Comparative analysis of allele and genotype frequencies of *HLA-G* gene in embryo implantation failure, assisted reproduction treatment, spontaneous recurrent miscarriage and fertile control couples

GELMINI, Georgia Fernanda; NARDI, Fabiola da Silva; COSTA, Cynthia Hernandes; VARGAS, Rafael Gustavo; ROXO, Valéria Maria Munhoz Sperandio ; BICALHO, Maria da Graça.
Laboratório de Imunogenética e Histocompatibilidade – LIGH
Departamento de Genética, Universidade Federal do Paraná – UFPR, Curitiba, Paraná, Brasil.
georgiagel@msn.com

INTRODUCTION: **Human leucocyte antigen (HLA)-G is a non-classical HLA-class Ib gene with lower degree of polymorphism and more restricted tissue distribution than classical MHC *loci*. HLA-G products have been related to reproduction in several clinic conditions such as spontaneous recurrent miscarriage, embryo implantation failure or preeclampsia, acting as modulators of the maternal immune system. In the present study we compare allele and genotype frequencies of *HLA-G* gene in four different Southern Brazilian Caucasian groups (IF, ART, RM and fertile control), and investigate the possible association between *HLA-G* alleles and difficult natural conception.**

METHODS: **The embryo failure implantation group (IF) was comprised of 40 couples with at least two unsuccessful fresh embryo transfers (IF). The assisted reproduction treatment (ART) group was composed of 19 couples (women under 35 years without history of endometriosis and anatomical abnormalities) undergoing treatment with unexplained infertility. The spontaneous recurrent miscarriage group (RM) was comprised of 60 couples with a history of RM, defined as three or more consecutive abortions occurring until the 20th gestational week, with clinically verified pregnancies and no live-born infant. The fertile control group was composed of 103 couples with at least two successful pregnancies and without history of idiopathic miscarriages or other reproductive problems. *HLA-G* was assessed by sequencing and alleles were defined by variations on exons 2 and 3. The genotypes and alleles were compared and analyzed by the G test, Fisher´s exact test or χ^2 corrected, as appropriated. All *P*-values were corrected (*Pc*) using Bonferroni correction for multiple comparisons.**

RESULTS: **The *G*01:01:08* allele was increased in RM couples (22.1%), as compared to IF couples (7.4%) (*Pc* = 0.0028), ART couples (5.3%) (*Pc* = 0.0224) and control couples (12.3%) (*Pc* = 0.021). The comparisons made between groups according to sex revealed significant differences among males: the *G*01:01:08* allele was found increased in RM males (26.7%) as compared to IF males (7.5%) (*Pc* = 0.0196) and ART males (0%) (*Pc* = 0.0014). We conclude that the *G*01:01:08* allele might influence the biologic function of the HLA-G protein and act as a possible risk factor for the embryo. No significant differences were found in the comparisons of *HLA-G* genotype frequencies among couples of the four different groups.**

Figure 1 – Distribution of allele frequencies among couples

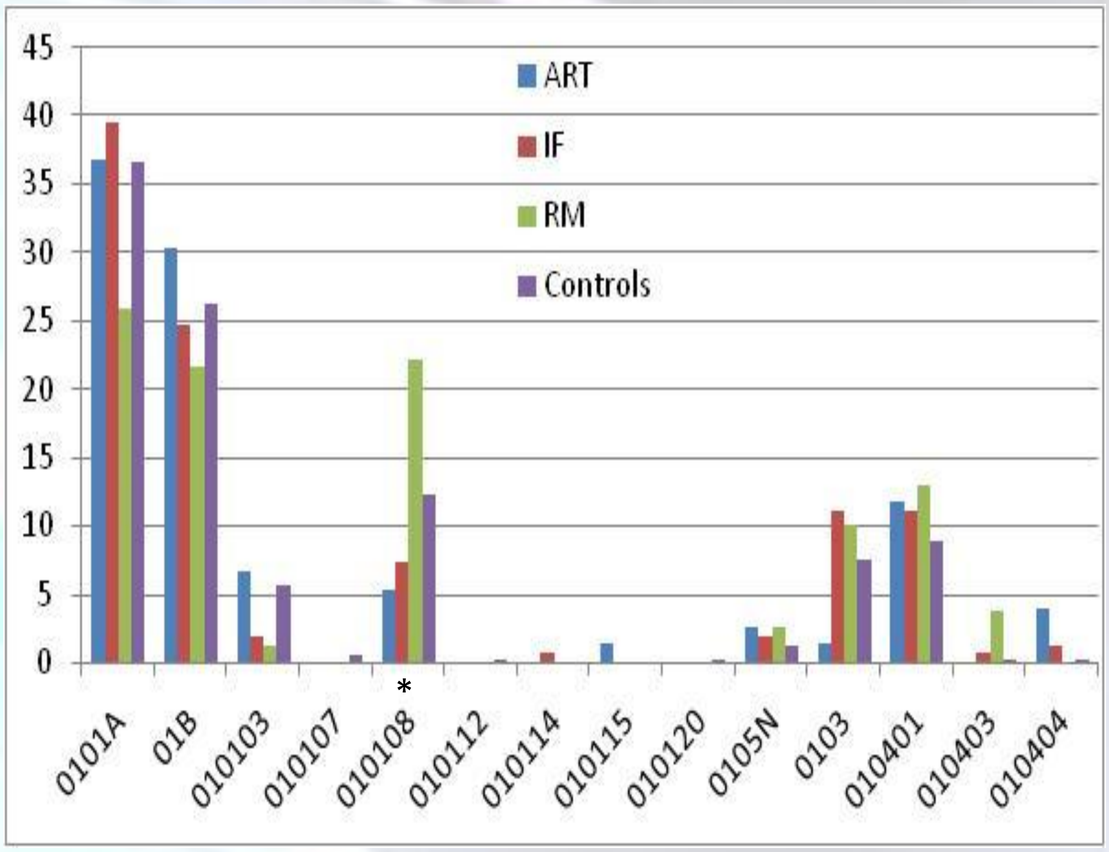
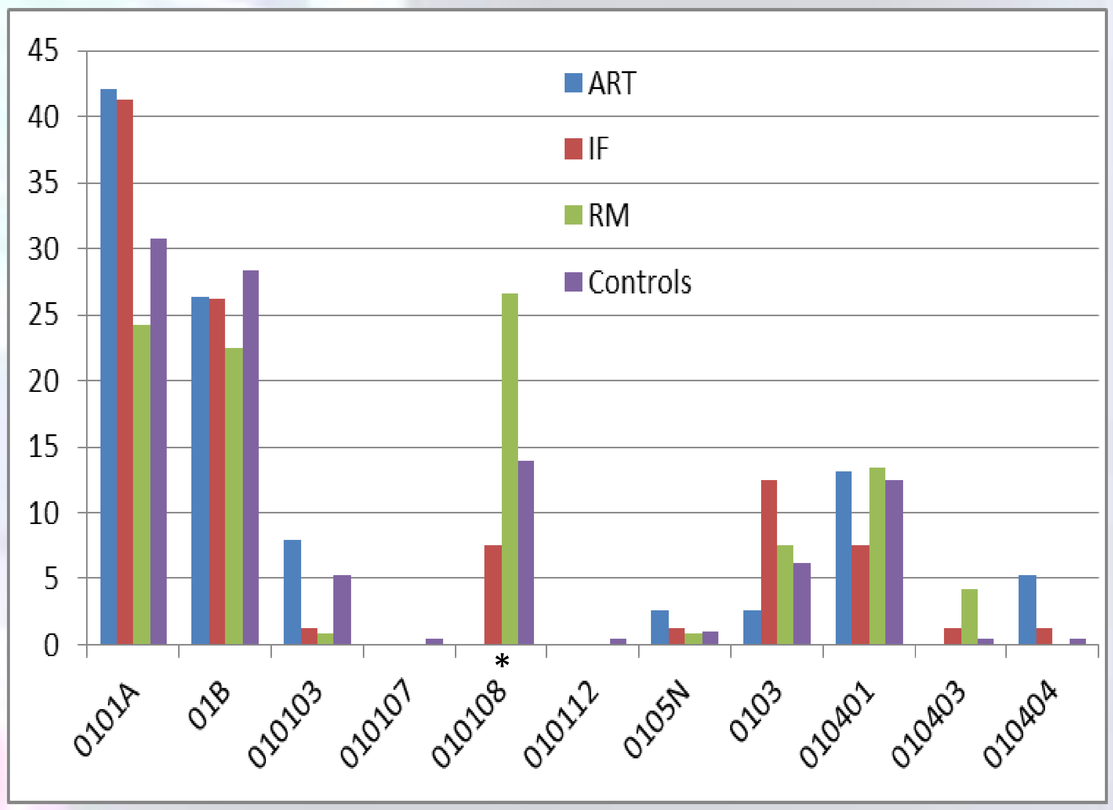


Figure 2 – Distribution of allele frequencies in males



CONCLUSIONS: These results emphasize that embryo implantation is under genetic control, and that the outcome of pregnancy is the result of a balance between activating and inhibitory signals in the fetal-maternal interface, which depend on maternal and paternal contributions and interactions.

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