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

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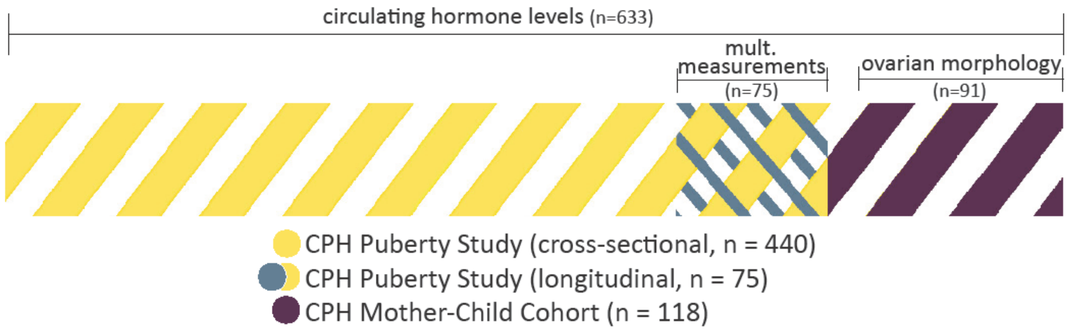
Introduction & Objectives

Single nucleotide polymorphisms (SNPs) related to genes encoding for the Follicle-stimulating hormone (FSH) β-subunit and the FSH receptor (*FSHB* & *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 peripubertal 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



Results

FSHR c.2039A>G minor alleles were positively associated with serum FSH (Beta=0.08, p=0.004), LH (Beta=0.06, p=0.012) and estradiol (Beta=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 (Beta=0.08, p=0.0001) (adjusted for Tanner stages). Single SNPs were not associated with follicles counts, however the cumulative minor allele count (*FSHB* c.-211 G>T and *FSHR* c.-29G>A) was negatively associated with the number of large follicles (≥5mm) and the ratio of small vs. large follicles (1 – 4 vs. ≥ 5mm) (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)

Fig. 2 Serum FSH levels according to Tanner subgroups

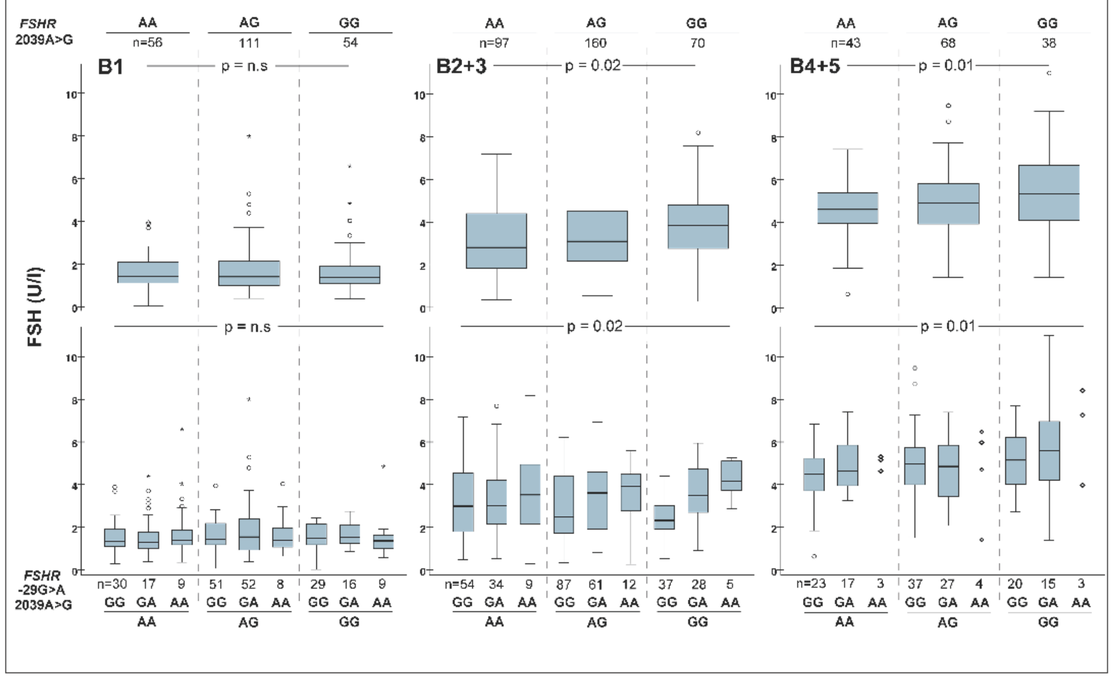
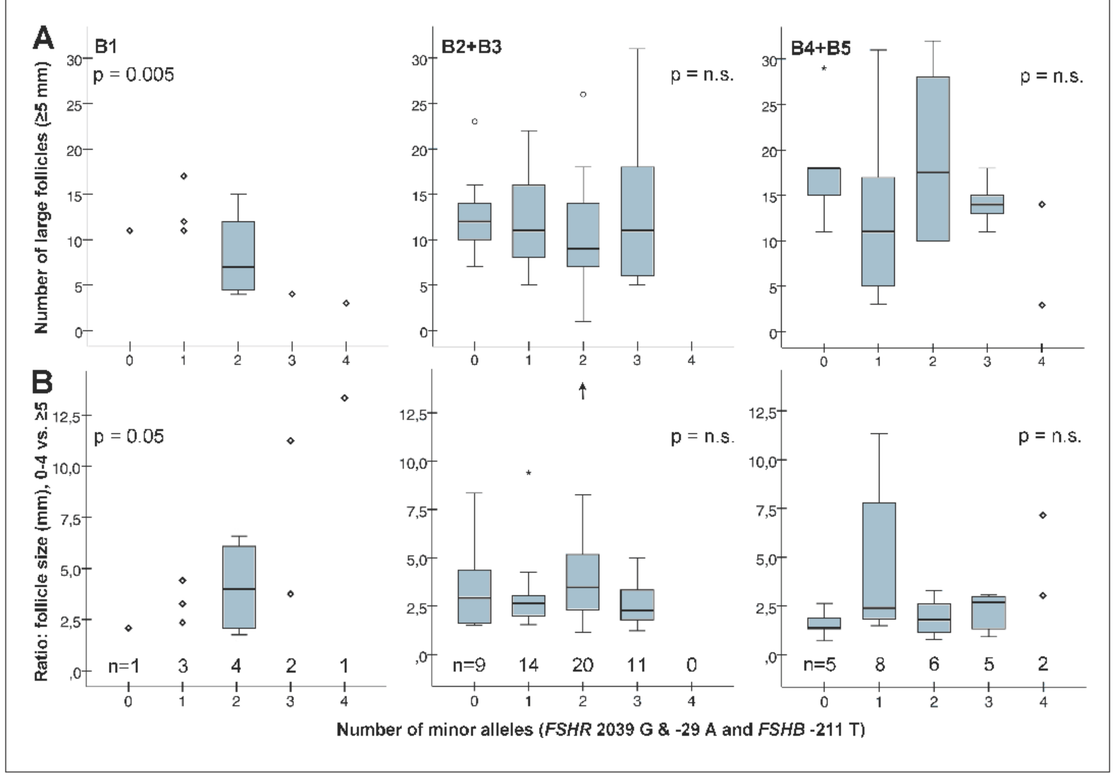


Fig. 3 Ovarian follicles according to Tanner subgroups



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 minor 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.

1. Hagen CP, et al., Pubertal onset in girls is strongly influenced by genetic variation affecting FSH action. Sci Rep 2014;4: 6412.
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3. Simoni M, et al., Mechanisms in endocrinology: Genetics of FSH action: a 2014-and-beyond view. Eur J Endocrinol 2014;170: R91-107.
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