Transcriptional Basis of Idiopathic Central Hypogonadism in Isolated Congenital Cryptorchidism with Defective Mini-Puberty

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Objective: Cryptorchidism represents the most common cause of non-obstructive azoospermia in man [Fedder et al., 2004]. Large prospective study showed that despite successful surgery infertility develops if due to defective mini-puberty the transformation of Ad spermatogonia was compromised (high infertility risk group; HIR) [Hadziselimovic, and Hoecht, 2008]. Incidence of a high infertility risk subgroup was reported to be as high as 47% [Bilius et al., 2015]. The available molecular data favors LH deficiency with *EGR4* as a master regulator to be responsible for infertility development [Hadziselimovic et al., 2009]. The study objective was to explore the causative role of isolated congenital cryptorchidism in azoospermia in the context of our previously published GeneChip data by utilizing whole-genome RNA profiling of testicular biopsies and DNA strand-specific RNA-sequencing [Hadziselimovic et al., 2009,2011].

Method: Fifteen cryptorchid patients, aged 7 months to 5 years, were selected based on histological results. During surgery, testicular tissue biopsies were collected and split in half for histological examination and RNA-sequencing. Utilizing semi-thin sections, seven were classified as high infertility risk (HIR) and eight as low infertility risk (LIR) group.

Results: Our previous independent study analyzing differentially expressed genes involved in germ cell and in the hypothalamus-pituitary-testicular axis development (using oligonucleotide microarray technology) reported 59 down-regulated genes in the HIR versus LIR group [Hadziselimovic et al., 2009,2011]. The differential gene expression analyses conducted in this study confirmed 57 of these gene targets. Observed multiple differences in gene expression between high and low-infertility risk group underscores the importance of an intact hypothalamic-pituitary-testicular axis during the period of mini-puberty. The important new finding was a decreased *PROK2, CHD7, FGFR1* and *SPRY4* genes expression in the HIR group (Fig.1). Furthermore, decreased signaling of five mediators of GnRHR gene, *DLX2*, *DLX3, MSX1*, *NR4A1* and *LHX3* genes and two LH-promoter regulating genes *EGR4* and *PITX1* gene were also observed in the high infertility risk group. Thus, insufficient gene expression directly involved in the modulation of αGSU and LHβ expression implies a direct effect on LH secretion and provides a plausible explanation for the reduced LH levels measured in HIR patients [Hadziselimovic et al., 1979, Verkauskas et al., 2016].

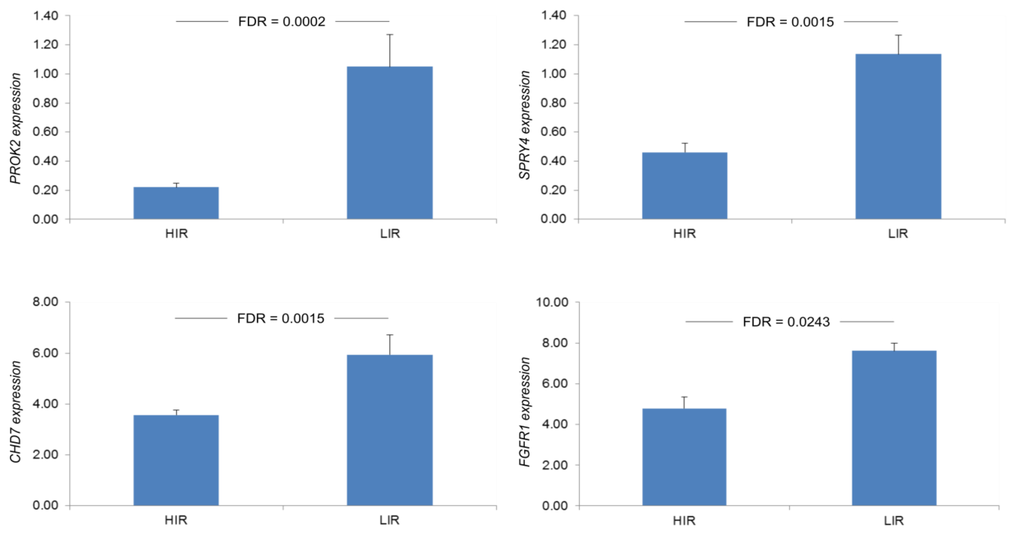

Figure 1.

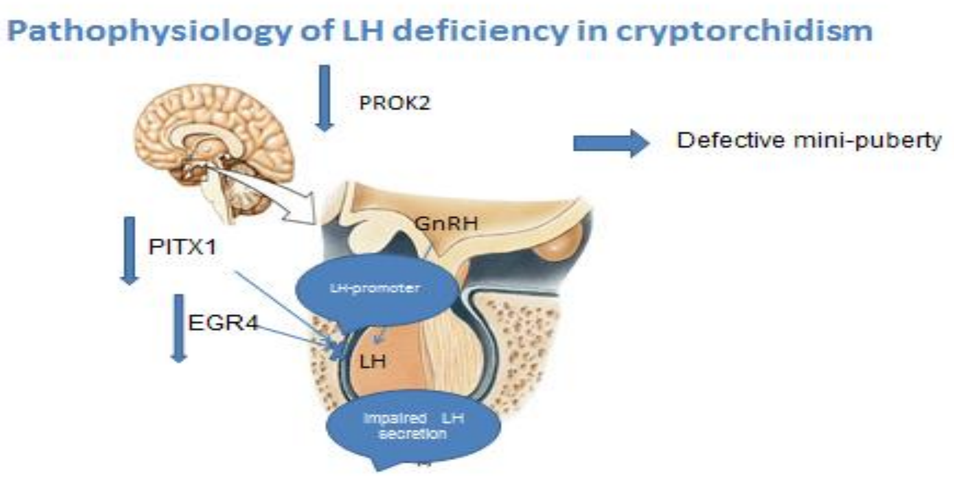

Figure 2.

Conclusion: Presented molecular data strongly supports the theory that insufficient *PROK2*/*CHD7*/*FGFR1*/*SPRY4* genes signal together with reduced *EGR4/PITX1* genes expression is responsible for deficient LH secretion during mini-puberty, and thus resulting in azoospermia or infertility development (Fig. 2).

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Nothing to declare