FSHB/FSHR genetic variants alter serum FSH levels and prepubertal ovarian follicular growth in healthy girls

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Introduction & Objectives

Single nucleotide polymorphisms (SNPs) related to genes encoding for the Follicle-stimulating hormone (FSH) β-subunit and the FSH receptor (FSHR) affect FSH production (FSHB c.211G>T) and receptor sensitivity/expression (FSHR c.2039A>G & FSHR c.29G>A) in vitro. FSHR c.2039A>G, but not FSHR c.29G>A, has been shown to be associated with increased FSH levels in adult women, while there are conflicting results on FSHB c.211G>T. Previously, we showed that FSHB c.-211G>T and FSHR c.-29G>A delay age at pubertal onset in girls [1]. This study aims to investigate the impact of the FSHB c.-211G>T, FSHR c.2039A>G and FSHR c.29G>A on circulating hormone levels and ovarian morphology in healthy girls.

Subjects & Methods

Participants were recruited as part of two population-based cohort studies (Fig. 1) of healthy children and adolescents: COPENHAGEN Puberty Study (2006 – 2014, a cross-sectional and ongoing longitudinal study) and Copenhagen Mother-Child Cohort (1997 – 2002, including transabdominal ultrasound of the ovaries in a subset of 91 prepubertal girls). Clinical examination, including pubertal breast stage (Tanner’s classification B1 – 5) was performed. Circulating levels of FSH, LH, estradiol, AMH, inhibin-B were assessed by immunoassays. Subjects were genotyped for SNPs by competitive PCR.

Fig. 1 Participants

circulating hormone levels (n=654).

<table>
<thead>
<tr>
<th>Multicenter (n=38)</th>
<th>pubertal morphology (n=118)</th>
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<td>CPH Puberty Study (cross-sectional, n = 440)</td>
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<td>CPH Puberty Study (longitudinal, n = 75)</td>
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<td>CPH Mother-Child Cohort (n = 118)</td>
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Results

FSHR c.2039A>G minor alleles were positively associated with serum FSH (β=0.08, p=0.004), LH (β=0.06, p=0.012) and estradiol (β=0.06, p=0.017) (adjusted for Tanner stages). In a combined model, FSHR c.29G>A & FSHR c.2039A>G was positively associated with FSH levels in early-pubertal girls (B2+B3, n=327, r=0.1, p=0.02) and in young adolescents (B4+B5, n=149, r=0.2, p=0.01) (Fig. 2). Serum AMH and inhibin B levels were not significantly influenced by the SNPs. FSHB c.-211 G>T minor allele count was positively associated with serum LH, but not FSH levels (β=0.08, p=0.0001) (adjusted for Tanner stages). Single SNPs were not associated with follicles counts, however the cumulative major allele count (FSHB c.-211 G>T and FSHR c.-29G>A) was negatively associated with the number of large follicles (≥5 mm) and the ratio of small vs. large follicles (1 – 4 vs. ≥ 5 mm) (n=91, p=0.04 & p=0.04, respectively) (adjusted for Tanner stages). When evaluating each Tanner subgroup, the cumulative minor allele counts of all three variants exhibited the same associations in prepubertal girls (Fig. 3) (B1, n=11, p=0.005 & p=0.04, respectively).

Conclusion

FSHR c.2039A>G was associated with serum FSH, LH and estradiol levels, and for the first time, we show an additional effect of FSHR c.29G>A on serum FSH levels in healthy girls. Moreover, morphological data suggest impaired FSH-induced maturation of ovarian follicles in SNP major allele carriers – in particular FSHB c.-211G>T and FSHR c.-29G>A. These findings underline the essential role of the FSH stimulus for follicle maturation – even in prepubertal girls. Further they may represent the morphologic parallel to our previous findings of delayed pubertal onset in these girls [1]. In general, interaction between FSHB/FSHR genetic variants and physiologic, e.g pubertal timing, as well as pathologic conditions, e.g. polycystic ovary syndrome [2,3] or reduced male reproductive parameters [4], is increasingly elucidated.

References