Introduction

Disorders of sex development (DSD) are a group of conditions affecting the reproductive system, commonly present in early infancy.

It may arise as a result of gonadal, adrenal or hormonal dysfunction and the overall birth prevalence has been reported to be as high as 1 in 300 (1).

It is recognized that DSD can be associated with various other conditions (2).

Objective

To report the frequency and range of DSD phenotypes observed in DDD participants who have one or more associated undiagnosed "neurodevelopmental delay" diagnostic Human Phenotype Ontology (HPO) terms and to identify novel genetic associations with DSD.

Method

Retrospective review of anonymized data from participants in the DDD study.

Patients included

We received data on a total of 603 patients with any HPO term under "Abnormality of the genital system:"

"Abnormality of the genital system:"

These data were extracted from 743 phenotyped DDD patients.

Of the 603 patients, 370 had at least one diagnosis within the HPO term "Neurodevelopmental delay:"

"Neurodevelopmental delay:"

Results

Of these 603 children, 50% (91) had at least one "neurodevelopmental delay" diagnosis with a total of 44 DSD phenotypes, the majority, 420 (94%) abnormalities of the external genitalia.

Of the male external genitalia abnormalities, 212 (54%) were testicular, 74 (19%) were hypospadias, 57 (15%) were penile and 47 (12%) were other abnormalities.

Testicular abnormalities included: unilateral cryptorchidism, bilateral cryptorchidism, hydrops and other phenotypes.

Causative mutations were found in 21 DSD genes (https://decipher.sanger.ac.uk), confirming a range of syndromic diagnoses with associated DSD, including KSBD syndrome, Muir-Torre syndrome, Alpha-thalassemia/mental retardation syndrome, Kabuki syndrome and Donnai-Barrow syndrome.

Of these likely pathogenic mutations, 14 (43%) were found in DSG2 genes not previously associated with DSD.

Neurodevelopmental phenotypes

Abnormalities of external male genitalia

Testicular abnormalities

Conclusion

The association of DSD with learning difficulties is not uncommon and a range of DSD phenotypes may be encountered. Recognition of these associations should not be overlooked in the management of patients with complex conditions.

External male genital malformations are common, particularly cryptorchidism, in the undiagnosed neurodevelopmental group. A proportion of these may be acquired (4).

6 of 14 (43%) mutated genes were found in DSG2 genes not previously reported to be associated with DSD.

Exome sequencing through projects like DDD increases diagnostic yield and the identification of mutations in developmental genes may improve our understanding about the pathogenesis of DSO.

UK wide studies such as the DDD study may inform our practice through increasing our knowledge of conditions commonly associated with DSD and may help to identify novel genetic associations. Increasing ability to establish molecular diagnosis will further improve clinical management and accurate genetic counselling for the families (3).

References


Acknowledgments

Thank you to the DDD study at the Sanger Institute, all the patients and families who participated in the study.