Results of exome sequencing in disorders of sex development

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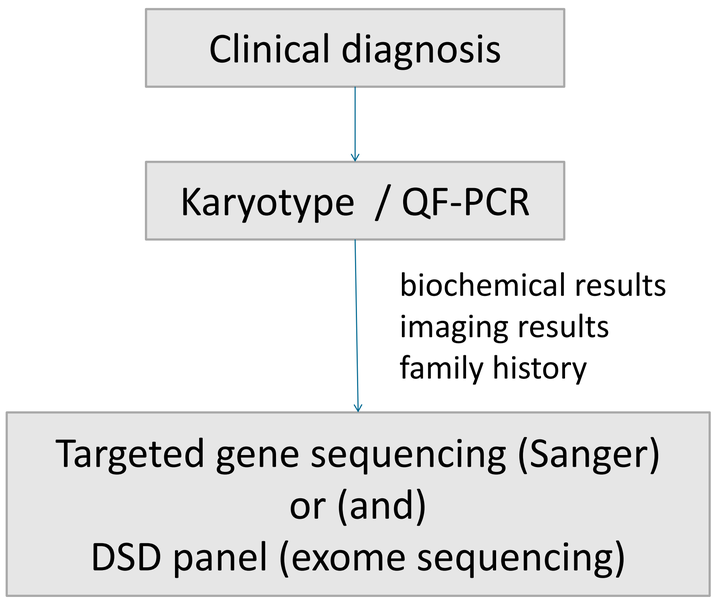
Disorders or Differences of sex development (DSD) are a heterogeneous group of congenital conditions, involving variations of chromosomal, gonadal, or anatomical development.
Diagnosis is based on:

- clinical investigation
- biochemical analysis
- imaging
- genetic evaluation

In recent years knowledge about genetic causes has increased, mainly due to improved genetic techniques.
In this study we investigated the yield of exome sequencing in our patient group with DSD.



The DSD gene panel as per September 2018 contains 56 genes[1].
The panel does not contain genes involved in Premature Ovarian Insufficiency/Hypogonadotropic Hypogonaism/ Hypospadia.

Results
From April 2014 till April 2018 exome sequencing was performed in 64 patients; of which 19 external referrals.

Exome sequencing revealed a likely pathogenic cause in 17% (11/64).
Direct sequencing of single genes revealed mutatioins in the following genes (the reason for single gene testing is shown in brackets):

- *SRY* (relative high frequency)
- *SRD5A2*, compound heterozygous mutations (biochemical profile)
- *DHCR7*, homozygous mutations
- *CYP21A2* (46,XX DSD, biochemical profile, not in DSD panel, n=11)
- *POR* (maternal virilisation)
- *FGFR1* (hypogonadotropic hypogonadism)

Open exome revealed mutations in:

- *SCRAP* (Floating harbou syndrome, hypospadia)
- *TOE1* (comp het, associated with cerebellar hypoplasia)

Results of exome sequencing of internal referrals

CYP17A1	2 (1 hom /1 het)
SRD5A2	3 (2 hom / 1 comp het)
NR5A1	3 (1 de novo / 1 mat inherited / 1 inheritance unknown)
HSD17B3	3 (1 hom / 2 het)
AR	1 (1 mosaic, de novo)
DHCR7	1 (1 hom)
DMRT1	1 (1 het, mat inherited)

Conclusion
In DSD exome sequencing is a valuable tool as a first-step diagnostic tool, but in selected cases when phenotype and biochemical tests suggest a specific genetic defect direct DNA sequencing can be appropriate.
The total yield of genetic testing (panel, Sanger, open exome) in DSD in our centre is 26% (19/72).
Early identification of a genetic cause is important for optimal management of the patient.

Reference:
1) https://order.radboudumc.nl/producten/wes-sexuele-differentiatiestoornissen?s=31

Additional information:
P2-P339
I declare that I have no potential conflict of interest.

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