Polymorphism in the epidermal growth factor gene is associated with birthweight in Sinhalese and white Western Europeans

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Birthweight predicts health later in life and is influenced by inherited factors. We investigated the association of the c.61G > A, and c.2566G > A polymorphisms in the epidermal growth factor (EGF) gene [GenBank NM_001963] with birthweight in three groups of healthy pregnant women, and in women with pregnancies affected by fetal growth restriction (FGR). Subjects comprised 171 Sinhalese women with normal pregnancies (Group A), 64 white Western European women with normal pregnancies (Group B), 101 white Western European women with normal pregnancies and their babies (Group C) and 107 women with pregnancies affected by FGR, their partners and their babies (Group D). Maternal EGF genotypes were associated with birthweight of healthy babies of women in Groups A (P = 0.03), B (P = 0.001) and C (P = 0.01). The association persisted following adjustment for confounding by gestational age, sex, maternal weight, parity and smoking habit. The trend from heaviest to lightest birthweights in all these groups was c.61AA > c.61GA > c.61GG and c.2566GG > c.2566GA > c.2566AA. The EGF haplotype associated with lower birthweight (c.61G, c.2566A) was transmitted at increased frequency from heterozygous parents to babies affected by FGR in Group D (P = 0.02). These findings support the hypothesis that growth factors expressed by the feto-maternal unit affect birthweight, and implicates polymorphism in the EGF gene in the aetiology of birthweight variability.

Keywords: birthweight/EGF/sinhalese/white Western European/genetic study

Introduction

Intrauterine growth is an important predictor of perinatal and adult health. Low birthweight is related to an increased risk of diseases in adult life, including coronary heart disease, hypertension and diabetes (McCarton et al., 1996). Fetal growth restriction (FGR) is associated with high perinatal mortality (Kramer et al., 1990) and intellectual impairment later in life (Lau and Rogers, 2004). Inherited factors influence birthweight (Klebanoff et al., 1989; Clausson et al., 2000; Ghezzi et al., 2003), but we know very little about the genes involved. Heritability of birthweight was estimated as 25–40% in one study of offspring of monzygotic and dizygotic twin sisters (Clausson et al., 2000). In another twin study, 30–40% of the variability in birthweight was attributed to maternal gene effects (Nance et al., 1983). In a genomewide screen for quantitative trait loci affecting birthweight, heritability was estimated to be 72% (Arya et al., 2006). There are no reports of studies specifically designed to address the question of heritability of FGR, but Clausson et al. (2000) analysed smallness for gestational age (SGA) as a dichotomous variable within their twin study and reported a heritability of 34%, similar to that for birthweight considered as a continuous variable.

Adequate fetal growth is dependent on the efficient exchange of nutrients and gases via the placenta. The formation of a healthy placenta requires cytrophoblastic invasion of maternal tissues and remodelling of the maternal spiral arteries supplying the placental bed. This process demands the orchestrated expression of growth factors and their receptors, metalloproteinases and their inhibitors and cell adhesion molecules. Growth restricted pregnancies are characterized by deficient trophoblastic invasion, incomplete spiral artery remodelling and increased apoptosis of placental trophoblastic cells (Brosens et al., 1977; Kingdom et al., 2000). Epidermal growth factor (EGF) may be of particular importance in initiating and establishing placental development (Maruo et al., 1992). EGF is expressed at the maternal–fetal interface from very early pregnancy, and stimulates cytrophoblast proliferation and differentiation and the secretion of placental hormones (Maruo et al., 1992). On in vitro assays, EGF promotes invasion of first trimester cytrophoblasts and produces morphologic changes such as extension of pseudopodia and ruffling of the cell membrane (Bass et al., 1994). This suggests that EGF may induce phenotypic differentiation along the invasive pathway. EGF also has anti-apoptotic effects on cultured trophoblast cells.
exposed to hypoxia or cytokines in vitro (Levy et al., 2000; Johnstone et al., 2005).

EGF at the feto-maternal interface is reported to be of maternal origin (Haining et al., 1991; Bass et al., 1994), and in this location EGF could affect trophoblast proliferation, differentiation and inva-
sion. EGF receptors (EGFR) are expressed by cytotrophoblast and are upregulated by EGF in these cells (DePalo and Das, 1988). EGF likely to be of fetal origin is present in amniotic fluid (Watanabe, 1990), and EGF mRNA transcripts and EGF protein have been identi-
fied in amnion and umbilical cord (Rao et al., 1995). Functional EGFR have also been demonstrated in umbilical cord tissue, including vascular endothelium and smooth muscle cells (Rao et al., 1995). An autocrine or paracrine role for EGF in modulating umbilical vascular tone has been proposed, which would in turn regulate the delivery of nutrients to the growing fetus.

Failure to achieve intrauterine growth potential is termed FGR. Low birthweight is used as a surrogate marker for FGR, which has been variously defined as birthweight below the 10th, 5th or 3rd centile of a matched population. Computer software is available for the esti-
mation of a corrected birthweight centile (CBC) which adjusts for gestational age at delivery, fetal sex, maternal parity, weight and height; all of these factors are significantly associated with birthweight (Gardosi et al., 1992). In addition, an association between maternal smoking and low birthweight has been repeatedly demonstrated (Lieberman et al., 1994). We hypothesized that genetic polymorphism in the maternal EGF gene is associated with variation in birthweight.

Materials and Methods

Subjects

We tested our hypothesis initially in a group of normal pregnant Sinhalese women in Sri Lanka (Group A) and carried out replicant studies in two groups of healthy pregnant white Western European women (Groups B and C) from Nottingham, UK. The study was further extended to white Western European maternal–paternal–fetal triads from pregnancies affected by FGR (Group D).

Group A comprised 171 nulliparous Sinhalese women who had normal pregnancies recruited from maternity units in Colombo, Sri Lanka, between August 2001 and January 2003. Group B comprised 64 nulliparous white Western European women who had normal pregnancies recruited between 1993 and 1998 as controls in a study of pre-eclampsia (Morgan et al., 1995); Group C comprised 101 nulliparous and multiparous white Western European women who had normal pregnancies recruited between 2000 and 2003 as controls in a study of FGR and Group D included 107 women who had pregnancies comp-
licated by FGR, their partners and babies recruited as cases for this study of FGR (Tower et al., 2006). All had singleton pregnancies.

FGR pregnancies were identified antenatally by ultrasound scan. Patients were approached if the fetal abdominal circumference, on locally used growth percentile charts, was ≤5th centile. Following delivery, the centile of the CBC was calculated using the GROW software, available at http://www.

perinatal.nhs.uk. This software calculates the birthweight centile adjusted for maternal ethnicity, weight, height and parity, gestation at delivery and fetal sex. FGR pregnancy was defined as CBC ≤ 5; normally grown pregnancies were defined as CBC > 5. Women with a history of chronic hypertension, dia-
abetes, renal, cardiovascular, endocrine or autoimmune disease and pregnancies affected by chromosomal abnormalities were excluded from the study.

All subjects were recruited with the approval of the Ethics Committees of the host institutions, and volunteers provided written informed consent to participation.

Nomenclature


In order to test our hypothesis, we selected two genetic markers with poten-
tial functional effects in the EGF gene: the c.61G > A polymorphism in the 5′ untranslated region of the gene (Shahbazi et al., 2002), which has been reported to modify gene expression and the non-synonymous c.2566G > A polymorph-
ism in exon 14 of the gene, which results in a substitution of the amino acid methionine by isoleucine in the LDL receptor homology domain of EGF (Semina et al., 1996).

Genotyping

DNA samples extracted from venous blood were available for all women and for partners of women in Group D. DNA samples extracted from umbilical cords were available for babies of women in Groups C and D.

The EGF c.61G > A polymorphism was genotyped using a PCR/RFLP assay described previously, using the restriction enzyme Alul (Shahbazi et al., 2002). The EGF c.2566G > A polymorphism was genotyped by mutation specific (MS)-PCR using two allele specific forward primers 5′-TTA TGT GTG GTT CTC AGA TTC CGC TAT GCC ATC AGT AAG and 5′-GGG CTA TGC CAT CAG GAA TA-3′ and a common reverse primer 5′-CAG ATTCCA GCC AAG GAA AGG-3′. The MS-PCR was con-
ducted in a final volume of 15 μl containing genomic DNA, 0.08 μM EGF-G, 0.08 μM EGF-A, 0.1 μM EGF-R, 20 μM of dNTP, 10 mM Tris-HCL, 50 mM KCl, 1.5 mM MgCl2, pH 8.3, 20˚ C and 1 U of Taq DNA Polymerase (Roche Diagnostics, Germany). The reactions were subjected to 35 cycles of denaturation at 94˚ C for 30 s, annealing at 60˚ C for 1 min and extension at 72˚ C for 5 min. The 182-bp and 162-bp PCR products generated from the c.2566G allele and the c.2566A allele, respectively, were resolved by electrohoresis 3.5% agarose.

As quality assurance measures, sequenced positive control samples and DNA-free blanks were included in all batches, and all genotypes were con-
firmed by two independent observers.

Statistical analysis

Hardy–Weinberg equilibrium (HWE) was evaluated by χ2 test. Linear regression analysis was performed to study the association of EGF polymor-
phisms with birthweight in healthy pregnancies, with inclusion of potential con-
 founding variables, including maternal weight, gestation at delivery, fetal sex, parity and smoking habit. The genotype was treated as a quantitative variable coded 0, 1 or 2 to represent the number of variant alleles, consistent with an additive model. Haplotype frequencies and hypothesis testing were performed using programs from the UNPHASED software suite (Dudbridge, 2003), which uses the expectation maximization algorithm to determine common haplotypes, and conducts a likelihood ratio test in a log-linear model. COCAPHASE was used to estimate haplotype frequencies from genotype data and to perform hypothesis testing using haplotypes in case–control association studies; TDTPHASE was used for hypothesis testing in case-parent trios.

Results

The characteristics of pregnancies of all four groups are shown in Table 1. In Group D, 52 women with FGR (48%) had abnormal umbil-
ical artery Dopplers [either raised resistance (>95th centile) or absent/reversed end diastolic flow]. Of these, 15 women (14%) had absent or reversed end diastolic flow. In the FGR group, 49 women (46%) had an amniotic fluid index of less than the 5th centile.

EGF c.61G > A and c.2566G > A genotypes were in HWE in both white Western European and Sinhalese populations, although there were significant racial differences in allele frequencies (Table 2). The two polymorphisms were in linkage disequilibrium in both popu-
lations (D’ > 0.90, r2 > 0.65); the two haplotypes c.61A, c.2566G and c.61G, c.2566A represented over 84% of haplotypes estimated by the maximum likelihood algorithm.

The results of linear regression analysis are shown in Table 2. There was a significant association between maternal EGF genotype and birthweight in healthy pregnancies in Sinhalese (Group A) and
EGF gene polymorphism is associated with birthweight

Table 1: Characteristics of study participants

<table>
<thead>
<tr>
<th>Ethnicity</th>
<th>Group A (n = 171)</th>
<th>Group B (n = 64)</th>
<th>Group C (n = 101)</th>
<th>Group D (n = 107)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal age (years)</td>
<td>Sinhalese</td>
<td>White European</td>
<td>White European</td>
<td>White European</td>
</tr>
<tr>
<td></td>
<td>27.1 (5.1)</td>
<td>27.5 (3.7)</td>
<td>29.3 (5.7)</td>
<td>26.5 (5.8)</td>
</tr>
<tr>
<td>Nulliparous</td>
<td>171 (100%)</td>
<td>64 (100%)</td>
<td>58 (57%)</td>
<td>65 (61%)</td>
</tr>
<tr>
<td>Maternal weight at booking (kg)</td>
<td>48.8 (8.0)</td>
<td>65.1 (9.9)</td>
<td>67.5 (13.1)</td>
<td>61.2 (10.6)</td>
</tr>
<tr>
<td>Gestation at delivery (weeks)</td>
<td>39.4 (1.1)</td>
<td>39.9 (1.4)</td>
<td>38.8 (1.5)</td>
<td>35.1 (4.4)</td>
</tr>
<tr>
<td>Current smoker</td>
<td>0 (0%)</td>
<td>7 (11%)</td>
<td>14 (14%)</td>
<td>52 (49%)</td>
</tr>
<tr>
<td>Fetal weight (kg)</td>
<td>3.02 (0.41)</td>
<td>3.53 (0.46)</td>
<td>3.39 (0.44)</td>
<td>1.87 (0.70)</td>
</tr>
<tr>
<td>Birthweight centile</td>
<td>47.8</td>
<td>52.0</td>
<td>43.5</td>
<td>1.0</td>
</tr>
<tr>
<td>Male infant sex</td>
<td>105 (61%)</td>
<td>40 (62.5%)</td>
<td>52 (52%)</td>
<td>44 (41%)</td>
</tr>
</tbody>
</table>

Data are presented as mean (SD) or number (%), with the exception of BWC, which are shown as median (inter-quartile range)

The presence of each additional c.61A allele and c.2566G allele was associated with a progressive increase in birthweight in babies of women in all three groups (Table 2). Fetal samples from healthy pregnancies were available for the babies of women in Group C only, and showed no evidence of association with birthweight (Table 2).

The association between EGF genotype and FGR was examined by case-control analysis of maternal genotypes, and transmission disequilibrium testing (TDT) of fetal genotypes. Case-control comparison of maternal EGF genotypes in 107 women in Group D and 101 women in Group C indicated no significant association of maternal EGF genotype with FGR (Table 3). TDT of mother-father-baby triads affected by FGR in Group D demonstrated significant haplotype transmission disequilibrium (P = 0.02; Table 4). Specifically, c.61G, c.2566A was the only haplotype transmitted significantly more often than the expected frequency of 0.5 from heterozygous parents to babies affected by FGR (P = 0.03). Increased transmission of the EGF c.61G, c.2566A haplotype was observed in both father-offspring and mother-offspring pairs. Analysis of subgroups demonstrated that this trend was independent of maternal smoking habit during pregnancy, although the smaller number of informative transmissions resulted in a loss of statistical significance on subgroup analysis.

Table 2: Infants’ birthweights in kilograms tabulated according to maternal or fetal EGF genotype

<table>
<thead>
<tr>
<th>EGF c.61G &gt; A</th>
<th>G allele frequency</th>
<th>Genotypes</th>
<th>Adjusted P</th>
<th>EGF c.2566G &gt; A</th>
<th>A allele frequency</th>
<th>Genotypes</th>
<th>Adjusted P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group A mothers&lt;sup&gt;a,b,c&lt;/sup&gt;</td>
<td>0.56</td>
<td>AA 37</td>
<td>AG 78</td>
<td>GG 56</td>
<td>0.209</td>
<td>0.55</td>
<td>GG 41</td>
</tr>
<tr>
<td>Mean birthweight (SD in kg)</td>
<td>3.12 (0.44)</td>
<td>3.01 (0.42)</td>
<td>2.95 (0.38)</td>
<td></td>
<td>3.13 (0.41)</td>
<td>3.02 (0.40)</td>
<td>2.93 (0.41)</td>
</tr>
<tr>
<td>Group B mothers&lt;sup&gt;b,c,d&lt;/sup&gt;</td>
<td>0.34</td>
<td>N 30</td>
<td>AG 25</td>
<td>GG 9</td>
<td>0.001</td>
<td>0.31</td>
<td>GG 32</td>
</tr>
<tr>
<td>Mean birthweight (SD in kg)</td>
<td>3.63 (0.50)</td>
<td>3.50 (0.45)</td>
<td>3.27 (0.19)</td>
<td></td>
<td>3.66 (0.49)</td>
<td>3.44 (0.45)</td>
<td>3.27 (0.17)</td>
</tr>
<tr>
<td>Group C mothers&lt;sup&gt;b,c,d,e&lt;/sup&gt;</td>
<td>0.40</td>
<td>N 35</td>
<td>GA 51</td>
<td>AA 15</td>
<td>0.013</td>
<td>0.35</td>
<td>GG 43</td>
</tr>
<tr>
<td>Mean birthweight (SD in kg)</td>
<td>3.47 (0.42)</td>
<td>3.38 (0.41)</td>
<td>3.22 (0.54)</td>
<td></td>
<td>3.48 (0.41)</td>
<td>3.35 (0.40)</td>
<td>3.18 (0.59)</td>
</tr>
<tr>
<td>Group C babies&lt;sup&gt;a,b,c,d,e&lt;/sup&gt;</td>
<td>0.42</td>
<td>N 32</td>
<td>GA 53</td>
<td>AA 15</td>
<td>0.042</td>
<td>0.37</td>
<td>GG 39</td>
</tr>
<tr>
<td>Mean birthweight (SD in kg)</td>
<td>3.39 (0.39)</td>
<td>3.42 (0.44)</td>
<td>3.22 (0.51)</td>
<td></td>
<td>3.43 (0.36)</td>
<td>3.37 (0.46)</td>
<td>3.24 (0.57)</td>
</tr>
</tbody>
</table>

Data were analysed by linear regression of birth weight on maternal EGF genotype, adjusting for the following confounders: <sup>a</sup>maternal weight at booking; <sup>b</sup>period of gestation; <sup>c</sup>sex of baby; <sup>d</sup>smoking status; <sup>e</sup>parity. All Sinhalese women were non-smokers. The GenBank reference sequence for EGF is NM_001963.

Discussion
The results reported here suggest that maternal EGF genotypes contribute to the variation in birthweight in healthy pregnancies. Demonstration of an association between maternal EGF genotypes and birthweight in three independent sample collections, representing two distinct ethnic groups, and careful correction for possible confounding factors, provides strong confirmation of the validity of these findings. The proportion of variation in birthweight which could be attributed to EGF genotype in this study was between 1% (Group C) and 10% (Group B). Compared with babies born to mothers who were homozygous for EGF c.61G or c.2566A, those born to mothers homozygous for EGF c.61A or c.2566G were on average between 250 and 390 g heavier in white Western European pregnancies, and 170–200 g heavier in Sinhalese pregnancies.

The observation that the EGF haplotype associated with the lowest birthweight, c.61G, c.2566A, is also transmitted preferentially to babies affected by FGR lends further support to the concept of an EGF susceptibility haplotype, in this case, acting in the fetus. It is important to recognize that the term ‘FGR’ does not merely refer to the lower extreme of the birthweight distribution, but implies a pathological failure to achieve birthweight potential due to a failure of trophoblast invasion (Khong et al., 1986). The molecular mechanisms underlying birthweight variability in otherwise healthy pregnancies, and those which result in the pathological features of FGR are therefore likely to differ. SGA is used as a convenient surrogate for FGR, but must inevitably include some babies who are constitutionally small. In this study, sequential antenatal measures of impaired fetal growth, the observation of reduced liquor volume (oligohydramnios) on ultrasound (Lin et al., 1990) and the presence of abnormal umbilical artery Doppler waveforms were utilized to improve the
identification of growth restricted pregnancies (Trudinger et al., 1985), thus minimizing the potential of constitutionally small babies being included along with babies with FGR in Group D. Our data suggest that although maternal EGF genotype plays an important role in determining birthweight in healthy pregnancies, it is the fetal EGF gene which is critical in pathological pregnancies. It should be noted, however, that the lower statistical power in analysis of dichotomous (FGR versus healthy) compared with continuous (birthweight) data may have resulted in failure to detect an effect of maternal genes affecting birthweight. There have been relatively few reports of attempts to identify genes affecting birthweight. In a recent genomewide screen, Arya et al. (2006) identified eight quantitative trait loci linked to birthweight with LOD scores > 1.2. The strongest linkage was on chromosome 6, but interestingly a suggestive locus was also detected on chromosome 4q. The maximum LOD score at this locus was at marker D4S1625, about 30 megabase pairs from the EGF gene.

Of the possible candidate genes affecting birthweight, insulin-like growth factor IGF-1 (IGF) has attracted particular attention since publication of a case report of severe intrauterine growth restriction in a patient with a homozygous partial deletion of the IGF-1 gene (Woods et al., 1996). Fetal homozygosity for functional IGF-1 mutations appears to cause both FGR and post-natal growth failure, whereas heterozygosity may be associated with more subtle manifestations of intrauterine growth restriction (Walenkamp et al., 2005). Interaction between EGF and IGF and IGF-binding protein-3 is well documented (Hembree et al., 1994; Edmondson et al., 1999), and illustrates the complex networks within which maternal and fetal genes must act to determine birthweight.

Acknowledgements

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Table 3: Haplotype frequency estimates of the EGF gene in white Western European women who delivered growth restricted infants (FGR) (Group D) and who delivered normal infants (Controls) (Group C)

<table>
<thead>
<tr>
<th>Maternal EGF haplotype</th>
<th>Group D mothers [FGR] (n = 107)</th>
<th>Group C mothers [Controls] (n = 101)</th>
</tr>
</thead>
<tbody>
<tr>
<td>c.61</td>
<td>c.2566</td>
<td></td>
</tr>
<tr>
<td>G</td>
<td>G</td>
<td>0.04</td>
</tr>
<tr>
<td>G</td>
<td>A</td>
<td>0.32</td>
</tr>
<tr>
<td>A</td>
<td>G</td>
<td>0.62</td>
</tr>
<tr>
<td>A</td>
<td>A</td>
<td>0.02</td>
</tr>
<tr>
<td>Likelihood ratio statistic</td>
<td>0.69</td>
<td></td>
</tr>
<tr>
<td>Degrees of freedom</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>P</td>
<td>0.71</td>
<td></td>
</tr>
</tbody>
</table>

Haplotypes with frequencies <0.03 (representing <6 chromosomes) have been dropped from hypothesis testing. The GenBank reference sequence for EGF is NM_001963.

Table 4: Transmission disequilibrium testing of fetal EGF haplotypes in growth restricted pregnancies (Group D)

<table>
<thead>
<tr>
<th>EGF haplotype</th>
<th>Heterozygous parents</th>
<th>Transmitted</th>
<th>Non-transmitted</th>
</tr>
</thead>
<tbody>
<tr>
<td>c.61</td>
<td>c.2566</td>
<td></td>
<td></td>
</tr>
<tr>
<td>G</td>
<td>G</td>
<td>28</td>
<td>13 (0.46)</td>
</tr>
<tr>
<td>G</td>
<td>A</td>
<td>63</td>
<td>41 (0.65)</td>
</tr>
<tr>
<td>A</td>
<td>G</td>
<td>58</td>
<td>25 (0.43)</td>
</tr>
<tr>
<td>A</td>
<td>A</td>
<td>15</td>
<td>3 (0.20)</td>
</tr>
<tr>
<td>Likelihood ratio statistic</td>
<td>9.53</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Degrees of freedom</td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>P</td>
<td>0.02</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Data are presented for the 82 informative parent–child pairs (164 alleles). The GenBank reference sequence for EGF is NM_001963.

These two SNPs were nevertheless selected for their possible functional effects. The non-synonymous c.2566G > A polymorphism does not lie within the region encoding mature EGF, but causes an isoleucine for methionine substitution in the EGF precursor, a 160 kDa protein which is known to be biologically active (Breyer and Cohen, 1990). The c.61G > A SNP in the 5’ untranslated region of EGF does not coincide with known transcription factor binding sites, but is adjacent to a putative nuclear factor-κB binding site (Shahbazi et al., 2002). EGF production by cultured peripheral blood mononuclear cells from 34 healthy individuals was reported to be significantly higher in cells homozygous for c.61G (Shahbazi et al., 2002). A subsequent study of 42 patients with glioblastoma multiforme reported higher EGF expression in tumour tissue associated with possession of one or two copies of the c.61G allele (Bhowmick et al., 2004). The association of the c.61G allele, which was associated with higher EGF expression in monocytes and glioblastoma cells, with low birthweight is consistent with observations in transgenic mice over-expressing EGF, which had birthweights only half that of their normal littermates (Chan and Wong, 2000).

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