Male fertility genes located in Y-chromosomal regions display differential mRNA profiles in response to GnRH treatment of cryptorchidism-dependent infertility

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Objectives and aim; Undescended testes in patients with defective mini-puberty contain germ cells that fail to differentiate normally into Ad spermatogonia and ultimately leads to infertility. Six months treatment with the gonadotropin-releasing hormone GnRH increases luteinizing hormone and testosterone secretion and rescues fertility in the majority of pathological cryptorchid testes. Several Y chromosomal genes in the male-specific Y region (MSY) are essential for spermatogenesis, testis development and function, and were associated with azoosperma, infertility and cryptorchidism. In this study, we analyzed the expression of MSY genes in testes with Ad spermatogonia (low infertility risk patients) as compared to testes lacking Ad spermatogonia (high infertility risk) before and after curative GnRH treatment.

Patients and Methods; We selected 15 patients with isolated cryptorchidism, based on histological results, and divided them into 2 groups. Seven belonged to the Ad− (lacking Ad spermatogonia) and 8 to the Ad+ (presenting Ad spermatogonia) group. The patients had a median age of 18.5 months (range 8–59 months) and were age matched. Data from Ad− bilateral cryptorchid boys treated with GnRH (10 µg intranasally on alternate day) following the first orchidopexy (surgery) (4 patients) were retrieved from a randomized study. Initial biopsies revealed no Ad spermatogonia, indicating defective mini-puberty (Ad− group). The second testis was managed by orchidopexy and biopsied 6 months after the initial surgery. Thus, results from 21 biopsies were compared. RNA sequencing data were used to analyze manually selected marker genes. Only genes with at least one read per million, in at least two samples, were included. P values and fold-changes were calculated for the treatment factor and differentially expressed genes were defined as those displaying a false discovery rate (FDR) of less than 0.05 and an absolute change in expression of at least two-fold.

Results; We found 21 genes that are significantly differentially expressed between Ad- and Ad+ samples (FDR<0.05). Furthermore, we identified 23 differentially expressed genes when we compared GnRH treated and untreated Ad- patient samples, all of which showed significant differences (FDR<0.05).

Conclusions; Our findings implicate Y-chromosome genes known to be important for spermatogenesis in the curative hormonal treatment of cryptorchidism-induced infertility. RBMY is critical for male fertility in a mouse and constitutes a major candidate for molecular functions that may help explain the curative effect of GnRHa treatment.