



## The incidence of pre-eclampsia among couples consisting of Japanese women and Caucasian men

Shigeru Saito<sup>a,d,\*</sup>, Yoshiharu Takeda<sup>b</sup>, Masatoshi Sakai<sup>a</sup>,  
Masao Nakabayahi<sup>b</sup>, Satoshi Hayakawa<sup>c</sup>

<sup>a</sup> Department of Obstetrics and Gynecology, University of Toyama, Toyama, Japan

<sup>b</sup> Aikku Hospital, Maternal & Child Health Center, Tokyo, Japan

<sup>c</sup> High Technology Research Center, Nihon University, Tokyo, Japan

<sup>d</sup> The 21st COE Program, Iwate University, Japan

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### Abstract

Recent data from Hiby (2004) have suggested that a combination of maternal killer immunoglobulin receptor (KIR) AA genotype and fetal HLA-C2 genotype increases the risk of pre-eclampsia. Different human populations have a reciprocal relationship between KIR AA frequency and HLA-C2 frequency. Japanese people have highest frequency of KIR-AA alleles and lowest frequency of HLA-C2 alleles. However, Caucasians have a moderate frequency of KIR-AA and HLA-C2 alleles. If this hypothesis is correct, the incidence of pre-eclampsia among couples consisting of Japanese women and Caucasian men should be higher than that among couples consisting of Japanese women and Japanese men. Therefore, we investigated the incidence of pre-eclampsia among 324 couples consisting of Japanese women and Caucasian men. The incidence of pre-eclampsia in these couples consisting of Japanese women and Caucasian men was similar to that in Japanese women and Japanese men. Our data do not support that of Hiby et al. [Hiby, S.E., Walker, J.J., O'Shaughnessy, K.M., Redman, C.W.G., Carrington, M., Trowsdale, I., Moffett, A., 2004. Combinations of maternal KIR and fetal HLA-C genes influence the risk of pre-eclampsia and reproductive success. *J. Exp. Med.* 200, 957–965], although we did not check the haplotypes for HLA-C and KIR.

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\* Corresponding author at: Department of Obstetrics and Gynecology, University of Toyama, 2630 Sugitani, Toyama-shi, Toyama 930-0194, Japan. Tel.: +81 76 434 7355; fax: +81 76 434 5036.

*E-mail addresses:* s30saito@ms.toyama-mpu.ac.jp, jri@ms.toyama-mpu.ac.jp (S. Saito).

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## 1. Introduction

A number of hypotheses on the etiology of pre-eclampsia have been reported (Roberts et al., 1989; Arngrimsson et al., 1990; Perry and Martin, 1992; Meekins et al., 1994; Robillard et al., 1994; Zhou et al., 1997; Dekker et al., 1998; Redman et al., 1999; Koelman et al., 2000; Saito and Sakai, 2003). One commonly discussed hypothesis is the immunogenetic maladaptation hypothesis (Dekker et al., 1998; Robillard et al., 2002; Koelman et al., 2000; Saito and Sakai, 2003; Chaouat et al., 2005). Immune recognition of fetal (paternal) antigens is suggested by the increased risk of pre-eclampsia in first pregnancies (MacGillivray, 1983; Skjaerven et al., 2002) and in multiparous women after changing partners (Robillard et al., 1999; Li and Wi, 2000; Trogstad et al., 2001). There is also an increased risk in women who have received donated gametes, such as artificial donor insemination (AID) (Hoy et al., 1999), oocyte donation and embryo donation (Soderstrom-Anttila et al., 1998). These findings suggest that maternal tolerance to paternal antigens is important for the maintenance of pregnancy, and immunogenetic maladaptation of tolerance system might induce pre-eclampsia. Extravillous trophoblasts (EVT) express four unique class I MHC molecules: HLA-G, HLA-E, HLA-F and HLA-C (Kovats et al., 1990; Ishitani et al., 2003; King et al., 1996). Only HLA-C is polymorphic, so paternal HLA-C on EVT can be recognized by killer immunoglobulin receptors (KIR) on maternal NK cells (Moffett-King, 2002). Recently, Hiby et al. (2004) reported interesting data showing that the combination of maternal KIR-AA, which has no activating receptors, and the fetal HLA-C2 group is associated with pre-eclampsia. They showed also that additional activating KIRs decrease the incidence of KIRs pre-eclampsia when the fetus has an HLA-C2 allele.

Recent data demonstrate that populations with a high KIR-AA genotype frequency have a low frequency of HLA-C2 alleles and vice versa (Williams et al., 2002; Yawata et al., 2002; Norman et al., 2001; Crum et al., 2000; Cook et al., 2003; Toneva et al., 2001; Rajalingam et al., 2002; Whang et al., 2003; Wang et al., 1997). Hiby et al. (2004) hypothesized that the KIR-AA/HLA-C2 combination in a given population would be selected against by deleterious effects such as pre-eclampsia. Japanese people have the highest frequency of KIR-AA genotype at around 60%, and the lowest frequency of HLA-C2 genotype at around 9% (Yawata et al., 2002). Conversely, Australian aborigines and New India have the lowest frequency of KIR-AA genotype and highest frequency of HLA-C2 genotype (Norman et al., 2001; Cook et al., 2003; Rajalingam et al., 2002). If the hypothesis of Hiby et al. (2004) is correct, the incidence of pre-eclampsia in couples consisting of Japanese women and Australian aborigine or New India men should be high. However, such couples are very rare. On the other hand, the number of couples consisting of Japanese women and Caucasian men has been increasing. Caucasians have moderately high frequencies of KIR-AA genotype and HLA-C2 genotype. The frequency ratio of the HLA-C2 genotype is 30–35%, which is three to four times higher than that in Japanese (Williams et al., 2002; Hiby et al., 2004). Therefore, we investigated the frequency of pre-eclampsia in couples consisting of Japanese women and Caucasian men.

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