

# The Frequency And Range Of Disorders Of Sex Development (DSD) And Novel Genetic Associations In Children With Neurodevelopment Disorders – Insights From The DDD Study



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## 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'.

These data were extracted from 7439 phenotyped DDD patients.

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

## Results

Of these 603 children, 370 (61%) had at least one 'neurodevelopmental delay' diagnosis with a total of 447 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.

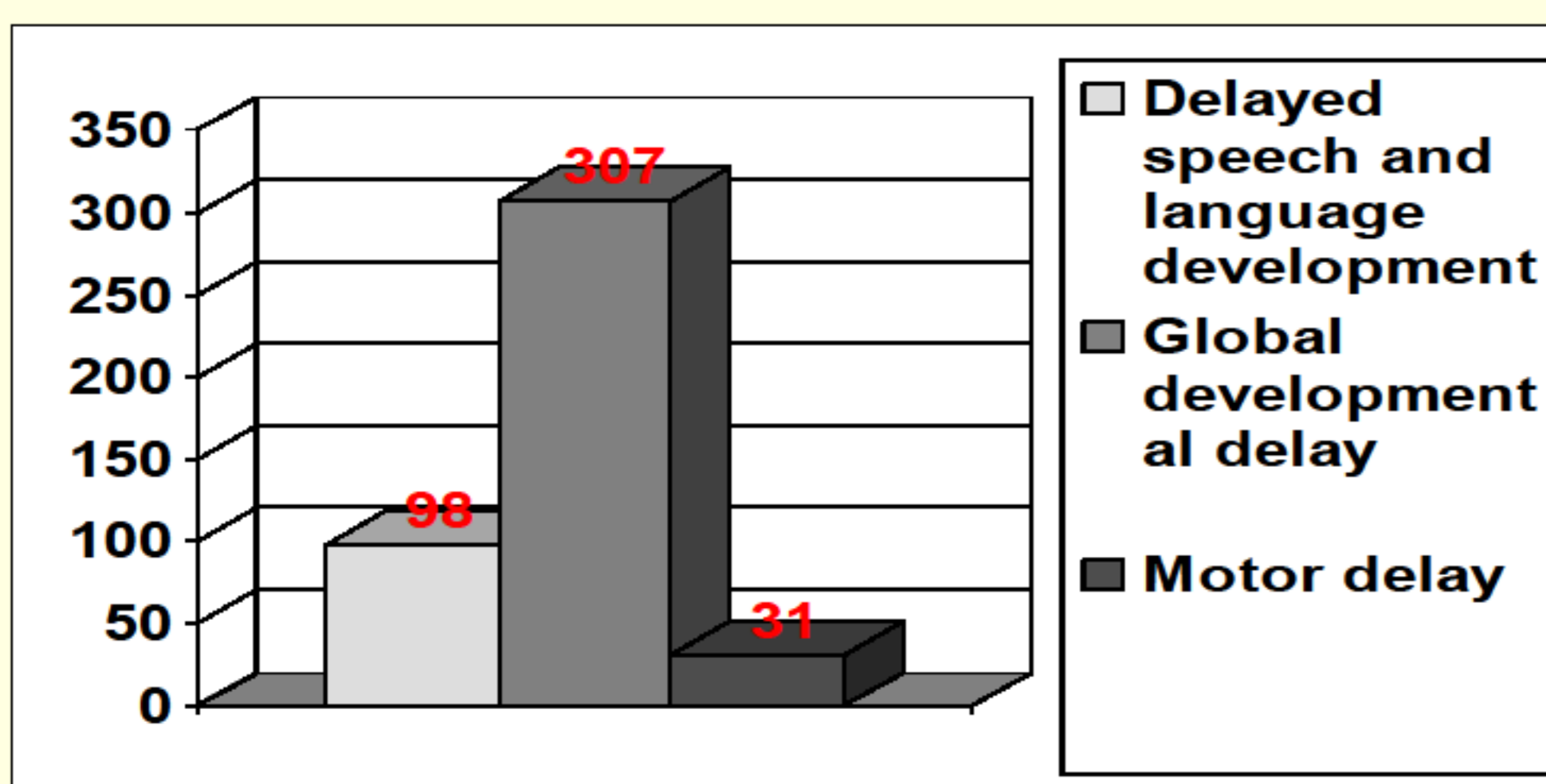
Testicular abnormalities included: unilateral cryptorchidism, bilateral cryptorchidisms, hydrocele and other phenotypes.

Causative mutations were found in 14 DDG2P genes (<https://decipher.sanger.ac.uk/>), confirming a range of syndromic diagnoses with associated DSD, including: KBG syndrome, Meier-Gorlin syndrome, Alpha-thalassemia/mental retardation syndrome, Kabuki syndrome and Donnai-Barrow syndrome.

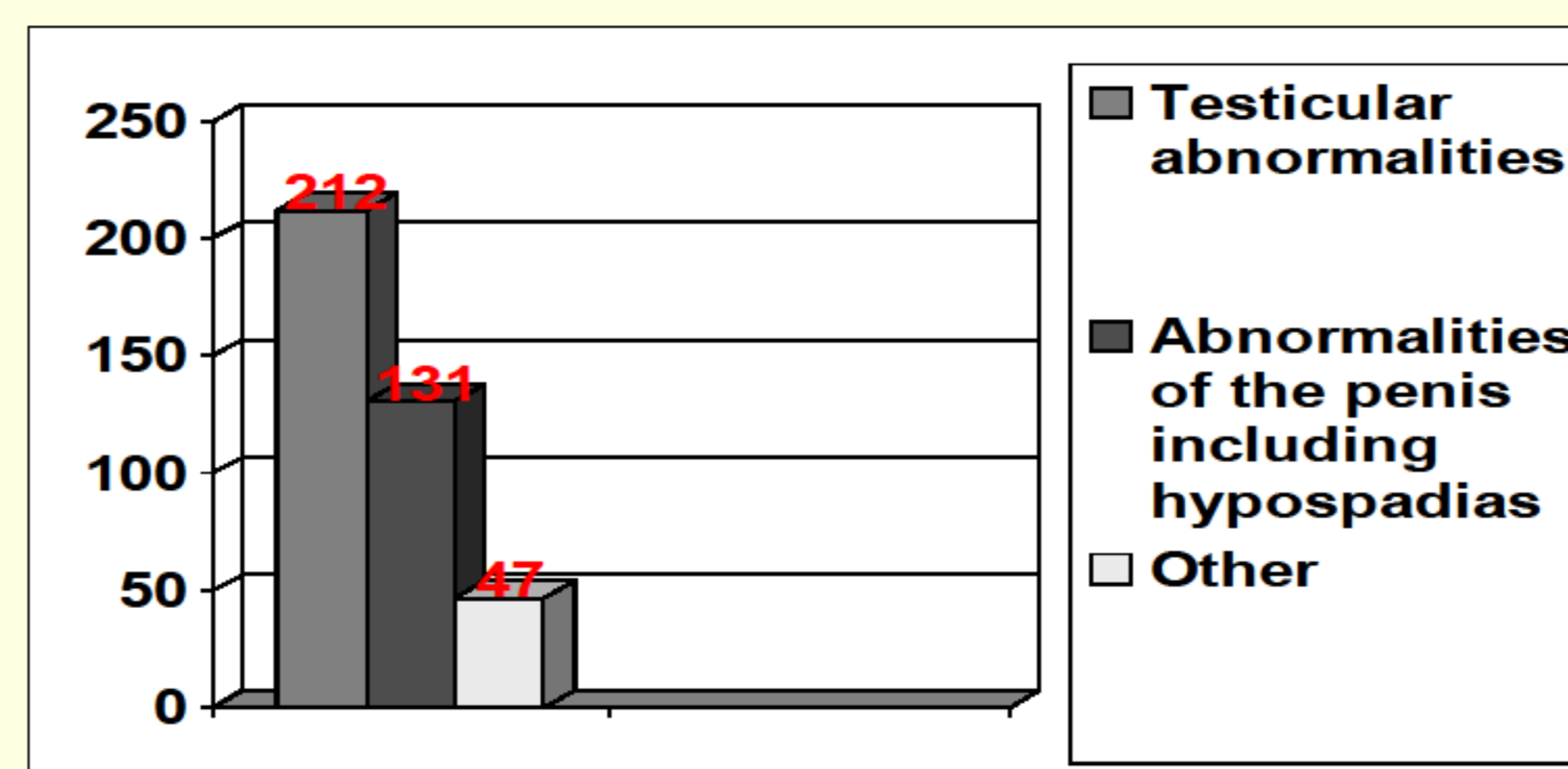
Of these likely pathogenic mutations, 6 of 14 (43%) were found in DDG2P genes not previously associated with DSD.

Gene	Phenotype described before	DSD phenotype described before	DSD phenotype
PACS1	Mental retardation	Cryptorchidism (Schuurs-Hoeijmaker et al.2012)	Hypoplastic male genitalia
ATRX	Alpha-thalassemia, myelodysplasia syndrome, somatic Alpha –thalassemia, mental retardation syndrome Mental retardation-hypotonic facies syndrome, x-linked	Hypospadias, cryptorchidism, underdevelopment of scrotum, small penis	Genital hypoplasia
LRP2	Donnai-Barrow syndrome	Genitourinary abnormality rare – uterine abnormality reported Bicornate uterus (OMIM)	Clitoromegaly
CHD2	Epileptic encephalopathy, childhood onset	None	Micropenis
ARHGAP31	Adams-Oliver sy1, congenital scalp defects, distal limb reduction anomalies	None	Micropenis, B/L cryptorchidism
B4GALT7	Ehler-Danlos syndrome, progeroid, type 1	Bilateral cryptorchidism – 2 cases, Hernandez	Tight penoscrotal web
EP300	Colorectal cancer, somatic, Rubinstein-Taybi syndrome type 2	Hypogonadism and cryptorchidism (OMIM)	Cryptorchidism
RARS2	Pontocerebellar hypoplasia, type 6	None	Cryptorchidism
FOXP1	Mental retardation with language impairment and autistic features	None	Cryptorchidism
OCRL	Dent disease 2, Lowe syndrome	None	Cryptorchidism
KDM6A	Kabuki syndrome 2	Hypospadias, cryptorchidism, and (more rarely) micropenis hypoplastic labia (Armstrong et al 2005).	Cryptorchidism
CDT1	Meier-Gorlin syndrome 4	Hypoplastic genitalia and hypoplastic breasts-Guernsey et al 2011	Bilateral cryptorchidism
SCN2A	Epileptic encephalopathy, early infantile 11, seizures, benign familial infantile type 3	None	Cryptorchidism
ANKRD11	KBG syndrome	Cryptorchidism Tekin et al (2004), Brancati et al (2004)	Cryptorchidism

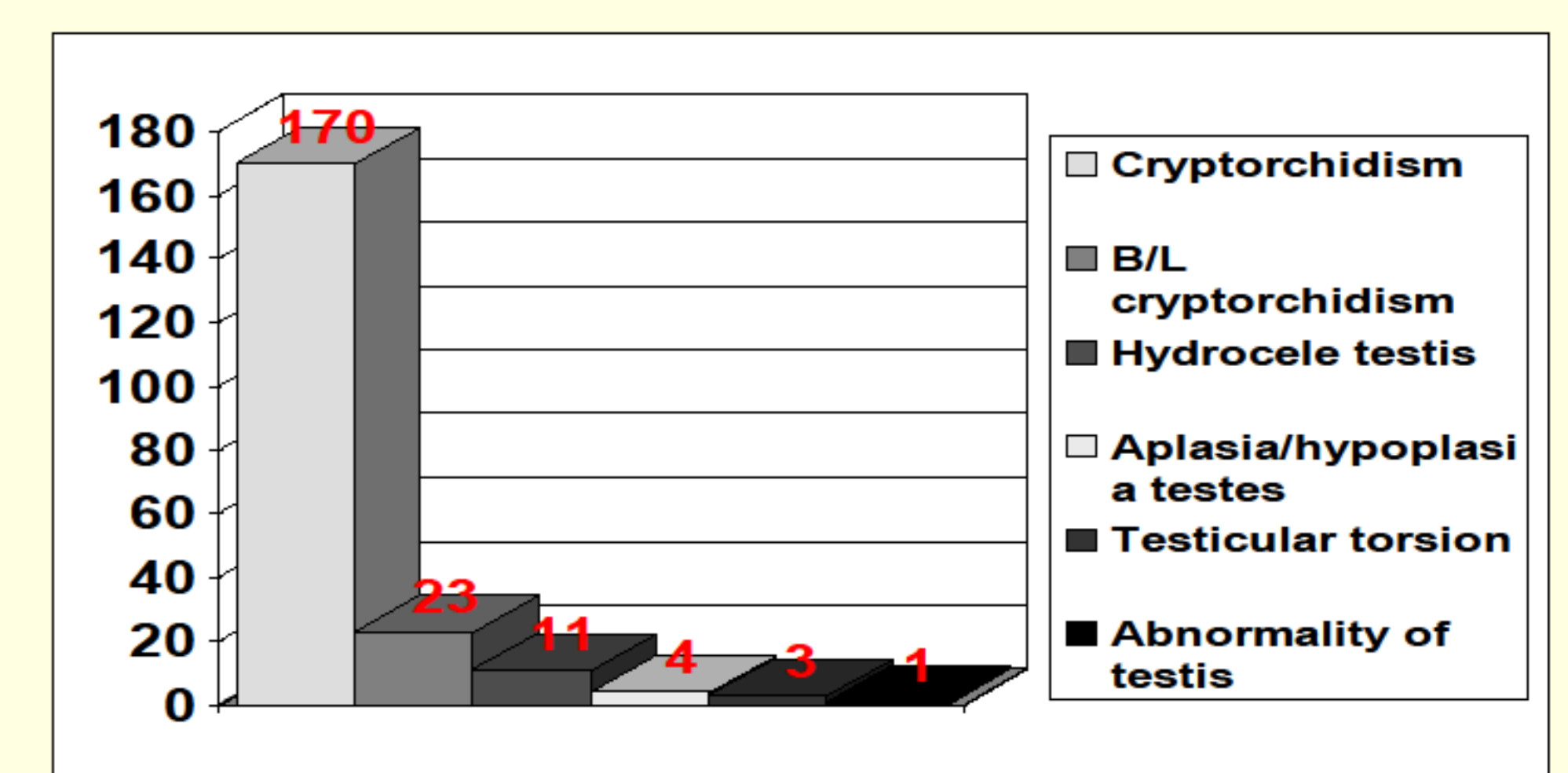
### Neurodevelopmental phenotypes



### 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 abnormalities 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 DDG2P genes not previously reported to be associated with DSD.

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

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

- Ahmed SF, Dobbie R, Fintayson AR, et al Prevalence of hypospadias and other genital abnormalities among singleton births, 1988-1997, in Scotland, Arch Child Fetal Neonatal Ed. 2004;89:F149-F151
- Kathryn Cox et al . Novel associations in Disorders of Sex Development: Findings from the I-DSD Registry J Clin Endocrinol Metab. Feb 2014;99 (2): E348-E355
- S. Faisal Ahmed et al. UK guidance on the initial evaluation of an infant or an adolescent with a suspected disorder of sex development Clinical Endocrinology (2011)75, 12-26
- Haire A R, Flavioli J, Groom D Dhandapani B, Unidentified undescended testes in teenage boys with severe learning disabilities, Arc Dis Child 2015; 100:479-480

## Acknowledgments

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

