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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

AUTHOR CONTRIBUTION

Qiong Yu: Wrote the paper. **Hao Chen:** Analyzed the data. **Zhi-Chao Yang:** Contributed essential reagents, analyzed the data. **Zhi-Hui Deng:** Designed the research study, contributed essential reagents, analyzed the data. All authors have read and approved the final manuscript. All authors performed the research.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Complete genomic characterization of a new *KLRC2* allele, *NKG2C*03*

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The novel *NKG2C*03* allele encodes a hybrid of the *NKG2C*01* and *NKG2C*02* primary structures.

KEYWORDS

alleles, genetic polymorphism, HLA-E, human genetics, natural killer cell lectin-like receptors, *NKG2C* receptor

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The CD94:KKG2 family of heterodimeric receptors, expressed on subsets of human natural killer (NK) and T lymphocytes, monitor the expression of HLA-E, presenting peptides mostly derived from the signal sequence of other HLA class I alpha chains.^{1,2} CD94:KKG2 heterodimers deliver inhibitory or activating signals, depending on the KKG2 subunit (mainly KKG2A and *KKG2C*, respectively). CD94 and all KKG2 subunits are type II membrane-integral glycoproteins of the C-type-lectin-like superfamily, with 49%–94% identity in their coding sequence. Their genes are located in the Natural Killer gene Complex (NKC) on chromosome 12, which encompasses nearly 2 Mbp, and encodes additional homologs of the same family.

The activating *KKG2C* (or CD159c) subunit is encoded by the *KLRC2* gene (more often referred to as *KKG2C*), with a length of ca. 6 kbp comprising a 696-bp coding sequence segmented into six exons.^{1,3,4} Homozygous complete *KLRC2/KKG2C* gene deletions are seen in up to 8% and 32%, respectively, of Spanish Caucasoids and other populations.^{3,5,6} Several studies have addressed the distribution, functional effect, and importance of *KKG2C* deletion in different populations and health conditions, particularly cytomegalovirus infection, which specifically triggers differentiation and expansion of NK cells that express high *KKG2C* levels, and display a characteristic phenotype and function.^{3,5,6} In contrast, studies on *KKG2C* sequence polymorphism are scarce,^{1,3,4} possibly because the receptor family is often deemed, albeit inexactly, non-polymorphic. A common complementary DNA sequence was designated *KKG2C*01* by Shum et al,^{1,3,4} who also named *KKG2C*02* a second sequence, found in individuals of different ethnicities, and diverging from the former by two single-nucleotide nonsynonymous polymorphisms (c. 5G > A, Ser2Asn, and c.305C > T, Ser102Phe). The first change affects the cytoplasmic tail, whilst the second is located in the stem that connects the transmembrane region with the ligand-binding domain.

We report here a novel allele, identified in two unrelated Spanish Caucasoids, that encodes asparagine 2, like *KKG2C*02*; and serine 102, like *KKG2C*01*; being the rest of their primary structures identical (Figure 1). The complete *KKG2C* coding region was amplified from an *KKG2C*-hemizygous donor in two overlapping genomic segments, using a proof-reading DNA polymerase and two pairs of oligonucleotide primers in separate reactions—

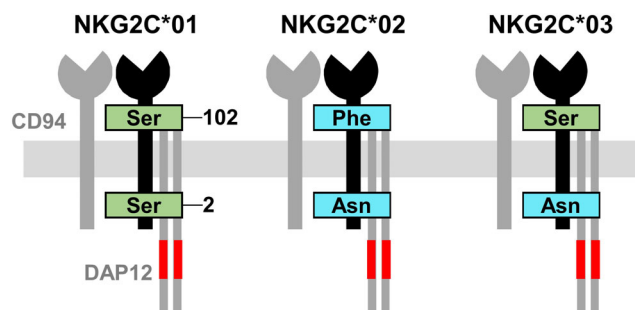


FIGURE 1 Representation of the CD94:KKG2C receptor, including the signaling adaptor DAP12 and its immunoreceptor tyrosine-based activation motifs (ITAMs, in red). Well-characterized polymorphisms of the KKG2C primary structure are shown

KLRC2F-383/KLRR+485b (5'-ctattttatcttatggcacacaatcc-3'/5'-ctggatagctttattgaagtgtca-3'), and *KLRFg669/KLRR+623* (5'-cagtgtggatcttcaatg-3'/5'-gtcataaacaatcccatcag-3') (PCR conditions available upon request). Sequence analysis revealed the new allele to be most similar to the *KKG2C*01* sequence in NKC clone with accession number AC277791.1–5815 identities in 5820 nucleotides, the most relevant difference being the codon 2 substitution AGT > AAT (Ser2Asn). Following the previously used format,⁴ we have designated the new allele with the name *KKG2C*03* (GenBank MW291142). The limited number of nucleotide changes that separate the few genomic *KKG2C*01/*02* sequences available in public databases does not allow for asserting whether *KKG2C*03* is an intermediate evolutionary step between previously known alleles or evolved from these by interallelic recombination or point mutation. The structural and functional importance of CD94/KKG2 sequence polymorphisms, as well as the detailed three-dimensional configuration of the involved stem and cytoplasmic domains, remain unexplored.

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CONFLICT OF INTEREST

The authors declare no potential conflict of interest.

AUTHOR CONTRIBUTIONS

Judit Asenjo designed and performed experiments, analyzed and interpreted data, and wrote the manuscript. **Aura Muntasell** and **Miguel López-Botet** designed the study and revised the manuscript. **Manuela Moraru** designed the study and directed research. **Carlos Vilches** designed the study, directed research and wrote the manuscript.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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