KIR and HLA-C: Immunogenetic regulation of human birth weight

Lydia E. Farrell1,2, Susan E. Hibi1,2, Richard Apps3,4, Olympe Chazara1,2, Lill Trogstad5, Håkon K. Gjessing6, Per Magnus6, Mary Carrington3,4 and Ashley Moffett1,2

1) Department of Pathology, University of Cambridge, Cambridge CB2 1QP, United Kingdom
2) Centre for Trophoblast Research, University of Cambridge, Cambridge CB2 1QP, United Kingdom
3) Cancer and Inflammation Program, Laboratory of Experimental Immunology, Leidos Biomedical Research Inc., Frederick National Laboratory, Frederick, MD 21702, USA
4) Ragon Institute of Massachusetts General Hospital, Massachusetts Institute of Technology and Harvard University, Cambridge, MA 02139, USA
5) Division of Infectious Disease Control, Norwegian Institute of Public Health, 0403 Oslo, Norway
6) Division of Epidemiology, Norwegian Institute of Public Health, 0403 Oslo, Norway

Correspondence: Lydia E. Farrell, e-mail lf284@cam.ac.uk

ABSTRACT

Pregnancies resulting in very small or very large babies are at higher risk of obstetric complications with increased morbidity for both mother and baby. Using data from the Medical Birth Registry of Norway we have shown how human birth weight is still subject to stabilizing selection. Particular combinations of maternal/fetal immune genes have been implicated in pregnancies resulting in a low birth weight baby (<5th birth weight centile). More specifically, an inhibitory maternal KIRAA genotype with a paternally derived fetal HLA-C2 ligand. At the other end of the birth weight spectrum the presence of an activating maternal KIR2DS1 gene is associated with increased birth weight in linear or logistic regression analyses of all pregnancies >5th centile (p=0.005, OR=2.65). Thus, inhibitory maternal KIR combined with fetal HLA-C2 is more frequently associated with low birth weight, whereas activating maternal KIR with fetal HLA-C2 ligand is associated with increasing birth weight. Our findings using the MoBa cohort have replicated the association of KIR and HLA-C seen in poor placentation, and confirm the importance of maternal/fetal immune gene interactions in determining the outcome of pregnancy.

Large numbers of a specialised type of lymphocyte known as uterine NK cells are found in the decidua during placentation [11]. Uterine NK cells express Killer cell Ig-like Receptors (KIR) and fetal EVT express their cognate ligand HLA-C, the only classical HLA class I molecule found on trophoblast [12]. We have proposed that this maternal KIR/fetal HLA-C interaction functions to mediate uterine NK cell control of trophoblast invasion [11,13-15].

This receptor ligand interaction is unusual in that both KIR and HLA are highly polymorphic gene systems. They also segregate independently and are encoded on separate chromosomes. KIR genotypes vary with content, copy number and at allelic variation at individual KIR loci. Around 500 different genotypes have already been described to date [16]. To simplify this complexity, KIR haplotypes are classified as either A or B based on gene content. The KIR A haplotype is highly stable, varying little at the gene content level and carrying fewer genes. Notably it encodes KIR2DL1 and KIR2DL3, both inhibitory receptors for HLA-C. The KIR B haplotype is much more variable with the potential to encode inhibitory KIR2DL1 and KIR2DL2, and also activating KIR2DS1, all of which bind HLA-C [11].

HLA-C alleles can be subdivided into two groups C1 and C2 based on a dimorphism at position 80 of the...
and/or pre-eclampsia associated with pregnancies with low birth weight increased maternal mortality and morbidity seen in pregnancies with high birth weights.

In pregnancies where the fetus was particularly paternally derived, maternal KIR frequencies were associated with these disorders. All these conditions share a genetic association with high birth weight pregnancies (>90th centile) had low KIR A4 and high KIR2DS1 frequencies.

The effect of KIR2DS1 on birth weight was tested in both categorical and continuous analysis. Using birth weight in grams as a continuous variable, the presence of a maternal KIR2DS1 conferred an average birth weight increase of 78g (p=0.005) in a linear regression model. The frequency of maternal KIR2DS1 was significantly higher in pregnancies with high compared with median birth weight in categorical analysis (Table 2, [10]).

The effect of KIR AA genotypes on pre-eclampsia and FGR was previously observed particularly in pregnancies with a fetus carrying a paternally derived C2. This was shown by both categorical and continuous analysis across the birth weight spectrum. The effect of maternal KIR2DS1 on birth weight is thus dependent on the presence of fetal C2, particularly paternally derived fetal C2.

In other words the presence of fetal C2 amplifies the effect of maternal KIR2DS1. When the fetus has more C2 groups than the mother (C1/C2 fetus with C1/C1 mother, and C2/C2 fetus with C1/C2 mother), an average increase of 245g (p=0.002) was seen. Furthermore, presence or absence of KIR2DS1 as a categorical variable when combined with more C2 in the fetus showed that maternal KIR2DS1 has a significant effect when the fetus is carrying more C2 than the mother, (OR 2.93, 95% CI 1.66-5.18, p=0.0002).

In pregnancies where the fetus was C1/C2 we could determine parent of origin of the C2 group. In both categorical and continuous analyses, the presence of maternal KIR2DS1 only has an effect on birth weight.

![Figure 1](https://via.placeholder.com/150)

**Figure 1.** Distribution of birth weights in the Norwegian population with percentage of babies transferred to the special care baby unit for the years 1967-2010 (n=795,068). (Originally published in *Journal of Immunology*: Hiby S, Apps R, Chazara O, et al. Maternal KIR in combination with paternal HLA-C2 regulate human birth weight. *J. Immunol* 2014; 192: 5069-5073. Copyright © [2014] The American Association of Immunologists, Inc.)
KIR and HLA-C: Immunogenetic Regulation of Human Birth Weight

Table 1. KIR known to bind HLA-C and their HLA-C ligands.

<table>
<thead>
<tr>
<th>KIR</th>
<th>HLA-C Ligand</th>
<th>KIR Haplotype location</th>
<th>Activating/Inhibitory</th>
</tr>
</thead>
<tbody>
<tr>
<td>2DL1</td>
<td>C2</td>
<td>A and some B</td>
<td>Inhibitory</td>
</tr>
<tr>
<td>2DL2</td>
<td>C1, some C2</td>
<td>B</td>
<td>Inhibitory</td>
</tr>
<tr>
<td>2DL3</td>
<td>C1</td>
<td>A</td>
<td>Inhibitory</td>
</tr>
<tr>
<td>2DS1</td>
<td>C2</td>
<td>B</td>
<td>Activating</td>
</tr>
<tr>
<td>2DS2</td>
<td>Possibly C1</td>
<td>B</td>
<td>Activating</td>
</tr>
<tr>
<td>2DS4</td>
<td>Some C1 and some C2</td>
<td>A (often deleted)</td>
<td>Activating</td>
</tr>
</tbody>
</table>

Table 2. Presence of maternal KIR2DS1 associates with increased birth weight in both categorical and continuous analysis n=1316. This is enhanced when the fetus has more HLA-C2 epitopes than the mother n=304 and specifically paternally derived C2 n=204. Data summarised from tables I, II, and IV-VII in Hiby S, Apps R, Chazara O, et al. Maternal KIR in combination with paternal HLA-C2 regulate birth weight. J. Immunol 2014; 192: 5069-5073.

<table>
<thead>
<tr>
<th>Presence of maternal KIR2DS1</th>
<th>Continuous analysis</th>
<th>Categorical analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Weight</td>
<td>p-value</td>
</tr>
<tr>
<td>Presence of maternal KIR2DS1</td>
<td>78 g</td>
<td>0.005</td>
</tr>
<tr>
<td>Maternal KIR2DS1 with more C2 in fetus than mother</td>
<td>245 g</td>
<td>0.0002</td>
</tr>
<tr>
<td>Maternal KIR2DS1 with paternally derived fetal C2</td>
<td>196 g</td>
<td>0.016</td>
</tr>
</tbody>
</table>

when the fetal C2 is paternally derived (paternal C2 p=0.016, maternal C2 p=0.75) (Table 2).

Our findings using MoBa subjects have replicated the association of KIR and HLA-C with poor placentation (pre-eclampsia, and low birth weight) and confirm the importance of maternal KIR/fetal HLA-C interactions in determining the outcome of pregnancy. Of importance is that we now also show an effect in high birth weight pregnancies, implicating a role in the regulation of placentation in normal or excessive invasion. This effect has a clear direct impact on birth weight as a continuous variable, with an effect comparable or even greater than smoking during pregnancy, high altitude and sex of the baby [21-24].

KIR2DS1 is expressed by uterine NK cells and is functional although ascertaining exactly how NK cells operate to subtly define the extent of arterial transformation by trophoblast is an exciting challenge for the future. Nonetheless our findings indicate that a balance of KIR inhibitory and activating stimuli is necessary for optimal trophoblast invasion. NK derived cytokines such as GM-CSF, released in response to activation of KIR2DS1 by binding C2, are one possible mechanism [13].

Not all women with KIR AA genotypes and fetal C2 have a pregnancy disorder. We are now selecting patients from the MoBa cohort to study women who have recurrent pre-eclampsia as well as those who have a normal pregnancy followed by a pre-eclamptic pregnancy and vice versa. We aim to focus on KIR2DL1, the inhibitory KIR for HLA-C2 because there are 4 different KIR2DL1 alleles in the Norwegian population. Our prediction is that particular KIR2DL1 alleles will confer most risk.

Perhaps in the long term KIR/HLA-C genotyping might be a genetic predictor of birth weight to identify those at risk of FGR, pre-eclampsia or macrosomia.

ACKNOWLEDGEMENTS

Figure 1 reproduced with kind permission of the Journal of Immunology. This work was supported by Wellcome Trust Grants 090108/Z/09/Z and 085992/Z/08/Z, British Heart Foundation Grant PG/09/077/27964, and the Centre for Trophoblast Research. This work was also supported by Frederick National Laboratory for Cancer Research Contract HHSN261200800001E and by the Intramural Research Program of National Institutes of Health, Frederick National Laboratory, Center for Cancer Research. The content of this publication does not necessarily reflect the views or policies of the Department of Health and Human Services, nor does mention of trade names, commercial products, or organizations imply endorsement by the U.S. Government. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

REFERENCES


