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Maternal *KIR* in Combination with Paternal *HLA-C2* Regulate Human Birth Weight

Susan E. Hiby,[*,†,1] Richard Apps,[‡,§,1] Olympe Chazara,[*,†] Lydia E. Farrell,[*,†] Per Magnus,[¶] Lill Trogstad,[‖] Håkon K. Gjessing,[¶] Mary Carrington,[‡,§] and Ashley Moffett[*,†]

Human birth weight is subject to stabilizing selection; babies born too small or too large are less likely to survive. Particular combinations of maternal/fetal immune system genes are associated with pregnancies where the babies are ≤5th birth weight centile, specifically an inhibitory maternal *KIR AA* genotype with a paternally derived fetal *HLA-C2* ligand. We have now analyzed maternal *KIR* and fetal *HLA-C* combinations at the opposite end of the birth weight spectrum. Mother/baby pairs ($n = 1316$) were genotyped for maternal *KIR* as well as fetal and maternal *HLA-C*. Presence of a maternal-activating *KIR2DS1* gene was associated with increased birth weight in linear or logistic regression analyses of all pregnancies >5th centile ($p = 0.005$, $n = 1316$). Effect of *KIR2DS1* was most significant in pregnancies where its ligand, HLA-C2, was paternally but not maternally inherited by a fetus ($p = 0.005$, odds ratio = 2.65). Thus, maternal *KIR* are more frequently inhibitory with small babies but activating with big babies. At both extremes of birth weight, the *KIR* associations occur when their HLA-C2 ligand is paternally inherited by a fetus. We conclude that the two polymorphic immune gene systems, *KIR* and *HLA-C*, contribute to successful reproduction by maintaining birth weight between two extremes with a clear role for paternal HLA. *The Journal of Immunology*, **2014, 192: 5069–5073.**

Birth weight has been considered "perhaps the most clear cut example of a human character that is subject to stabilizing selection" and is pertinent for those studying genetic variants influencing human evolution, disease, and natural selection (1). The size of a human infant at the end of gestation determines both the risk of obstetric complications as well as the chances of survival of the baby in the neonatal period (2, 3). High maternal and fetal perinatal mortality rates are strongly associated with being too small or too large at birth, with the lowest perinatal mortality occurring very close to the mean of birth weight distribution (1, 4, 5). Mothers are also at risk at these two extremes: either from pre-eclampsia, a systemic syndrome triggered by poor placental perfusion, or from prolonged obstructed labor with the risk of postpartum hemorrhage and sepsis. Although genetic factors are known to be important, there is no consensus on what is the differential contribution of maternal and paternal genes to birth weight or which genes are responsible (6–8). Fetal growth in utero partly depends on the development of a maternal blood supply to the placenta that requires structural modifications of the uterine spiral arteries. Arterial transformation is mediated by infiltration of placental trophoblast cells into the maternal decidua and arterial walls (9). A growing body of evidence indicates that this process, which must be carefully balanced between under and over trophoblast invasion, is controlled by the maternal uterine NK cells (uNK) that are a distinctive feature of the decidua during placentation (10).

uNK express killer Ig–like receptors (KIR) that can bind to HLA-C, the only classical HLA molecule expressed by trophoblast (11, 12). Both *KIR* and *HLA-C* genes are polymorphic, meaning that in each pregnancy maternal *KIR* and fetal *HLA-C* genetic combinations can differ. *KIR* are highly variable both in the number of genes on a haplotype as well as allelic polymorphism at individual *KIR* loci (13). Two main *KIR* haplotypes are found in all human populations, *A* and *B*. *KIR A* haplotypes carry fewer genes, most of which encode inhibitory receptors, including KIR2DL1 and KIR2DL3, which bind HLA-C. *KIR B* haplotypes have varying numbers of additional, mainly activating receptors but only one, KIR2DS1, can bind to trophoblast HLA-C molecules (12). KIR distinguish between all HLA-C allotypes as two mutually exclusive epitopes, HLA-C1 or HLA-C2 (C1 or C2), defined by a dimorphism at position 80 of the α1 domain of the α helix (14). All C2 allotypes are bound specifically by KIR2DL1 and KIR2DS1. In white British the *KIR A* and *KIR2DS1* haplotype frequencies are 60% and 20%, respectively, and the *HLA-C2* allele frequency is nearly 30%.

Immunogenetic studies provide evidence for a co-operative interaction of uNK and trophoblast to regulate placentation. Three disorders of pregnancy, pre-eclampsia, fetal growth restriction (FGR), and recurrent miscarriage, share a common primary pathogenesis of defective arterial transformation by trophoblast (12, 15,

*Department of Pathology, University of Cambridge, Cambridge CB2 1QP, United Kingdom; [†]Centre for Trophoblast Research, University of Cambridge, Cambridge CB2 1QP, United Kingdom; [‡]Cancer and Inflammation Program, Laboratory of Experimental Immunology, Leidos Biomedical Research, Inc., Frederick National Laboratory, Frederick, MD 21702; [§]Ragon Institute of Massachusetts General Hospital, Massachusetts Institute of Technology and Harvard University, Cambridge, MA 02139; [¶]Division of Epidemiology, Norwegian Institute of Public Health, 0403 Oslo, Norway; and [‖]Division of Infectious Disease Control, Norwegian Institute of Public Health, 0403 Oslo, Norway

[1]S.E.H. and R.A. contributed equally to this work.

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Address correspondence and reprint requests to Prof. Ashley Moffett, Department of Pathology and Centre for Trophoblast Research, University of Cambridge, Tennis Court Road, Cambridge CB2 1QP, U.K. E-mail address: am485@cam.ac.uk

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Abbreviations used in this article: f, fetus; FGR, fetal growth restriction; KIR, killer Ig–like receptor; m, mother; MoBa, Norwegian Mother and Child Cohort Study; OR, odds ratio; uNK, uterine NK cell.

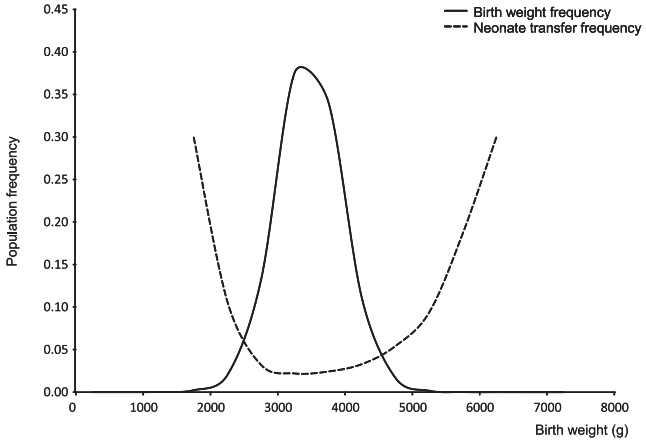

FIGURE 1. Distribution of birth weights in the Norwegian population with percentage of babies transferred to the special care baby unit for the years 1999–2008 (n = 795,068).

16). These pregnancy disorders all associate with the same combinations of maternal *KIR* and fetal *HLA-C* genotypes: two maternal *KIR A* haplotypes (*AA* genotype), specifically when *C2* is present in the fetus (12, 17, 18). In this scenario, strong inhibition of uNK will occur, mediated by KIR2DL1 (located on the *KIR A* haplotype) binding to trophoblast HLA-C2. The association appears particularly when a fetal *C2* allele is inherited from the father (12). Conversely, women who have the telomeric region of the *KIR B* haplotype, where the activating receptor for C2 (*KIR2DS1*) is located, are significantly protected from these pregnancy disorders when a fetal *C2* allele is present (12). Thus, these disorders of inadequate arterial transformation show that strong uNK inhibition mediated by binding to C2+ trophoblast is detrimental to placentation and that uNK activation counterbalances this effect. We have now analyzed *KIR* and *HLA* genotypes of pregnancies across the birth weight spectrum. Our new findings indicate a balance of maternal KIR and fetal HLA-C genotype frequencies in the human population allows birth weight to be kept at an optimum for maternal and fetal survival.

Materials and Methods

Study design

This study was designed to test the hypothesis that the polymorphic immune system genes, *KIR* and *HLA-C*, influence human birth weight. We have shown that certain maternal *KIR* and fetal *HLA-C* genes were associated with pregnancy outcome where the birth weight was ≤5th centile in a United Kingdom population (12). To analyze *KIR* and *HLA-C* frequencies in pregnancies with birth weights >5th centile, we supplemented our United Kingdom dataset with a large number of pregnancies from the Norwegian Mother and Child Cohort Study (MoBa) cohort where >90,000 well-documented pregnancies have been collected (19, 20).

Subjects

Details of the participants in our United Kingdom cohort study have been previously described (12, 17). Briefly, these comprised 747 pregnancies with pre-eclampsia (defined by new hypertension >140/90 mmHg after week 20 together with new protein urea >300 mg/24 h), 118 pregnancies with fetal growth restriction (birth weight ≤5th centile), and 404 normal pregnancies of primiparous women. From the MoBa cohort 995 normal pregnancies were analyzed. These were primigravida who had a single live born, normally formed infant with a gestation length of >259 d and <300 d determined from last menstrual period and confirmed by ultrasonogram. The mothers had no medical conditions, including hypertension, renal disease, pre-eclampsia, thyroid disease, gestational diabetes, or fetal hydrops. An additional 141 pregnancies with pre-eclampsia from the MoBa cohort were analyzed. These were defined by new hypertension >140/90 after 20 wk gestation combined with proteinuria >+1 dipstick on at least two occasions. Ethical approval for analysis of United Kingdom subjects was obtained from the Cambridge Research Ethics Committee (reference nos. 01/197 and 05/Q0108/367; Cambridgeshire, U.K.). The Regional Committee for Ethics in Medical Research and the Data Inspectorate have approved the MoBa study. In both cohorts informed written consent was obtained from all participants.

Genotyping

Typing of 12 *KIR* genes in the mothers and *HLA-C* groups *C1* and *C2* in both mothers and babies was carried out using PCR with sequence-specific primers as previously described (17, 18).

Statistical analysis

The separate analyses of United Kingdom and Norwegian subjects, in which pregnancies with pre-eclampsia and FGR were compared with those with median and high birth weights (Supplemental Fig. 1, Supplemental Table I) , was performed using the χ^2 and two-tailed Fisher's exact test (Open Source Epidemiologic Statistics for Public Health, version 2.3.1). The combined analyses of pregnancies from both the United Kingdom and Norwegian cohorts used all pregnancies where the babies' birth weight was >5th centile and there were no complications such as pre-eclampsia to test for effect of KIR on birth weight (Tables I–VII, Supplemental Table II). In this study, linear and logistic regression was performed using R functions lm and glm (21). Effect of *KIR2DS1* on birth weight in the presence of different maternal (m) and fetal (f) *HLA-C* types was tested for the groups of subjects defined in Table III. Two-sided p values <0.05 were considered statistically significant throughout.

Results

Birth weight extremes and neonatal morbidity

We first confirmed the association of neonatal morbidity with the extremes of birth weight using present-day data from 795,068 Norwegian first pregnancies from 1999 to 2008. We plotted the distribution of birth weights superimposed on the frequency of transfer to a special care neonatal unit (Fig. 1). This recapitulates the original data for United Kingdom pregnancies in the 1930s and clearly illustrates the "obstetric dilemma"; that is, there are major problems for babies born either too small or too large (1, 4).

Presence of maternal KIR2DS1 *associates with increased birth weight*

Our previous studies all focused on maternal *KIR* and fetal *HLA-C* genotypes in pregnancies affected by poor placentation (FGR, pre-eclampsia, or recurrent miscarriage), where we find that maternal *KIR AA* frequency was significantly higher and *KIR2DS1* frequency significantly lower than in healthy control pregnancies (12,

Table I. Presence of maternal *KIR2DS1* associates with increased birth weight: categorical analysis

Maternal *KIR2DS1* Genotype	Median Birth Weight (6–89th Centile) (%)	High Birth Weight (≥90th Centile) (%)	Effect of *KIR2DS1* on Birth Weight		
			OR	95% CI	p Value
Positive	n = 389 (39.1)	n = 148 (46.1)	1.38	1.07–1.79	0.01
Negative	n = 606 (60.9)	n = 173 (53.9)			

KIR2DS1 frequency is significantly increased in high compared with median birth weight pregnancies. Presence versus absence of *KIR2DS1* was tested for effect on birth weight as a categorical variable in a logistic regression analysis of 1316 pregnancies. Samples from both the United Kingdom and Norway cohorts were combined, with cohort and sex of the baby included as covariates.

CI, confidence interval; n, number of pregnancies.

Table II. Presence of maternal *KIR2DS1* associates with increased birth weight: continuous analysis

Subjects	Covariates	Effect of Presence of *KIR2DS1* on Birth Weight (g)			
		n	Mean Increase (g)	SE	*p* Value
United Kingdom	Sex of fetus	404	84	43	0.05
Norway	Sex of fetus	912	93	44	0.04
United Kingdom and Norway	Cohort and sex of fetus	1316	89	33	0.008
United Kingdom and Norway	Cohort, sex of fetus, and gestational age	1316	78	28	0.005

Presence of *KIR2DS1* associates significantly with increased birth weight. Presence versus absence of maternal *KIR2DS1* was tested for an effect on birth weight as a continuous variable in grams, in linear regression analyses of pregnancies >5th birth weight centile. Sex of the baby was included as a covariate in every analysis.

Mean, average increase in birth weight (in grams) conferred by presence of the test variable; *n*, number of pregnancies analyzed.

17, 18). A small number of pregnancies with birth weights ≥90th centile (high birth weight, $n = 66$) were available within our United Kingdom control cohort. In these pregnancies we see an opposite pattern for maternal *KIR* genotype with *KIR AA* decreased and *KIR2DS1* at higher frequencies than in controls (Supplemental Fig. 1). To obtain greater numbers of high birth weight pregnancies, we used mother and baby DNA samples from the Norwegian MoBa bank where >90,000 pregnant women have been recruited (19, 20). Detailed clinical data allowed us to choose mother/baby pairs where there was no known medical cause for fetal macrosomia such as gestational diabetes or fetal hydrops. There was a similar trend of high maternal *KIR AA*, low *KIR2DS1* frequency in pregnancies associated with poor placentation (birth weight ≤5th centile and pre-eclampsia) and low *KIR AA*, high *KIR2DS1* frequency in high birth weight pregnancies (Supplemental Fig. 1). Mothers of average (or median) birth weight babies possessed intermediate *KIR* frequencies. Thus, our previous observations regarding low birth weight pregnancy in the United Kingdom cohort replicate in the Norwegian cohort.

Given these preliminary findings that there are distinctive KIR frequencies in women with macrosomic babies, we further analyzed all those pregnancies with birth weights >5th centile. United Kingdom and Norwegian data were combined and *KIR2DS1* was tested for an effect on birth weight as either a categorical or continuous variable. The presence of maternal *KIR2DS1* was significantly more frequent in pregnancies with high compared with median birth weight in a logistic regression model, with cohort and sex included as covariates ($p = 0.010$, odds ratio [OR] 1.38) (Table I). We next used raw birth weight in grams as a continuous variable in linear regression analysis. Presence of *KIR2DS1* conferred a similar average increase in birth weight in each cohort (84 g in United Kingdom and 93 g in Norway) (Table II). Pooling all 1316 pregnancies and including cohort and sex of the baby as covariates in a linear regression model, presence of *KIR2DS1* showed a highly significant association with increased birth weight ($p = 0.008$, Table II). *KIR2DS1* showed the strongest effect on birth weight of all *KIR* genes that we analyzed. Genes in the telomeric *B* region are in strong linkage disequilibrium but presence of *KIR2DS5*, the locus adjacent to *KIR2DS1*, showed an increase in birth weight in the linear regression analysis that was only borderline significant and the *KIR AA* genotype showed no significant association with birth weight in pregnancies >5th centile (Supplemental Tables I, II). Birth weight also correlates with gestational age, but the effect of *KIR2DS1* on birth weight is independent of both fetal sex and gestational age (Table II, $p = 0.005$). These pregnancies are all within a window of 37–40 wk gestation. Adjusting for these small differences in gestational age, by including estimated gestational age as a covariate, the effect of *KIR2DS1* on birth weight became more significant ($p = 0.005$ compared with $p = 0.008$ when gestational age is ignored, Table II).

Maternal KIR2DS1 *and fetal* HLA-C2 *combinations affect birth weight*

Pre-eclampsia and fetal growth restriction are associated with *KIR AA* genotypes in combination with a *C2* group in the fetus, particularly when the *C2* group is inherited from the father and not from the mother (12). We tested whether association of increased birth weight with *KIR2DS1* was affected by the parental origin of fetal *C2*. Effect of *KIR2DS1* on birth weight was analyzed in pregnancies where the fetus (f) has an extra copy of *C2* compared with the mother (m) (Table III). In these pregnancies (mC1C1/fC1C2 and mC1C2/fC2C2) the additional fetal *C2* is by default from the father. This was compared with the effect of *KIR2DS1* on birth weight in pregnancies where there are fewer copies of *C2* in the fetus than the mother or the same number. In both categorical and continuous analyses of all pregnancies >5th centile, presence of maternal *KIR2DS1* has a significant effect only when a pregnancy has more *C2* in the fetus compared with the mother (categorical, $p = 0.0002$, OR = 2.93; continuous, $p = 0.0002$, average increase of 245 g when *KIR2DS1* present; Tables IV, V).

As an additional test for the relative contribution of paternal and maternal fetal *C2*, we also analyzed the effect of the presence of *KIR2DS1* in pregnancies where the fetus was *C1C2*. From this group we then chose pregnancies where it was possible to distinguish whether the single fetal *C2* was paternal (mC1C1/fC1C2) or maternal (mC2C2/fC1C2) in origin (Table III). In both categorical and continuous analyses of pregnancies >5th centile we find that the presence of *KIR2DS1* only associates with increased birth weight when the *C2* group is inherited from the father (categorical, paternal *C2* $p = 0.005$, OR = 2.65, maternal *C2* $p = 0.67$, OR = 0.81; continuous, paternal *C2* $p = 0.016$, maternal *C2* $p = 0.75$; Tables VI, VII). Thus, a combination of maternal *KIR2DS1* with a fetal *HLA-C2* inherited from the father protects against poor placentation but increases the risk of a macrosomic baby.

Table III. Groups of subjects defined by maternal and fetal *HLA-C* genotype used to analyze effect of *KIR2DS1* on birth weight

Group	*HLA-C* Epitopes: Mother/Fetus
Less C2 in fetus than mother	mC1C2/fC1C1 and mC2C2/fC1C2
Equal C2 in fetus and mother	mC1C1/fC1C1 and mC1C2/fC1C2 and mC2C2/fC2C2
More C2 in fetus than mother	mC1C1/fC1C2 and mC1C2/fC2C2
Single fetal C2 paternal	mC1C1/fC1C2
Single fetal C2 maternal	mC2C2/fC1C2

Table IV. Maternal *KIR2DS1* significantly increases birth weight when the fetus has more *HLA-C2* epitopes than the mother: categorical analysis

Subjects	Maternal *KIR2DS1* Genotype	Median Birth Weight (6–89th Centile) (%)	High Birth Weight (>89th Centile) (%)	Effect of *KIR2DS1* on Birth Weight			
				OR	95% CI		*p* Value
Less *C2* in fetus than mother (*n* = 280)	Positive	*n* = 76 (35.3)	*n* = 25 (38.5)	1.25	0.70	2.26	0.45
	Negative	*n* = 139 (64.7)	*n* = 40 (61.5)				
Equal *C2* in fetus and mother (*n* = 725)	Positive	*n* = 215 (39.6)	*n* = 75 (41.2)	1.10	0.78	1.55	0.59
	Negative	*n* = 328 (60.4)	*n* = 107 (58.8)				
More *C2* in fetus than mother (*n* = 304)	Positive	*n* = 95 (40.8)	*n* = 47 (66.2)	2.93	1.66	5.18	0.0002
	Negative	*n* = 138 (59.2)	*n* = 24 (33.8)				

Presence versus absence of *KIR2DS1* was tested for effect on birth weight as a categorical variable by logistic regression. United Kingdom and Norway cohorts were combined and then analyzed in groups defined by combinations of maternal and fetal *HLA-C* type (Table III). Cohort and sex of the baby were included as covariates.

CI, confidence interval; *n*, number of pregnancies.

Discussion

Maternal inhibitory *KIR2DL1* associates with pregnancy disorders linked to inadequate placentation, whereas maternal-activating *KIR2DS1* associates with increased birth weight. These results suggest that variations in immune system genes, *KIR* and *HLA-C*, are under selection as a result of the necessity to keep human birth weight within the limits defined by the harmful consequences of low and high birth weight. A territorial demarcation between the mother and her fetus resulting from the interaction of maternal KIR on uNK and fetal HLA-C expressed by invading trophoblast could be the basis for achieving such a compromise. Both the *KIR2DL1* and *KIR2DS1* associations, at opposite ends of the birth weight spectrum, occur particularly in pregnancies where the fetus carries an additional *HLA-C* group 2 allele compared with the mother or the fetus has a single *C2* allele that is of paternal but not maternal origin. Because C2 is the ligand for KIR2DL1/S1, this argues strongly for a role of the maternal KIR. It further indicates that maternal KIR responses especially to allogeneic C2 inherited from the father affect pregnancy outcome.

Our finding that the combined presence of maternal *KIR2DS1* with a fetal *C2* of paternal origin results in an average increase of ~250 g in birth weight represents a substantial effect, approaching 10% of the average birth weight and twice the difference between males and females at birth (22). This impact of HLA-C alleles of the C2 group when they are inherited from the father provides one possible explanation for the known paternal genetic influences on birth weight (6, 7, 23). It is also consistent with murine models, where the paternal MHC influences fetal growth (24). It remains to be seen in humans whether uNK respond to an extra dose of fetal C2 provided by the father or specifically to individual paternal HLA-C allotypes. Dissecting out the relative contributions of *C1* and *C2* groups in the mother as well as the father will require HLA typing down to allele level in large numbers of clinically well-characterized pregnancies, but does indicate some influence of education by maternal HLA-C in the uNK response to placentation (25).

Table V. Maternal *KIR2DS1* significantly increases birth weight when the fetus has more *HLA-C2* epitopes than the mother: continuous analysis

Subjects	Effect of *KIR2DS1* on Birth Weight (g)			
	n	Mean Increase (g)	SE	*p* Value
Less *C2* in fetus than mother	280	55	70	0.43
Equal *C2* in fetus and mother	725	43	46	0.35
More *C2* in fetus than mother	304	245	66	0.0002

Presence versus absence of maternal *KIR2DS1* was tested for an effect on birth weight as a continuous variable in linear regression models of subsets of pregnancies >5th birth weight centile defined by maternal/fetal *HLA-C* genotype (Table III). Cohort and sex of the baby were included as covariates.

Mean, average increase in birth weight (in grams) conferred by presence of *KIR2DS1*; *n*, number of pregnancies analyzed.

How these genetic findings translate into functional consequences is still unresolved. C2 group alleles are much stronger and more specific inhibitors for KIR than C1, and this may explain why fetal C2 is so important (26). When the inhibitory KIR2DL1 receptor on uNK binds to fetal HLA-C, expressed by trophoblast cells, poor placentation results; in the opposite scenario, KIR2DS1 ligation to C2 could stimulate uNK to promote placentation and increase birth weight. We have recently shown that a large proportion of uNK do express KIR2DS1, and when they are specifically activated in vitro by binding to HLA-C2 ligands, trophoblast invasion is promoted via NK-derived cytokines such as GM-CSF (27). Hematopoietic stem cell transplantation, a situation analogous to placentation where cells from two individuals are in contact, confirms KIR2DS1 can modulate NK responses to allogeneic C2 in vivo (28).

Our findings make sense when considered in an evolutionary context, as they reflect the nexus of risks associated with the human birth process (14). The evolution of bipedalism in hominids (~4 million years ago) was accompanied by profound anatomical changes to the pelvis. Additionally, subsequent acquisition of a large brain and a globular head required the dangerous rotation of the head during its passage through the pelvis at parturition. This situation is unique to humans and often results in obstructed labor. At the same time, the in utero development of this large brain would have required increased energy supplied from the mother via the uterine arteries. These characteristics of specifically human birth correlate with several features of the evolving KIR and MHC gene complexes. The late appearance of *MHC-C2* groups in primate evolution (in addition to humans, they are only found in gorillas and chimpanzees) may have been associated with the deep interstitial trophoblast that is characteristic of the great apes (14). The clear distinction between *KIR A* and *B* haplotypes is not seen in other primates, including chimpanzees. Maternal KIR2DS1 binding to C2-positive trophoblast could promote arterial transformation allowing for a better feto-placental blood supply. Because of the constraints imposed by the pelvis, however, the limit of human brain size has now been reached and *KIR B* haplotypes will now be selected against because of the complications associated with high birth weight pregnancies.

The prediction of fetal weight has traditionally been by measurement of symphysis fundal height (29). More recently clinicians have used ultrasound to follow fetal growth, but this requires specially trained personnel. These methods are both poorly predictive especially as birth weight increases (30, 31). Our results raise the possibility of using KIR and HLA-C genotyping to

Table VI. Maternal *KIR2DS1* significantly increases birth weight when a single fetal *C2* is paternally but not maternally derived: categorical analysis

Subjects	Maternal *KIR2DS1* Genotype	Median Birth Weight (6–89th Centile) (%)	High Birth Weight (≥90th Centile) (%)	Effect of *KIR2DS1* on Birth Weight			
				OR	95% CI		*p* Value
Single fetal *C2* paternal (n = 204)	Positive	n = 61 (38.9)	n = 29 (61.7)	2.65	1.34	5.26	0.005
	Negative	n = 96 (61.1)	n = 18 (38.3)				
Single fetal *C2* maternal (n = 102)	Positive	n = 28 (37.3)	n = 9 (33.3)	0.81	0.31	2.11	0.67
	Negative	n = 47 (62.7)	n = 18 (66.7)				

Presence versus absence of *KIR2DS1* was tested for effect on birth weight as a categorical variable by logistic regression. United Kingdom and Norway cohorts were combined and then analyzed in groups defined by combinations of maternal and fetal *HLA-C* type (Table III). Cohort and sex of the baby were included as covariates.

CI, confidence interval; *n*, number of pregnancies.

predict pregnancies at risk for fetal growth restriction or macrosomia. Further receptors in addition to KIR can impact uNK function and may also influence birth weight (32). Our findings suggest that the variable KIR interactions with HLA-C that govern NK cell responses could contribute to very different roles in both reproduction and response to infections over the life course of an individual woman (14). These two highly polymorphic human gene systems, KIR and HLA, may drive evolution (survival from infection and successful reproduction) by working alongside each other but always maintained in balance.

Table VII. Maternal *KIR2DS1* significantly increases birth weight when a single fetal *C2* is paternally but not maternally derived: continuous analysis

Subjects	Effect of *KIR2DS1* on Birth Weight (g)			
	n	Mean Increase (g)	SE	*p*
Single fetal *C2* paternal	204	196	81	0.016
Single fetal *C2* maternal	102	42	130	0.75

Presence versus absence of maternal *KIR2DS1* was tested for an effect on birth weight as a continuous variable in linear regression models of subsets of pregnancies >5th birth weight centile defined by maternal/fetal *HLA-C* genotype (Table III). Cohort and sex of the baby were included as covariates.

Mean, average increase in birth weight (in grams conferred by presence of *KIR2DS1*; *n*, number of pregnancies analyzed.

Disclosures

The authors have no financial conflicts of interest.

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