

***FTO* gene variant and risk of spontaneous abortion**

Jaroslav A Hubacek^{1,*}, Dita Kasparova², Dana Dlouha¹, Hynek Pikhart³, Martin Bobak³ and Tomas Fait²

1 Center for Experimental Medicine, Institute for Clinical and Experimental Medicine, Prague, Czech Republic

2 Department of Obstetrics and Gynecology, 1st Faculty of Medicine and General Faculty Hospital, Prague, Czech Republic

3 Department of Epidemiology and Public Health, University College London, London, UK

Sir,

We read with interest the study of Andraweera et al., published recently in *Acta Obstetrica et Gynecologica Scandinavica* [1], reporting a strong association between maternal *FTO* (rs9939609) genotype and the risk of miscarriage and recurrent pregnancy loss. Inspired by the report, we attempted to test a related hypothesis that the *FTO* polymorphism is associated with spontaneous abortions when tissue sample from aborted fetus is used instead of maternal DNA. Such an association would indirectly confirm the findings by Andraweera et al. [1].

We compared 457 tissue samples of spontaneous abortions during the first trimester (cases) with a general population sample of 6681 middle-aged adults (aged 45–69 years) used as controls [2]. All cases and controls were genotyped for the *FTO* rs17817449 polymorphism; this single nucleotide polymorphism is in almost complete linkage disequilibrium with neighboring rs9939609. No association between number of children and *FTO* genotype was detected among controls.

The distribution of the *FTO* genotypes did not differ between the cases and controls. The frequencies for GG vs. GT vs. TT alleles were 19.9% vs. 46.8% vs. 33.3% in cases and 19.3% vs. 47.7% vs. 32.9% among controls ($P = 0.92$). The odds ratio for GG vs. GT/TT carriers was 1.04 (95% CI 0.82–1.32; $P = 0.75$).

The *FTO* gene was first identified by a genome-wide association study as an independent genetic risk factor for obesity [3]; more recently, the polymorphism has also been implicated in other conditions, such as diabetes mellitus, myocardial infarction, renal failure or cancer. However, the exact biological role of the *FTO* gene remains unclear [4]. The gene is involved in demethylation of nucleic acids. As the correct fetal development is based on the DNA-methylation-based programming, in theory the *FTO* gene is a promising candidate gene for predisposition to spontaneous abortion. The potential role of *FTO* in fetal development is

further supported by the finding that in humans, *FTO* is highly expressed in placenta and its expression appears to correlate with increased fetal weight and length [5].

The fact that our study did not find any difference in *FTO* genotype between spontaneous abortions and healthy adults may be due to at least two reasons. First, the geographical localization and ethnic composition of our study sample differs from that in the study by Andraweera et al. [1]. Second, there was a major difference in the selection of cases between the studies. Our study has focused on analysis of aborted fetal tissues, not on females with experience of pregnancy loss. It is possible that the methylation status and subsequent fetal development depends on the genetic characteristics/*FTO* variant of females with a history of recurrent pregnancy loss, rather than on characteristics of the fetus. On the other hand, one would expect that even if the main risk factor is maternal genotype it would be detected in studies using fetal DNA (as it reflects the genotype inherited from the mother). Further studies are needed to confirm or refute the putative association between the *FTO* and recurrent miscarriage.

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References

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