DISORDERS OF SEX DEVELOPMENT: CLINICAL AND GENETIC DIVERSITY.

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INTRODUCTION

Disorders/differences of sex development (DSD) are a group of rare congenital conditions. Clinical management of patients with DSD is often difficult and requires multidisciplinary approach.

RESULTS

Out of 28 patients, pathogenic, likely pathogenic and variants with unknown significance were identified in 11 patients (39 %). In combination with clinical phenotype these variants were determined as **causative** for DSD.

Most of these 11 patients (82%) had likely causative variants in one gene (of monogenic origin), while 18% had variants in two genes simultaneously (of oligogenic origin).

43% of the identified gene variants **have not been previously reported.**

The variants in NR5A1 were associated with gonadal dysgenesis in two patients; the variants in MAP3K1 were also found in another two patients with gonadal dysgenesis, variants in AR – in three patients with CAIS, variant in MAMLD1 was associated with proximal form of hypospadias, variant in CYP17A1 was associated with testosterone biosynthetic defect. Among the two patients with variants of oligogenic origin, one had variants in MAP3K1 and MAMLD1 genes and was clinically characterized by hypospadias; the second had variants in AR and SEMA3A and was diagnosed with PAIS. There were also two patients with variants in NR5A1 of familial inheritance.

METHODS

Twenty-eight patients aged 1 to 18 years with different forms of 46, XY DSD were included. The subjects have undergone a clinical examination, karyotype analysis followed by the next generation sequencing (NGS) using MiSeq (Illumina). All variants identified by NGS were confirmed by Sanger sequencing. We performed bioinformatics analysis using OMIM, «1000 genomes», ESP6500, Genome Aggregation Database projects. To assess the clinical significance of the identified variants we used ClinVar database and American College of Medical Genetics and Genomics criteria.

CONCLUSIONS

cNGS-based targeted sequencing is a promising technique to improve the differential diagnosis, genetic counseling and management strategies for patients with DSD.

CONFLICTS OF INTEREST

There are no conflicts of interest.

CONTACT INFORMATION

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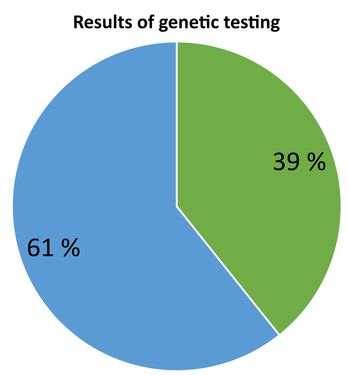
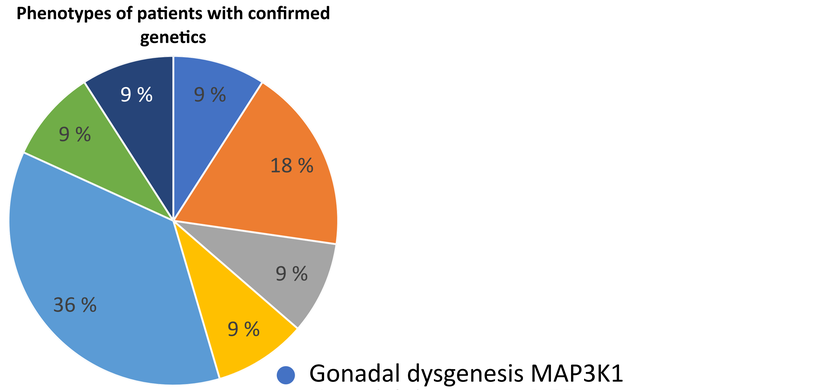


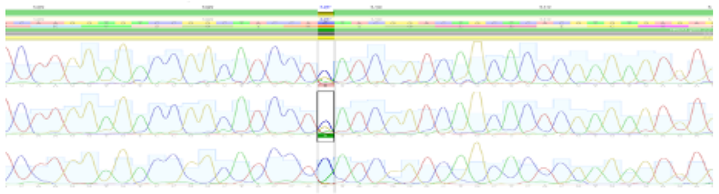


Monogenic origin - 82%
Oligogenic origin - 18%

Previously reported - 57%
Previously unreported - 43%

Family variants - 18% (both NR5A1)

Family form case example



NR5A1 (2 patients), 46,XY
Female sex of rearing
Gonadal function - as male
Spontaneous virilization during puberty (1 patient)
Opportunity of development in male sex with preservation of reproductive function