**WES analysis of a cohort of 94 patients presenting with 46,XY and 46,XX DSD**

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**Introduction**

Differences of Sex Development (DSD) are diagnosed in approximately one out of 4'500 newborns. Currently, due to the lack of knowledge on the complete gene and protein pathways involved in sex development and DSD, causative genetic variants can only be identified in about 50% of the affected patients. We used whole exome sequencing (WES) on a group of 94 Patients presenting with 46,XY and 46,XX DSD, in order to identify causative variants and potential new DSD genes.

**Methods**

A. **Current data**

- 71 patients diagnosed with 46,XY DSD
- 23 patients diagnosed with 46,XX DSD

Whole Exome Sequencing (WES)

B. **Variants in genes related to DSD**

B.1 **Identification of potential new DSD candidate genes**

I. **Filtering of variants**

<table>
<thead>
<tr>
<th>Gene</th>
<th># Patients</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>AKAP13</td>
<td>0</td>
<td>Undiagnosed testes and hypogonadism (TM), AG (TP), adrenal insufficiency (AI), RILS (genital dysgenesis) (RD)</td>
</tr>
<tr>
<td>CDBC88C</td>
<td>6</td>
<td>Adrenal insufficiency (AI), undiagnosed testes and hypogonadism (TM), RILS (genital dysgenesis) (RD), adrenal insufficiency (AI), RILS (genital dysgenesis) (RD)</td>
</tr>
<tr>
<td>NAP1P1</td>
<td>8</td>
<td>RILS (genital dysgenesis) (RD), Klinefelter syndrome (K), RILS (genital dysgenesis) (RD), adrenal insufficiency (AI), RILS (genital dysgenesis) (RD)</td>
</tr>
<tr>
<td>NWD1</td>
<td>0</td>
<td>Undiagnosed testes and hypogonadism (TM), adrenal insufficiency (AI), RILS (genital dysgenesis) (RD)</td>
</tr>
<tr>
<td>PDZD2</td>
<td>12</td>
<td>Undiagnosed testes and hypogonadism (TM), Klinefelter syndrome (K)</td>
</tr>
</tbody>
</table>

Expression pattern

Known functions

Involvement in sex development pathways

# of patients with variants

5855 affected genes common between at least two patients

**Conclusions**

WES is a powerful tool for diagnostics that allowed us to identify potential causative variants in 21 of 71 46,XY DSD and in 12 of 23 46,XX DSD patients. The diagnosis of patients with already known variants can directly be confirmed, while unknown variants first need to be further analyzed. Comparison of all rare variants shared between patients and further filtering steps led to the identification of the five new potential DSD genes: AKAP13, CDBC88C, NAP1P1, NWD1 and PDZD2. Further experiments in vivo (mouse/fly) and/or in vitro (appropriate human cell models) are needed to confirm their influence in sex development and its differences.

References: