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NEW ALLELE ALERTS

HLA Immune Response Genetics WILEY

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

The CD94:NKG2 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:NKG2 heterodimers deliver inhibitory or activating signals, depending on the NKG2 subunit (mainly NKG2A and *NKG2C*, respectively). CD94 and all NKG2 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 *NKG2C* (or CD159c) subunit is encoded by the *KLRC2* gene (more often referred to as

Manuela Moraru and Carlos Vilches share last authorship.

NKG2C), with a length of ca. 6 kbp comprising a 696-bp coding sequence segmented into six exons.[1,3,4] Homo- and heterozygous complete *KLRC2/NKG2C* 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 *NKG2C* deletion in different populations and health conditions, particularly cytomegalovirus infection, which specifically triggers differentiation and expansion of NK cells that express high *NKG2C* levels, and display a characteristic phenotype and function.[3,5,6] In contrast, studies on *NKG2C* 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 *NKG2C*01* by Shum et al,[1,3,4] who also named *NKG2C*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 *NKG2C*02*; and serine 102, like *NKG2C*01*; being the rest of their primary structures identical (Figure 1). The complete *NKG2C* coding region was amplified from an *NKG2C*-hemizygous donor in two overlapping genomic segments, using a proof-reading DNA polymerase and two pairs of oligonucleotide primers in separate reactions—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 *NKG2C*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 *NKG2C*03* (GenBank MW291142). The limited number of nucleotide changes that separate the few genomic *NKG2C*01/*02* sequences available in public databases does not allow for asserting whether *NKG2C*03* is an intermediate evolutionary step between previously known alleles or evolved from these by inter-allelic recombination or point mutation. The structural and functional importance of CD94/NKG2 sequence polymorphisms, as well as the detailed three-dimensional configuration of the involved stem and cytoplasmic domains, remain unexplored.

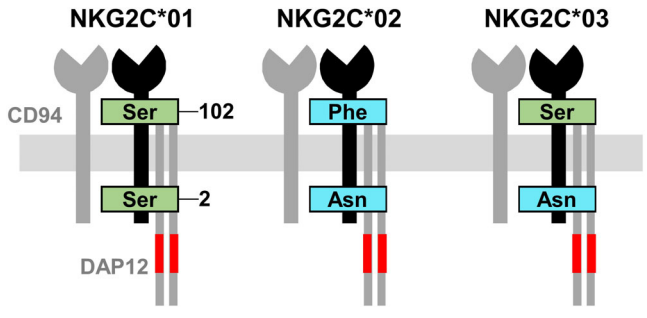

FIGURE 1 Representation of the CD94:NKG2C receptor, including the signaling adaptor DAP12 and its immunoreceptor tyrosine-based activation motifs (ITAMs, in red). Well-characterized polymorphisms of the NKG2C primary structure are shown

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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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