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HLA-C1 ligands are associated with increased susceptibility to systemic lupus erythematosus

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ABSTRACT

Recently, the role of killer cell immunoglobulin-like receptor (KIR) in autoimmune diseases has received increasing attention. The present study was undertaken to determine the association of KIR genes and the human leukocytes antigen (HLA) ligands with Systemic Lupus Erythematosus (SLE) and accompanying oxidative stress. Presence or absence of 17 KIR and 5 HLA loci was performed using the polymerase chain reaction-sequence specific primer (PCR-SSP) method by case-control study. A total of 45 SLE patients, and 60 healthy controls, all of Sicilian descent, were enrolled. Plasma values of the anti-oxidant molecule Taurine were determined in all subjects by capillary electrophoresis UV detection. The carrier frequency of the KIR2DS2 gene was significantly increased in SLE patients compared to healthy controls (73.3 versus 45.0%; OR = 3.36; 95% CI = 1.46–7.74; p = .005) suggesting a role of KIR2DS2 gene in the susceptibility to disease. We also observed a strong positive association between the presence of HLA-C1 ligands group and the disease (82.2% in SLE patients versus 41.7% in controls; OR = 6.47, 95% CI = 2.58–16.26; p < .0001). Stepwise logistic regression analysis supported the effect of the HLA-C1 ligands in SLE patients (OR = 7.06, 95% CI = 0.07–2.19; p = .002), while the KIR genes were no longer significant. Interestingly, we found that SLE patients HLA-C1 positive showed significantly decreased plasma levels of antioxidant activity marker Taurine (69.38 ± 28.49 μmol/L) compared to SLE patients HLA-C1 negative (108.37 ± 86.09 μmol/L) (p = .03). In conclusion, HLA-C1 ligands group was significantly associated with an increased risk of SLE as well as an increased oxidative stress status overall in SLE patients.

1. Introduction

SLE is a chronic inflammatory disease, which mostly affects young women, characterized by an overproduction of autoantibodies to nuclear antigens. Some of these autoantibody assemble in immune-complexes and affect skin, kidneys, haematological tissues, joints, and serosal membranes, causing different clinical manifestations [1,2].

SLE is considered as a multi-factorial disease with strong contributions from genetic and environmental factors. In particular, genes located in the HLA region as HLA-DRB1*03:01 (DR3 allelic group) and HLA-DRB1*15:01 (DR2 allelic group) confer most of the genetic susceptibility for the development of the disease in all Caucasian population, as previously reported [3,4]. Nevertheless, numerous genes outside the HLA region also contribute to increased genetic risk, getting more difficult to understand the aetiology of the disease [5,6]. Accordingly, a common functional variant in the promoter of human Uncoupling Protein-2 gene (−866G > A), confers susceptibility for SLE (unpublished observations).

Recently, Spada et al. [7] have suggested the possible role of NK cells in SLE pathogenesis, showing a deregulation of NK cell activity

Abbreviations: CI, confidence Interval; HLA, human leukocyte antigen; KIR, killer cell immunoglobulin-like receptor; NK, natural killer; OR, odds ratios; PCR-SSP, polymerase chain reaction-specific sequence primer; SLE, systemic lupus erythematosus

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and altered cytokine production from these cells. It is well known that KIRs are crucial for NK regulation through their interaction with HLA Class I molecules [8]. According to their function, KIR can be divided into inhibitory KIR (KIR2DL1-4, KIR2DL5A, KIR2DL5B, and KIR3DL1-3) and activatory KIR (KIR2DS1-5, and KIR3DS1). KIR2DL4 is involved in both inhibitory and activatory signals. KIRs bind specifically defined alleles of HLA-C, HLA-B, or HLA-A [9].

KIR and HLA are highly polymorphic molecules, with some HLA-KIR combinations or KIR haplotypes having a propensity toward higher activation or lower levels of inhibition of NK cells, affecting immune response. Accordingly combinations of HLA alleles and KIR genes have been associated with several diseases such as infectious diseases, inflammatory disorders, cancer [10–12].

In addition, a growing number of studies report that KIR expressed on NK cells may play an important role in autoimmune disorders including SLE [13–23]. However, current results are inconsistent and population specific, as reported by a recent meta-analysis [24] and only a paper reported data on HLA ligands [18].

The aim of this study is to verify if KIR polymorphisms and their known HLA ligands influence the susceptibility or resistance to SLE in our homogeneous population. Moreover, we performed meta-analyses of the genes, which we found associated with SLE to validate our results.

2. Materials and methods

2.1. Patients and controls

Forty-five Caucasoid Sicilian patients with SLE (40 females and 5 males), age range 21–63 years (41.46 ± 10.89), were consecutively enrolled (so due to chance the female/male ratio was slightly different from the expected) at Rheumatology Unit of the Palermo University Hospital according to the American College of Rheumatology 1997 revised criteria [25]. SLE activity was calculated at the time of blood sampling. Baseline information including age, involved organs, duration and severity of the disease, smoking, body mass index and hypertension were collected by face-to-face interviewing. The control group consisted of 60 healthy individuals, age range 22–64 years (39.25 ± 11.48) with no history of autoimmune diseases. Both patients and controls were born in West Sicily as their parents and grandparents, so our population was genetically homogenous. The suitability of SLE sample size was checked (http://ps-power-and-sample-size-calculation.software.informer.com/) on the basis of the results of a previous study on KIR and SLE [15,26]. The Ethic Committee of Palermo University Hospital approved the study protocol, conducted in accordance with the Declaration of Helsinki and its amendments. Informed consent was obtained for collection of samples from all patients and controls.

2.2. Typing

Peripheral whole blood samples were collected, and genomic DNA was extracted from leukocytes by a commercial kit (PureLink® Genomic DNA, ThermoFisher Scientific, Waltham, MA, USA). KIR and HLA profiles were obtained by PCR-SSP, performing 28 reactions for each individual according to the manufacturer's instructions. The KIR genotyping was performed using KIR-TYPE kit (BAG Health Care GmbH). Fourteen KIR genes (2DL1, 2DL2, 2DL3, 2DL4, 2DL5, 2DS1, 2DS2, 2DS3, 2DS4, 2DS5, 3DL1, 3DL2, 3DL3, 3DS1) and 2 pseudogenes (2DP1, 3DP1) were investigated. For HLA class I ligands, a KIR/HLA ligands kit was used (Epitop-TYPE kit; BAG Health Care GmbH, Lich, Germany). DNA of cases and controls was genotyped for the presence of the following KIR ligands groups: HLA-C1, HLA-C2, HLA-B-Bw4-80T (threonine at position 80), HLA-B-Bw4-80I (isoleucine at position 80) and HLA-A-Bw4. KIR gene profiles were determined by the presence or absence of each KIR gene.

The HLA-Cw genotypes were determined using the commercially available HLA Class I C Locus DNA Typing Tray kit (One Lambda, Thermo Fisher Scientific Brand, California, USA). The kit is based on the PCR-SSP method. To detect the specific HLA-Cw alleles, primer mixes are already available in the kit, and PCR amplification is performed according to the manufacturer's instructions .

2.3. Taurine analysis

It was conducted in collaboration with the University of Sassari. Plasma values of the anti-oxidant molecule taurine were determined by capillary electrophoresis UV detection as previously described [27].

2.4. Meta-analysis

The primary source of studies addressing the role of KIR genes in SLE was the PUBMED database limited to English language literature. The medical subject headings used for PUBMED search were: “systemic lupus erythematosus” or “SLE,” killer cell immunoglobulin-like receptors” or “KIR”. Last search was updated on May 31, 2017. The abstracts found were read to identify papers reporting of the frequencies in Caucasoid controls and patients of KIR genes found positive in our study. The papers were read in their entirety to assess their appropriateness for inclusion in the meta-analysis. Extraction of data was performed independently by CC, CMG and DDB who compared results and agreed on a consensus; disagreements were settled by discussion.

2.5. Statistics

The comparisons of frequencies of KIR genes and haplotypes between case and control groups were tested by contingency tables (χ^2 test) constructed to determine statistical differences of the two groups analysed. The data were tested for goodness of fit between the observed and expected genotype and haplotype values and their fit to the Hardy–Weinberg equilibrium. The magnitudes of risk associations are reported by odds ratios (OR) and confidence intervals (95% CI). Statistical analysis was performed by using Graphpad Prism Software (Sand Diego, CA, USA). The p value of = 0.05 was adopted as the significance limit. A logistic regression model was also carried out, in order to derive a reduced and easily interpretable model for predicting onset. The unpaired Welch's correction of Student's *t* test was used for analysis of two nonparametric quantitative data.

For meta-analysis the data were analysed using Review Manager, version 5.1, a statistical software package for managing and analysing all aspects of a Cochrane Collaboration systematic review (The Cochrane Collaboration, Oxford, UK, 1999). The overall OR between the frequencies of genes in both cases and controls was estimated with models based on both fixed-effects and random-effects assumptions. The fixed effects model considers only within-study variability. The random effects model uses weights that include both the within-study and between-study variance. Because of the high heterogeneity between the populations of most of the studies included in this meta-analysis, we have presented the results of random-effects models that are the most conservative ones [28]. The 95% CI of the OR was also calculated.

3. Results

3.1. Genetic analysis

To assess if genetic variants of KIR and their HLA ligands play a role in SLE we first compared the frequencies of these genes in patients with SLE and controls (Table 1). We observed a significantly higher frequency of the activating KIR2DS2 gene in patients compared to healthy controls (73.3% vs. 45.0%, p = .005; OR = 3.36, 95% CI = 1.46–7.74) suggesting a role of KIR2DS2 gene in the susceptibility to disease. A

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