ENDOCRINE & MOLECULAR GENETIC FINDINGS IN XY BOYS INVESTIGATED FOR A DISORDER OF SEX DEVELOPMENT: THE GLASGOW EXPERIENCE

M. ALIMUSSINA[1], S. PATJAMONTRI[1], A.K. LUCAS-HERALD[1], M. MCMILLAN[1], J.D. MCNEILLY[3], L.A. DIVER[2], E.S. TOBIAS[2,4], R. MCGOWAN[1,2], S.F. AHMED[1]

1. Developmental Endocrinology Research Group, University of Glasgow, Royal Hospital for Children, Glasgow, UK
2. West of Scotland Centre for Genomic Medicine, Queen Elizabeth University Hospital, Glasgow, UK
3. Biochemistry Department, Queen Elizabeth University Hospital, Glasgow, UK
4. Academic Medical Genetics and Pathology, University of Glasgow, Queen Elizabeth University Hospital, Glasgow, UK

ESPE 2021
The 59th Annual Meeting Online
22-26 September 2021

INTRODUCTION

Advances in diagnostic capability in the field of disorders of sex development (DSD) hold great promise but need a regular review.

AIM

To study the range of endocrine and molecular genetic variation in a group of boys undergoing investigation for XY DSD.

METHOD

157 boys with median age of 0.9 years (0, 18) evaluated by the DSD Diagnostic Board in Glasgow from 2016 to 2021 were included.

Information on clinical assessment including family history of DSD, presence of associated abnormalities, the appearance of external genitalia calculated as an External Masculinisation Score (EMS), biochemical and molecular genetic investigations (chromosomal microarray and 7/21/56 gene panel analysis) was obtained from the medical records.

Sequence variants were classified according to ACMG guidelines and, in addition to pathogenic and likely pathogenic variants, variants of uncertain significance (VUS) were assigned as causative or coincidental, depending on whether the phenotype was consistent with genotype, or not.

RESULTS

Table 1. Clinical characteristics of the cohort

N=157	Median (Range) or N (%)
Age, years	0.9 (0,18)
External Masculinization Score (EMS)	8.5(2,12)
Positive Family History of DSD	43 (27)
Parental Consanguinity	11 (7)
Associated Malformations	98 (62)
Recognised Genetic Syndrome	12 (8)

Figure 1. Comparison of phenotypes of XY DSD boys with or without family history of DSD, associated malformations, and between subgroups of endocrine abnormalities identified

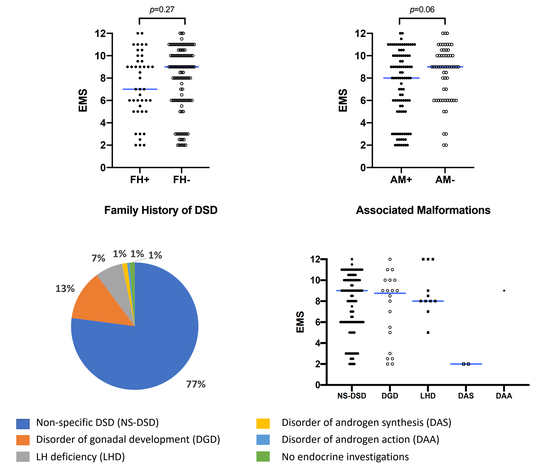
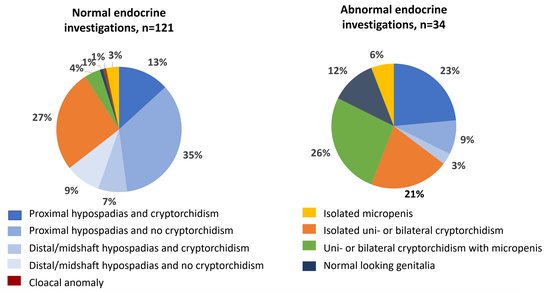


Figure 2. Range of phenotypes of boys with XY DSD with normal and abnormal endocrine investigations



Endocrine assessment revealed an abnormality in 22% of cases with gonadal dysgenesis being the most common endocrine disorder and proximal hypospadias being the commonest phenotypical feature

Figure 3. Comparison of phenotypes of XY DSD boys with or without genetic abnormality identified by chromosomal microarray

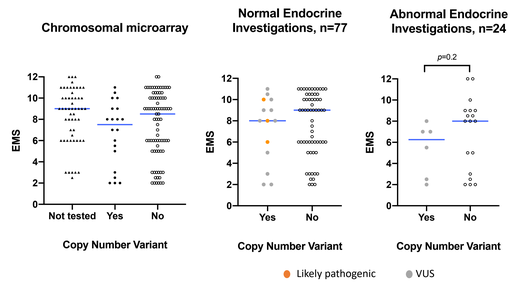
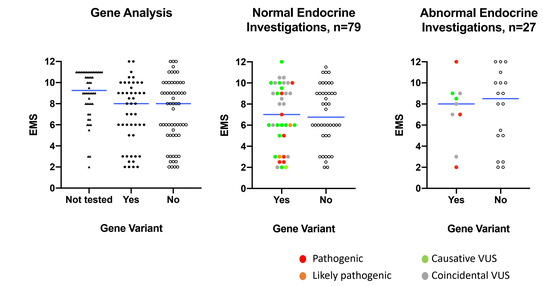
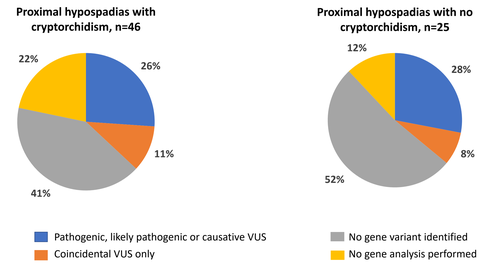


Figure 4. Comparison of phenotypes of XY DSD boys with or without genetic abnormality identified by gene analysis



The degree of undermasculinisation seems to be unrelated to the presence of genetic abnormality

Figure 5. Genetic findings in patients who had proximal hypospadias with and with no cryptorchidism at the time of the first clinical presentation



Among boys with with proximal hypospadias (n=71), about ¼ had genetic findings that were consistent with the phenotype

CONCLUSIONS

The degree of undermasculinisation in boys with DSD appears unrelated to the presence of molecular genetic or endocrine abnormalities. Causative genetic variants are as common as one in four among patients with proximal hypospadias. Coincidental VUS are commonly encountered in patients with non-specific DSD who have no evidence of a gonadal dysfunction or disorder of androgen synthesis, and this requires a careful and standardised interpretation.

ACKNOWLEDGEMENTS

Funder: Bolashak Scholarship (Kazakhstan)

CONTACT INFORMATION

Email: m.alimussina.1@research.gla.ac.uk