# Towards an integrated approach in the diagnosis of 46, XY disorder of sex development

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## BACKGROUND AND METHODS

46, XY differences and/or disorders of sex development (DSD) are clinically and genetically heterogeneous conditions. Although complete androgen insensitivity syndrome has a strong genotype-phenotype correlation, other types of 46, XY DSD are less well-defined and thus the precise diagnosis is challenging.

Objective: This study focused on comparing the relationship between clinical assessment and genetic findings in a cohort of well-phenotyped patients with 46, XY DSD.

Methods: The clinical assessment included external masculinization score (EMS), endocrine profiling and radiological evaluation. Array-comparative genomic hybridization (array-CGH) and a targeted 46, XY DSD gene panel sequencing were performed.

## RESULTS

**Figure 1.** Integrated approach combining clinical, endocrine and genetic investigations.

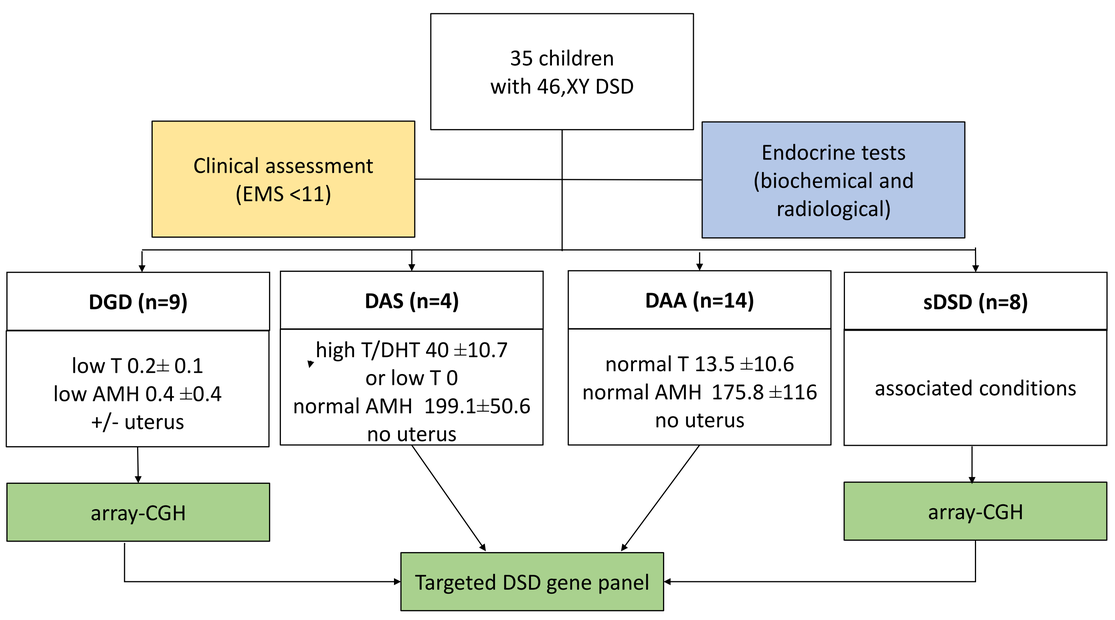


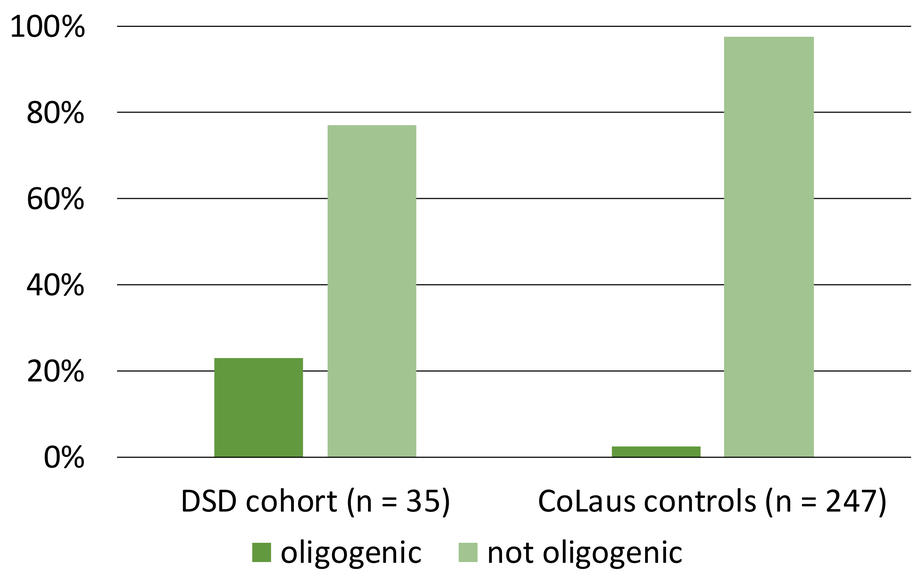

**Table 1.** Identified variants in patients with definitive genetic diagnosis.

| ID | Sex | DSD category | Clinical diagnosis | DSD Gene | Inherit-ance | GnomAD frequency | DNA change | Protein change | SIFT | MT | ACGM classification |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | M | DAS | 5αRD | *HOXA13* | AD | | c.539C>T | p.Pro180Leu | D | D | Likely pathogenic |
| | | | | *ARX* | XL | 0.00% | c.1315_1320dupGCCGCC | p.Ala439delinsGlyArgPro | | | VUS |
| 2 | F | DAS | DAS | *HSD17B3* | AR | 0.01% | c.729_735delGATAACC | p.Ile244Argfs*11 | | | Pathogenic |
| | | | | *HSD17B3* | AR | 0.03% | c.277+4A>T | | | | Pathogenic |
| | | | | *CYP17A1* | AR | | c.666+5G>A | | | | VUS |
| 3 | M | DAA | NSDUM | *WT1* | AD | | c.605T>G | p.Leu202Arg | D | U | Likely pathogenic |
| 4 | M | DAA | NSDUM | *AR* | XL | | c.2199C>A | p.Asp733Glu | D | D | Pathogenic |
| | | | | *SOX9* | AD | | c.847A>G | p.Ile283Val | D | D | VUS |
| | | | | *POR* | AR | 0.01% | c.1586C>T | p.Thr529Met | D | D | VUS |
| 5 | F | DAA | CAIS | *AR* | XL | | c.1715A>G | p.Tyr572Cys | D | D | Pathogenic |
| 6 | F | DAA | CAIS | *AR* | XL | | c.2086G>A | p.Asp696Asn | D | D | Pathogenic |
| 7 | F | DAA | CAIS | *AR* | XL | | c.2546dupA | p.Asn849Lysfs*32 | | | Pathogenic |
| 8 | F | DAA | CAIS | *AR* | XL | | c.2222C>A | p.Ser741Tyr | D | D | Pathogenic |
| | | | | *POR* | AR | 0.03% | c.571G>C | p.Val191Leu | T | D | VUS |
| 9 | F | DAA | CAIS | *AR* | XL | | c.1822C>T | p.Arg608* | U | D | Pathogenic |
| 10 | F | DAA | CAIS | *AR* | XL | | c.2222C>T | p.Ser741Phe | D | D | Pathogenic |
| 11 | F | DAA | CAIS | *AR* | XL | | c.2086G>A | p.Asp696Asn | D | D | Pathogenic |
| | | | | *DHCR7* | AR | 0.01% | c.89G>C | p.Gly30Ala | D | D | VUS |
| 12 | F | DAA | PAIS | *NR5A1* | AR;AD | | c.274C>T | p.Arg92Trp | D | D | Pathogenic |

RESULT: Nine patients received a clinical diagnosis of disorder of gondal development (DGD), 4 patients of a disorder of androgen synthesis (DAS), 14 patients of a disorder of androgen action (DAA), and 8 had syndromic DSD.

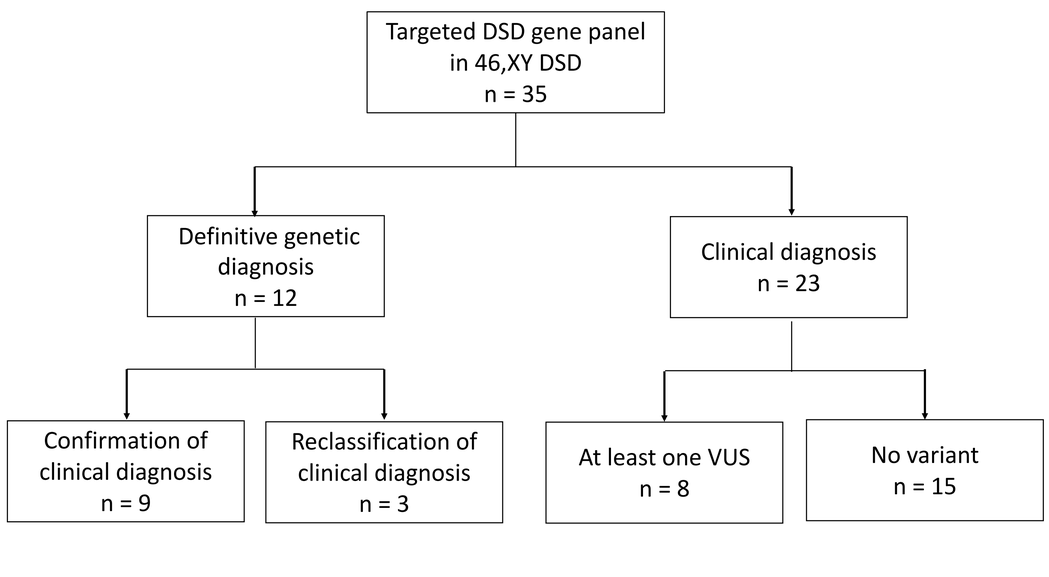
RESULT: 11 pathogenic variants and 2 likely pathogenic variants were identified, thus a definitive genetic diagnosis was possible in 12 cases (34%).

**Figure 2.** Oligogenic variants in DSD cohort and controls.




RESULT: There was a statistical enrichment in oligogenic variants in our DSD cohort compared to CoLaus controls (23% vs 2.5%; *P*=.0003)

**Figure 3.** The result of integrated approach in the diagnosis of 46,XY DSD.




RESULT: The genetic result confirmed the initial clinical diagnosis in 9 patients (75%), while in the remaining quarter it guided futher clinical assessement resulting in a reclassifiaction of their clinical diagnosis.

## CONCLUSIONS

In summary, the study showed that an integrated approach is the best routine practice in the diagnosis of 46, XY DSD. The combination of the variable utility of conventional endocrine tests with the identification of variants of uncertain significance and/or possible oligogenic inheritance results in potential obstacles to rendering an accurate diagnosis. This can be overcome by careful and systematic analysis followed by reporting the data and comparing with other centers. Furthermore, only 34% of patients harbor pathogenic mutations in DSD genes. The remaining patients argue for multi-national studies to identify additional genes involved in the pathogenesis of DSD.