analysis of *KIR2DL5* in one family gave results that were inconsistent with variants *2DL5.1* (*2DL5A*001*) and *2DL5.2* (*2DL5B*002*) being alleles of the same gene (Vilches et al. 2000a). In following up on this observation, the investigation of six families described here demonstrates that *KIR* haplotypes containing two *KIR2DL5* genes (*KIR2DL5A* and *KIR2DL5B*) segregate in the human population and are not rare. Furthermore, analysis of gene linkage by PCR and nucleotide sequencing shows that the two *KIR2DL5* genes are not next to each other, but some distance apart and separated by other *KIR* genes: *2DL5A*001* being telomeric to *3DS1* and *2DL5B*002* being telomeric to *2DL2* (Vilches et al. 2000a; Wilson et al. 2000). Thus *2DL5A* is in the telomeric half of the *KIR*-gene cluster, while *2DL5B* is in the centromeric half (Fig. 2a).

With regard to *KIR2DL5*, four types of haplotype were defined, with relative frequencies *2DL5A*$^{-}$*B*$^{-}$ >

2DL5A^{+}*B*$^{-}$ ~ *2DL5A*$^{-}$*B*$^{+}$ > *2DL5A*$^{+}$*B*$^{+}$. The frequency of the *2DL5A*$^{+}$*B*$^{+}$ haplotypes is slightly greater than expected from random segregation, but the association is not statistically significant. This result is consistent with the analysis of the segregation of alleles for other *KIR* genes showing little linkage disequilibrium between markers in the two halves of the *KIR*-gene complex (Shilling et al. 2002). These data indicate that recombination in the middle of the *KIR*-gene complex is particularly frequent.

Only two of the four published *KIR2DL5* variants were found in the donor panel studied here and they comprised one allele of *KIR2DL5A* (*2DL5A*001*) and one allele of *KIR2DL5B* (*2DL5B*002*). The high nucleotide sequence identity (99.58%) between the exons and introns of *2DL5A*001* and *2DL5B*002* (Vilches et al. 2000a) indicates that these genes derive from the recent duplication of a common ancestor. Although the additional two *KIR2DL5* variants are more similar in nucleotide sequence to *2DL5A*001* (Fig. 2b), their position within the *KIR*-gene cluster is identical or similar to that of *2DL5B*002* (Vilches et al. 2000a) and thus they appear as alleles of *2DL5B* (*2DL5B*003* and *2DL5B*004*, Fig. 2a). Of note, whereas *2DL5A* appears to always be expressed, as assessed by the presence of its mRNA in NK cells and T lymphocytes, *2DL5B* includes both transcribed (**003*) and non-transcribed (**002* and **004*) alleles, a feature that correlates with polymorphisms in the promoter region (Vilches et al. 2000a).

Two forms of *KIR2DL5* identified in the common chimpanzee have high sequence similarity with the four human *KIR2DL5* variants (Khakoo et al. 2000; Rajalingam et al. 2001). However, there is no particular affinity between individual human and common chimpanzee variants (Fig. 2b). This suggests that the duplication leading to *KIR2DL5A* and *KIR2DLB* may have occurred subsequent to the split of the human and chimpanzee species.

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