Genetic variation in the FSH signalling pathway affects female reproductive hormones during infancy

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Introduction

Mini-puberty is a brief physiological activation of the hypothalamic-pituitary-gonadal (HPG) axis in the first months of life[1]. Recent studies have shown that genetic variations in the FSH pathway affect peripubertal levels of serum FSH[2] and pubertal timing in girls[3]. The relation between these polymorphisms and early reproductive markers during female mini-puberty has not yet been clarified.

Objectives

Our objective was to evaluate the effect of genetic variations affecting the FSH receptor (single nucleotide polymorphisms (SNPs): *FSHR* -29G>A and *FSHR* 2039A>G) and the FSH beta subunit (SNP: *FSHB* -211G>T) on circulating levels of female reproductive hormones and breast tissue diameter during the postnatal gonadotropin surge.

Results

- *FSHR* -29AA carriers showed significantly lower levels of serum FSH compared to GG and GA (Fig. 1A) and higher AMH levels, but this was not significant (Fig. 1B). *FSHR* -29G>A was negatively associated with FSH (r = -0.208, p = 0.006) and positively associated with AMH (r = 0.328, p = 0.003) in a linear regression analysis
- Significantly lower circulating estradiol was observed in *FSHR* 2039GG carriers compared to carriers of AA and AG (Fig. 1C). Inhibin B was lower in *FSHR* 2039GG carriers, but this was non-significant (Fig. 1D). Carriers of *FSHR* 2039GG had reduced breast tissue diameter, but this was non-significant (Fig. 1E); in a linear regression analysis, breast tissue diameter correlated negatively to *FSHR* 2039GG (r = -0.969, p = 0.022)
- There were no significant findings for *FSHB* -211G>T

Methods

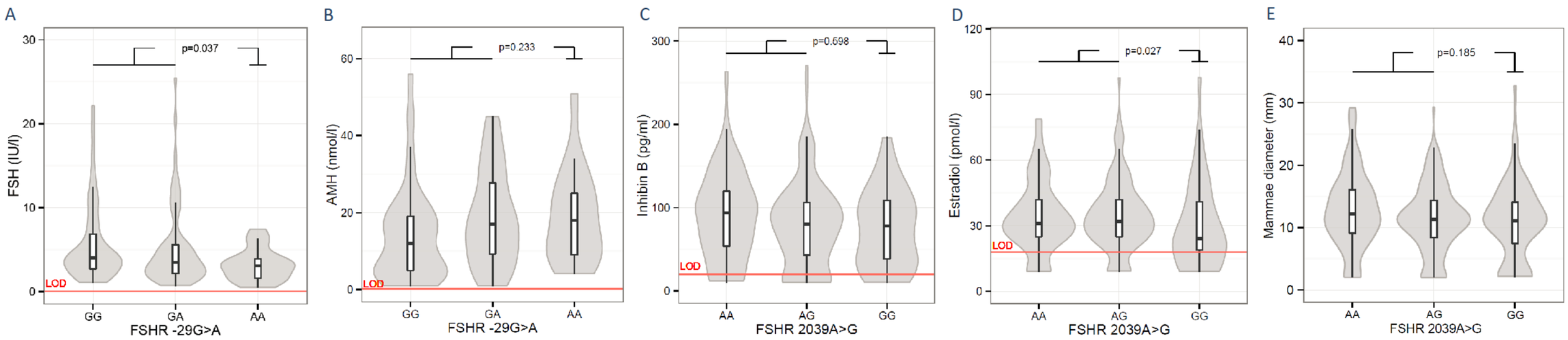
This study is based on data and a bio bank from girls of The Copenhagen Mother-Child Cohort, a birth cohort study of healthy Danish children. At the age of 3 months, breast tissue diameter was determined with a small slide gauge, and blood samples were obtained. Reproductive hormones were measured by immunoassays, and girls were genotyped for FSH SNPs using KASP™ assays. Differences between hormone levels were evaluated with Mann-Whitney U test or Independent Samples T test (e.g. *FSHR* -29GG+GA vs. AA) and in a multiple linear regression analysis, adjusting mutually for the other SNPs.

Table 1 Hormone levels and breast diameter according to genotype

FSHR -29G>A	GG	GA	AA
FSH (IU/L) *n* = 236	4.0 (3.7-4.4) 136	3.5 (2.9-4.3) 83	3.1 (1.6-3.9) 17
AMH (nmol/L) *n* = 223	12 (8-15) 130	17 (12-21) 76	18 (9-25) 17
Estradiol (pmol/L) *n* = 245	32 (29-35) 140	31.5 (28-36) 86	28 (20-35) 19
Inhibin B (pg/mL) *n* = 233	78 (65-90) 134	91.5 (75-102) 82	55 (28-102) 17
Breast tissue (mm) *n* = 397	11.3 (10.6-12.1) 216	12.2 (11.2-13.1) 151	11.7 (9.5-13.9) 30
***FSHR* 2039A>G**	**AA**	**AG**	**GG**
FSH (IU/L) *n* = 236	3.4 (2.9-4.2) 65	4.0 (3.5-4.4) 129	3.8 (3.5-5.3) 42
AMH (nmol/L) *n* = 223	16.5 (12-22) 60	13 (10-17) 119	15 (8-21) 44
Estradiol (pmol/L) *n* = 245	31 (28-36) 66	32.5 (30-35) 134	24 (20-32) 45
Inhibin B (pg/mL) *n* = 233	93.5 (67-108) 62	80 (66-90) 127	79.5 (45-99) 44
Breast tissue (mm) *n* = 397	12.8 (11.6-14.1) 99	11.4 (10.7-12.1) 214	10.9 (9.6-12.2) 84

Hormone values are given as medians (95% CI), while breast tissue diameter is the mean sum of left and right breast (95% CI).

Fig. 1 Hormone levels and breast tissue diameter according to genotype



The figures 1A-E show violin plots of the data. The violin plots are smoothed histograms (or density traces) plotted symmetrically and vertically around a normal box plot. Hence, they graphically present the distributional characteristics of the data batches[4]. For further interpretation of Fig. 1A-E, see the results paragraph.

Conclusion

Our study revealed an effect of FSH SNPs on reproductive hormone levels as well as breast tissue diameter in girls in mini-puberty.

- As expected, reduced *FSHR* transduction (*FSHR* 2039GG) was associated with lower estradiol and inhibin B levels and decreased breast tissue diameter
- We observed an additive effect of minor alleles for *FSHR* -29G>A on FSH and AMH
- We were, however, puzzled to find a *negative* association of *FSHR* -29 minor allele with FSH levels with correspondingly high AMH levels. Whether this reflects immature regulation of the HPG axis during the neonatal gonadotropin surge remains to be elucidated

References

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