Phenotypic And Genetic Assessment Of Boys With A Suspected XY Disorder Of Sex Development

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Background

Boys who present with atypical genitalia pose a great diagnostic challenge and it is unclear as to who should be investigated.

Objectives

1. To determine the prevalence of biochemical and molecular genetic tests in a cohort of boys with XY DSD
2. To collate the phenotypes of patients with results of laboratory investigations and presence of associated malformations (AM).

Methods

New and existing cases of XY DSD who had endocrine and/or genetic evaluation during 2016 and 2017 were identified. Information on clinical assessment including family history, appearance of external genitalia, biochemical and molecular genetic investigations and associated abnormalities was obtained from the medical records.

Results

	Median (Range) or N (%)
Age (years)	0.9 (0.01,17.91)
External Masculinization Score (EMS)	9 (2, 12)
Positive Family History of DSD	13/54 (24)
Parental Consanguinity	3/54 (6)
Associated Malformations	31/54 (57)
Recognised Genetic Syndrome	10/54 (19)

Table 1. Clinical Characteristics (n=54)

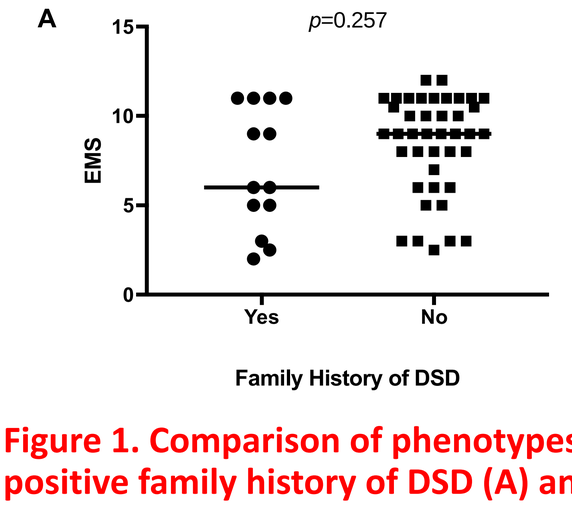

Figure 1. Comparison of phenotypes of 46 XY DSD boys with or without positive family history of DSD (A) and associated malformations (B)

No significant differences in phenotypes between those in whom associated malformations and family history of DSD were present or not

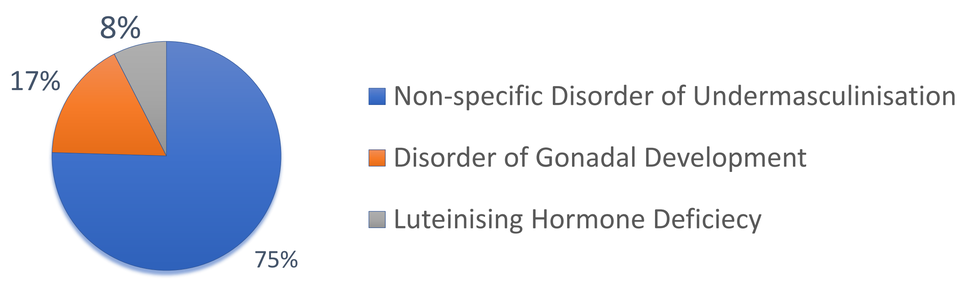

Figure 2. Endocrine assessment results (n=53)

Endocrine assessment revealed an abnormality in 25% of cases

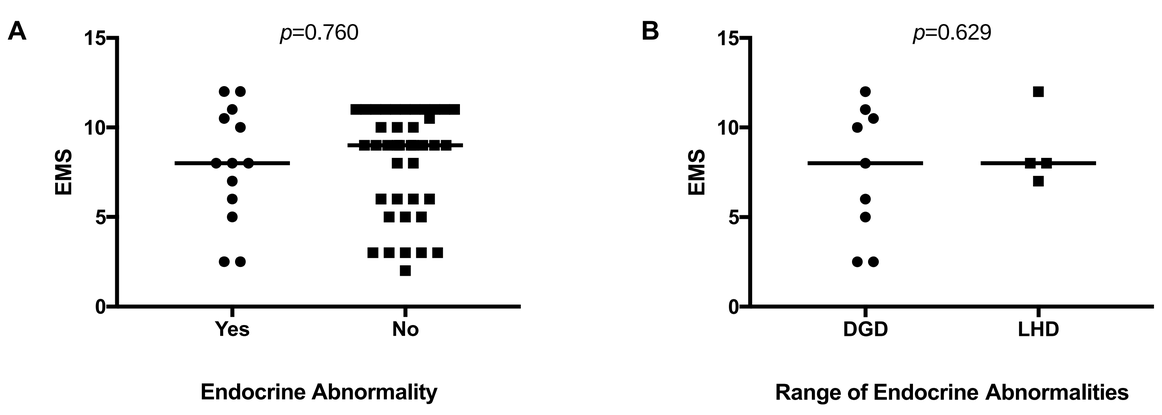

Figure 3. Comparison of phenotypes of boys with or without endocrine abnormality (A) and between subgroups of abnormalities identified (B)

No significant differences in phenotypes between 46 XY DSD boys with normal and abnormal endocrine investigations were found

Results continued

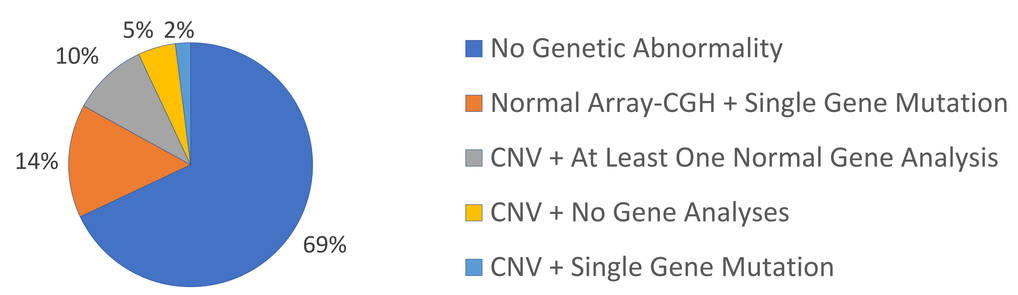

Figure 4: Genetic assessment results (n=42)

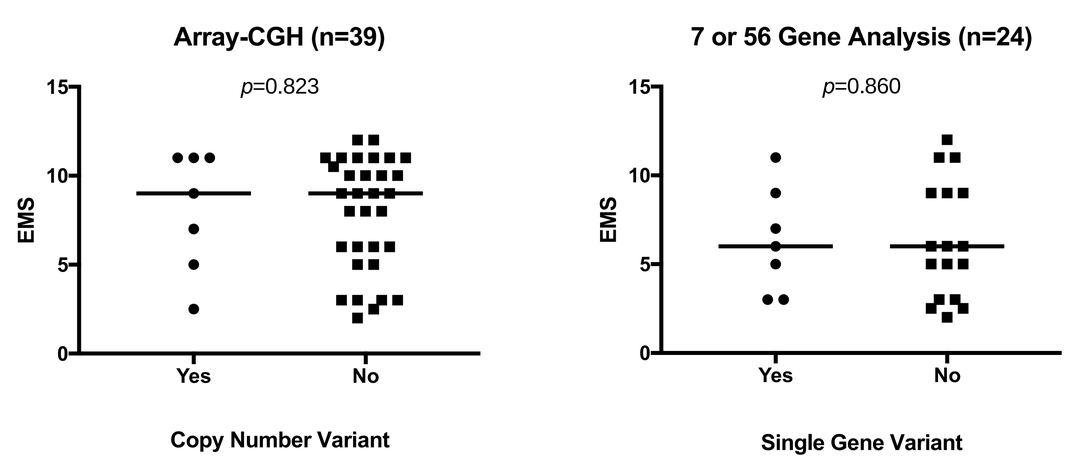

Figure 5. Comparison of phenotypes of XY DSD boys with or without genetic abnormality identified by Array-CGH and Gene Panel Analysis

The appearance of external genitalia seems to be unrelated to the presence of genetic abnormality

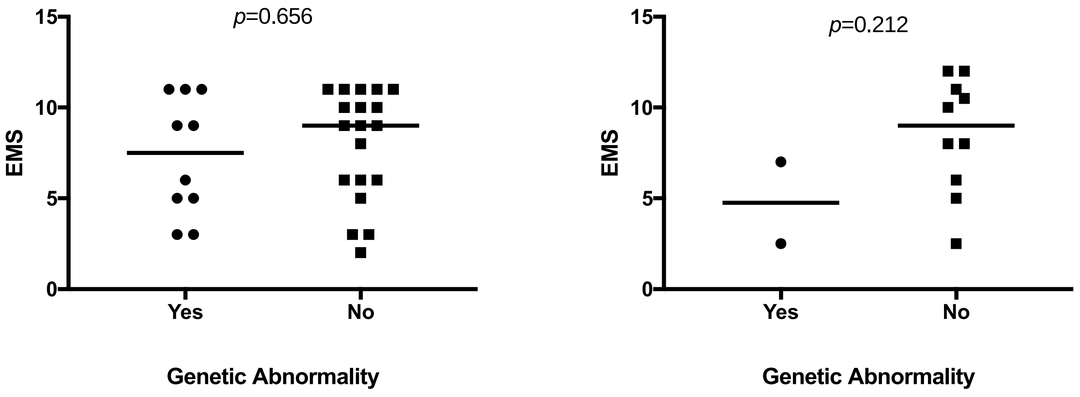

Figure 6. Collating phenotypes to the results of genetic investigations in 46 XY DSD boys with normal and abnormal endocrine tests

Of the 12 boys with genetic abnormalities and available results of endocrine assessment, 83% had normal testes function

Endocrine Results	EMS	FH	Gene Variants	Pathogenicity Class (ACMG, 2015)	Inheritance Pattern	CNV
NSDUM	11	-	N			Del 4q35.1-q35.2 Dup 10q24.2-q26.3
NSDUM	11	-	N			Dup 4q11-q13.1
NSDUM	11	+	N			Dup 8p11.21-p11.1
NSDUM	9	-	N			Dup 11q24.2-q24.3
LHD	7	-	*ANOS1**	V	XLR	Dup 16p13.11
NSDUM	5	+	N			Del 2q14.1
DGD	2.5	-	N			Del 1q44
NSDUM	9	-	*HSD17B3*** x 2	III, IV	AR	N
NSDUM	6	-	*HSD3B2*** *POR***	V III	AR AR	N
NSDUM	5	-	*HSD3B2*** *MAP3K1*** *SPRY4***	V III III	AR AD AD	N
NSDUM	3	+	*HSD17B3*** x 2	III, IV	AR	N
NSDUM	3	-	*PROK2***	IV	AD	N
NA	11	+	*GATA4***	III	AD	N

Zygosity: * hemizygous, ** heterozygous

Table 2. Genetic Abnormalities Identified in XY Boys

Conclusions

The severity of under-masculinization of external genitalia in XY DSD boys seems to be unrelated to the presence of endocrine and array-CGH genetic abnormalities and is not associated with concomitant morbidities. A comprehensive diagnostic strategy that includes more extended genetic investigation requires further exploration.

57ESPE 233--P1

Sex differentiation, gonads and gynaecology or sex endocrinology

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Poster presented at: 57th ESPE 2018 Meeting ATHENS GREECE 27-29 September 2018

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