Cryptorchid boys with abrogated mini-puberty display differentially expressed genes involved in sudden infant death syndrome.

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The long QT syndrome is the most frequent a well-established causative factor for the sudden infant death syndrome (SIDS). The non-transcriptional regulation of slowly activating delayed rectifier K+ currents and suppression of L-type Ca2+ currents by testosterone is a regulatory mechanism of cardiac repolarization that potentially contributes to the control of QTc intervals. SIDS has been described in patients with septo-optic dysplasia, Leopard syndrome (both have cryptorchidism in common) and mutations in TSPYL (leading to deficient T secretion). We hypothesize that impaired testosterone secretion during mini-puberty may increase the SIDS risk in cryptorchid boys by altering the expression of gene relevant for this syndrome.

Patients and Methods 15 boys with isolated cryptorchidism were selected and classified seven as Ad− (lack of Ad spermatogonia, abrogated mini-puberty, High Infertility Risk (HIR)) and eight as Ad+ (Ad spermatogonia present, intact mini-puberty, Low Infertility Risk (LIR)). During orchidopexy for bilateral cryptorchidism, biopsies are obtained for histology and RNA-Sequence analysis. Seven HIR patients are randomized for treatment either with surgery followed by GnRHa treatment or surgery alone. Randomization of patients to be treated or to remain untreated was completely unbiased by any parameter other than undescended testes. Among eight biopsies, four were taken before (testis 1) and four were taken after six months of GnRHa treatment. They were compared to six samples, three of each were taken before (testis 2) and after six months of surgery alone, respectively.

Gene ID	Name	log2FC HIR/LIR	FDR HIR/LIR	log2FC GnRHa	FDR GnRHa
CACNA1C	calcium voltage-gated channel subunit alpha 1	- 0.5	**0.01**	**0.5**	**0.026**
HCN4	hyperpolarization activated cyclic nucleotide-gated potassium channel 4	**-2.10**	**0.0005**	**1.21**	**0.008**
KCND3	potassium voltage-gated channel subfamily D member 3	-0.88	0.038	n.d.	n.d.
KCNH2	potassium voltage-gated channel subfamily H member 2	-1.04	0.03	-0.7	0.006
PKP2	plakophilin 2 / paralog PKP1	-1.60	0.0002	n.d.	n.d.
HCN2	HCN potassium channel 2	- 2.3	0.001	n.d.	n.d.
TBX20	T-box 20	-2.35	0.0007	n.s.	n.s.
GPD1L	glycerol-3-phosphate dehydrogenase 1	+ 0.28	0.007	-0.58	0.01
PDE4D	cAMP-specific phosphodiesterase	+ 0.44	0.01	- 0.46	0.04
AKAP9	A-kinase anchoring protein	+ 0.28	0.01	- 0.66	0.005
CALM1	Calmodulin 1	+ 0.27	0.007	- 0.88	0.001

Conclusions; Defective mini-puberty induces differential expression of several genes important for cardiomyopathy and cardiac channelopathies. GnRHa upregulates genes whose loss of function is implicated in SIDS indicating that testosterone may be involved as an etiological factor. Consequently, careful cardiologic surveillance of HIR cryptorchid boys is warranted.

Nothing to declare