Steroid sulfatase contributes to systemic androgen activation in pre-pubertal boys – lessons from steroid sulfatase deficiency

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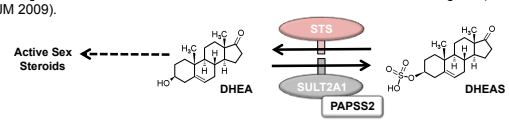
Introduction

The enzyme Steroid Sulfatase (STS) cleaves sulfate groups from steroid sulfate esters, including the adrenal androgen metabolite DHEAS, thereby making DHEA available for downstream activation towards sex steroids. STS deficiency (STSD) due to inactivating deletions or mutations in the *STS* gene causes X-linked ichthyosis (OMIM 308100), a skin condition characterized by dry scales thought to be due to the epidermal accumulation of cholesterol sulfate. A defect in PAPSS crucially supporting DHEA sulfation by SULT2A1 - the opposite enzymatic reaction of STS - results in androgen excess due to increased conversion of DHEA to active androgens (Noordam et al., NEJM 2009).



What is the impact of STS on androgen metabolism during childhood?

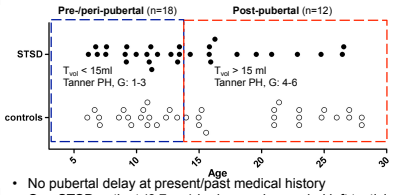
Summary and conclusions

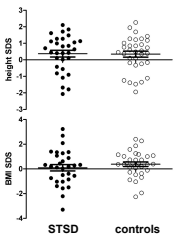
- We have investigated androgen metabolism in a large cohort of patients with STSD; the cohort is genetically characterised and covers two key developmental periods, adrenarche and puberty.
- There are no physical abnormalities in our STSD cohort, including no pubertal delay or clinical signs of hypogonadism
- Sulfated steroids/ androgen precursors are elevated, reflecting the incapacity of de-sulfation in STSD
- Reduced DHEA (and testosterone) levels indicate biochemical evidence of decreased androgen activation by STS
- 5α-reductase activity is increased in STSD, suggesting increased androgen activation as a compensatory mechanism for the decreased availability of precursor steroids for downstream conversion towards active androgens
- An increased DHEA/DHEAS ratio during adrenarche suggests a distinct role for STS in androgen metabolism before puberty

Results

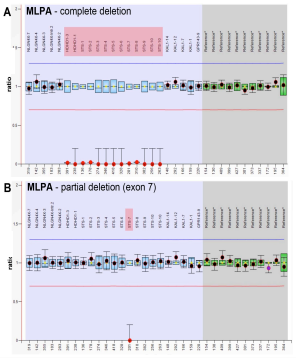
Patients characteristics and genetic analysis

- 30 STSD patients (age range: 6-27 yrs) and 38 male, age- and BMI-matched healthy controls.

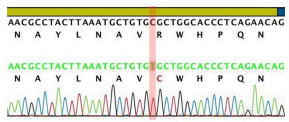




- No pubertal delay at present/past medical history
- One STSD patient (6.7 yrs) had an undescended left testicle
- All patients had an established diagnosis of STSD/XLI based on typical clinical (n=23) or biochemical findings (n=7).



Exon 9: g.114,414 C>T; c.1,360 C>T; **p.R454C**



Multiplex-ligand-dependent probe amplification (MLPA):
- 27 STSD had a complete deletion of the *STS* gene and the neighbouring HDHD1 gene (90%)
- One patient had a partial deletion of exon 7 only

Saenger sequencing:
- Two brothers were found to harbour a previously described missense mutation (p.R454C).

No deletions of further neighbouring gene loci were identified.

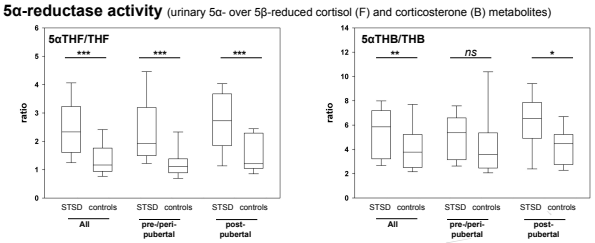
Urinary steroid profiling (GC/MS)

Urinary androgen metabolite secretion (µg/24h)

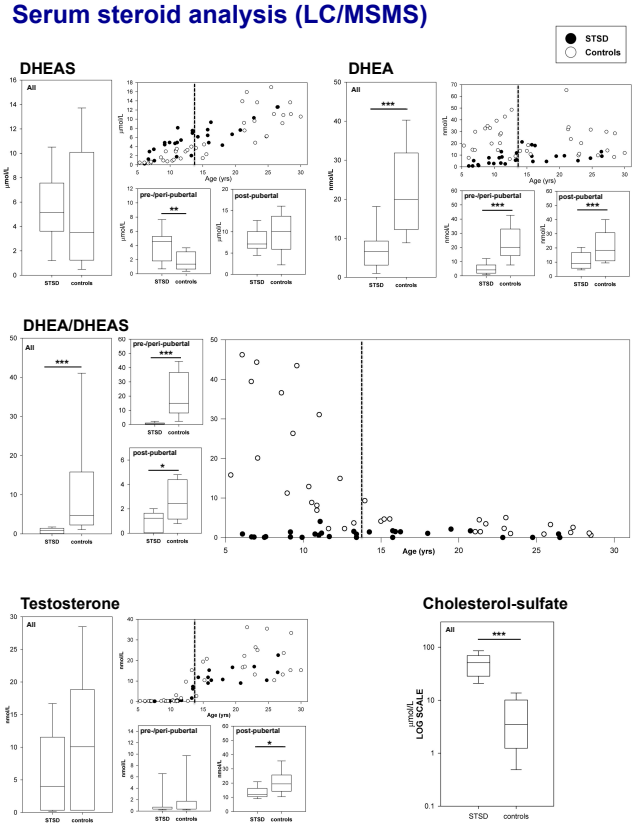
	Metabolite	Subgroup	STSD*	controls*	p-value**
Active androgen metabolites	**Androsterone**	all	409 (155, 2192)	403 (117, 2301)	0.82
		pre-/peri-pubertal	143 (60, 309)	124 (56, 206)	0.47
		post-pubertal	2440 (1521, 3670)	2468 (2035, 3365)	0.87
	Etiocholanolone	all	231 (96, 1018)	329 (98, 1569)	0.31
		pre-/peri-pubertal	109 (70, 130)	110 (40, 229)	0.76
		post-pubertal	1021 (917, 1332)	1663 (1045, 2048)	0.16
	DHEA	all	207 (117, 716)	43 (10, 165)	**< 0.001**
		pre-/peri-pubertal	105 (52, 236)	11 (3, 34)	**< 0.001**
		post-pubertal	626 (291, 1905)	165 (62, 784)	**0.04**
Androgen precursor metabolites	**16-OH DHEA**	all	520 (211, 767)	115 (39, 366)	**< 0.001**
		pre-/peri-pubertal	217 (137, 535)	39 (13, 76)	**< 0.001**
		post-pubertal	744 (656, 985)	398 (170, 580)	**< 0.001**
	5-PT	all	160 (83, 318)	51 (13, 163)	**0.005**
		pre-/peri-pubertal	77 (53, 69)	14 (4, 62)	**< 0.001**
		post-pubertal	338 (189, 792)	234 (78, 366)	0.07
	5-PD	all	401 (295, 657)	143 (92, 317)	**< 0.001**
		pre-/peri-pubertal	289 (180, 380)	79 (54, 131)	**< 0.001**
		post-pubertal	687 (529, 1062)	317 (215, 364)	**0.001**

*: median (25th, 75th centile)
**: Mann-Whitney non-parametric test

5α-reductase activity (urinary 5α- over 5β-reduced cortisol (F) and corticosterone (B) metabolites)



Serum steroid analysis (LC/MSMS)



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