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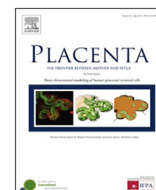

FGF1 and FGF2 mutations in preeclampsia and related features

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Background: Fibroblast growth factor (*FGF*) 1 and *FGF*2 were previously linked with preeclampsia (PE), possibly through altering decidual and placental *FGFR2* expression. Since common variation in *FGF1* and *FGF2* might influence *FGF1* and *FGF2* activity, this study evaluated whether common *FGF1* and *FGF2* variants are linked with PE and associated features.
Methods: The association between *FGF1* rs34011 and *FGF2* rs2922979 SNPs and PE were tested in 300 women with PE, and 300 age-matched control women.
Results: The allelic distribution of *FGF1* rs34011 ($P < 0.001$) but not *FGF2* rs2922979, variants were significantly different between PE cases and control women. Marginal association of *FGF2* rs2922979 was seen after controlling for key covariates. Setting homozygous major allele genotype (1/1) as reference, significantly higher frequencies of heterozygous rs345011, and reduced frequency of heterozygous rs2922979 genotype carriers were seen in PE cases; the distribution of the remaining genotypes were comparable between cases and controls. Carriage of rs2922979 minor allele correlated with fasting glucose ($P = 0.02$), while the presence of rs34011 minor allele was not correlated with PE-associated features.
Conclusions: Our study suggests that the genetic variants of *FGF1* rs34011, more so than *FGF2* rs2922979, may play a role in PE pathogenesis in Tunisian women. These findings need confirmation in other ethnic populations.

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1. Introduction

Preeclampsia (PE), defined by hypertension and proteinuria [1], is a significant cause of maternal and fetal/neonatal morbidity and mortality [2,3], and its susceptibility is influenced by interactions between maternal and fetal factors [4–6]. While its exact physiopathology remains ill-defined, PE is initiated by placental factors that enter the maternal circulation. The pathogenesis of PE involves altered trophoblast cell activity, impaired placental perfusion, vascular endothelial injury, and oxidative stress [4], eventually resulting in endothelial dysfunction [7]. Insofar as angiogenesis is central to normal placental, fetal growth and development [8], several growth factors reportedly regulate angiogenesis [9], and in turn PE pathogenesis. These include acidic fibroblast growth factor (a*FGF*; *FGF*1), and basic fibroblast growth factor (b*FGF*; *FGF*2), both of which are widely expressed during embryonic development, and act by controlling neovascularization.

FGF1 and *FGF2* are prototypical cytokines belonging to the *FGF* family, which contains 22 members of heparin-binding, structurally related cytokines [10]. Although they share several properties, *FGF*-1 and *FGF*-2 differ by their mode of action. The expression of *FGF*1 and *FGF*2 vary in different tissues, and both play distinct roles during differentiation [10]. *FGF*1 is a key regulator of angiogenesis and tumorigenesis [11], and variations in *FGF*1 gene were associated with hypertension, which was attributed to upregulation of

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FGF1 expression in glomerular mesangial and endothelial cells [12]. FGF1 stimulates the branching of the myocardial arteries, and stimulates the formation of new blood vessels, largely by preventing their regression. This prompted recommending inclusion of *FGF1*-based therapeutics in ischemic heart disease [13]. On the other hand, *FGF2* stimulates angiogenesis in vivo, and is a pleiotropic regulator in vitro of the proliferation, migration, differentiation, and survival of many cell types, including endothelial cells, smooth muscle cells, and pericytes [14,15].

Several polymorphisms in *FGF1* and *FGF2* gene were identified, of which the *FGF1* promoter rs34011 (-1385C/T), and the *FGF2* intron-1 rs2922979 (754C/G), were the most investigated. Both variants alter the expression of FGF1 and FGF2 proteins, and were associated with several pathologies, including Alzheimer's Disease, proliferative diabetic retinopathy (PDR), endometriosis (EM), and adenomyosis [16–18]. While it can be hypothesized that polymorphisms in *FGF1* and *FGF2* genes might contribute to PE development, the (likely) association of these variants to PE development was not previously investigated. We evaluate the association of *FGF1* rs34011 and *FGF2* rs2922979 with PE and associated features among Tunisian women with PE.

2. Subjects and methods

2.1. Study subjects

This was a retrospective case-control study, involving 300 unrelated women with PE (mean age 31.3 ± 7.0 yr), who were recruited between May 2012 and June 2013 from the outpatient Gynecology service of Farhat Hached University Hospital (Sousse, Central Tunisia), Fattouma Bourguiba University Hospital (Monastir, Central Tunisia), Taher Sfar University Hospital (Mahdia, Eastern Tunisia), and Gafsa Hospital (Southern Tunisia). The inclusion criteria were PE during natural pregnancy, defined as gravidic hypertension, and assessed after 20 weeks of gestation as systolic blood pressure (BP) > 140 mmHg, diastolic BP > 90 mmHg, and/or rise in systolic BP > 30 mm, or diastolic BP > 15 mm Hg on at least two measurements, 6 h apart, along with significant proteinuria (>300 mg/24 h) or proteinuria of >2+ (determined by the dipstick method).

While 76 PE cases (25.2%) developed severe early-onset PE form before 34 weeks of gestation according to these criteria, no cases of HELLP syndrome (hemolysis, elevated liver enzymes, low platelets) were recorded. The control group included 300 unrelated women with normal pregnancy (mean age 30.5 ± 5.8 yr), who were recruited from the same geographical area, with no known personal or family history of PE. Local ethics committees approved the study protocol, and both PE cases and control women gave written informed consent for their participation in the study. Demographic data of participants and clinical characteristics of patients are shown in Table 1.

2.2. FGF1/FGF2 genotyping

Genomic DNA was extracted from EDTA anti-coagulated peripheral venous blood by the proteinase K/salting-out method. *FGF1* -1385A/G (rs34011) and *FGF2* 754C/G (rs2922979) genotype analysis was performed by PCR-RFLP analysis. For *FGF1* -1385A/G, DNA was amplified using the primers: (forward) 5′-TCA AGC AAT TCT CCT GCC TT-3′, and (reverse) 5′-CCA CTT CAA GGG ATT ATG GTG-3′, followed by an overnight digestion with HhaI (New England Biolabs, Ipswich, MA) at 37 °C. The *FGF2* 754C/G polymorphism was assessed by PCR-RFLP analysis of the 334-bp PCR product, using the following primers: (forward) 5′-AAG CGG CTG TAC TGC AAA AAC-3′ and (reverse) 5′-GGT ACT GGT TTA CAG GGC AAA T-3′. After an overnight digestion with *Hha*I, *FGF1* -1385A/G and FGF2 754C/G digested products were separated by electrophoresis on 3% and 4% agarose gel, respectively. For *FGF1* -1385A/G, the A allele was represented by 53 and 302 bp DNA bands, while the G allele was identified as 53, 141 and 161 bp bands. *FGF2* 754C allele yielded 21, 38, 113 and 162 bp bands, whereas the G allele (which is not cleaved at the restriction site) yielded 38, 113 and 183 bp fragments.

2.3. Statistical analysis

Data were analyzed using SPSS 20 (SPSS Inc., Chicago, IL, USA). Continuous data were expressed as mean ± SD, while categorical variables were presented as percent of total. Intergroup significance was determined by Student's *t*-test (*continuous data*), and $\chi 2$ test (*categorical variables*). Each polymorphism was tested for the Hardy–Weinberg equilibrium (HWE) using $\chi 2$ goodness-of-fit test using SNPStats software (http://bioinfo.iconcologia.net/snpstats/). HWE predicts that comparable allele ratios or rates will be seen in the controls and PE cases unless there is a form of selection for or against this. QUANTO (http://hydra.usc.edu/gxe/) was used in calculating the power, assuming 5% PE prevalence, and 100% genotype call rate. The PE predictors were evaluated by logistic regression analysis, first at the univariate, and later at the multivariate levels. The corresponding crude odds ratio (OR) and 95% confidence interval (95% CI), and adjusted OR (aOR) and 95% CI were calculated; the main covariates that were adjusted for were BMI, region, newborn weight, gestation age, and pregnancy status. Statistical significance was set at $P < 0.05$.

3. Results

3.1. Study subjects

The demographic and clinical features of PE cases and control women are shown in Table 1. Women with PE were matched to controls with respect to age at examination, and delivery methods. Women with PE had significantly higher BMI, elevated systolic and diastolic BP, and gestational age at blood sampling. Significant differences between PE cases and control women were also noted with regards to the newborn weight, and to the pregnancy status. Accordingly BMI, regional origin, newborn weight, gestation age, and pregnancy status were selected as the covariates that were controlled for in subsequent analysis.

3.2. Association studies

The association between *FGF1* rs34011 and *FGF2* rs2922979 and PE in case-control subjects is summarized Table 2. The tested SNPs were in HWE among study subjects. Minor allele frequency (MAF) of *FGF1* rs34011, but not *FGF2* rs2922979, was significantly different between PE cases and control women. Adjusting for key covariates resulted in marginal, but significant differences in MAF of *FGF2* rs2922979 between PE cases and control women. Setting homozygous major allele genotype carrier as reference (OR = 1.00), data from Table 2 demonstrated increased PE risk with *FGF1* rs34011 genotypes. On the other hand, reduced frequency of heterozygous rs2922979 genotype carriers were seen in PE cases, thus suggesting a protective nature to this genotype.

3.3. Association analysis

Multivariate logistic regression analysis models were used to investigate the relationship between carriage of *FGF1* rs34011 and *FGF2* rs2922979 minor allele and PE-associated features; separate

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