Evaluation of molecular characteristics and steroid metabolomics in a large cohort of children with 3β-hydroxydehydrogenase 2 deficiency

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Table 1. Sequence variations and genotype-phenotype relationships in 31 children with 3βHSD2 deficiency

| Mutation | Phenotype Characteristics | Genotype
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<tbody>
<tr>
<td>388G &gt; T</td>
<td>Mild, first-mother absent</td>
<td>388G&gt;T homozygote</td>
</tr>
<tr>
<td>388G &gt; T</td>
<td>Mild, first-mother absent</td>
<td>388G&gt;T heterozygote</td>
</tr>
<tr>
<td>388G &gt; T</td>
<td>Mild, first-mother absent</td>
<td>388G&gt;T compound</td>
</tr>
<tr>
<td>388G &gt; T</td>
<td>Mild, first-mother absent</td>
<td>388G&gt;T mixed</td>
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Results: Eleven homozygous (6 novel) in 31 children from 24 families (19 male/12 female; mean age: 6.6±5.1 years) were identified (Fig 2A). The missense variants 5% of wild-type 3βHSD2 activity in vitro were associated with non-salt losing clinical phenotype (Table 1, Fig 2B). There was a significant genotype-phenotype correlation in children with 3βHSD2 deficiency (Fig 3). The plasma ratio (of Preg+ to Preg−) was superior (17) to (17)/Preg−) to (17-HSD2 deficiency from the other groups. Heterozygote canister and functional 3βHSD2 deficiency patients showed higher Δ4 to Δ5 steroids than controls (Fig 4A, 4B, 5A). 11-oxygenated androgens were significantly lower in patients with 3βHSD2 deficiency (Fig 5B).

Conclusions:

- There is a good correlation between glucocorticoid and mineralocorticoid functions in vitro and biochemical 3βHSD2 deficiency, whereas genital and gonadal phenotype and behaviour are more complex and variable.
- In contrast to common knowledge, mineralocorticoid deficiency is not apparent in 1/3 of the cases.
- This 46, XY DSD is a "sexue non " in affected males whereas ambiguous genitalia is only rarely seen in 46, XX individuals due to decreased production of potent androgens via classical or alternative pathways.
- On the other hand, premature pubarche is very common on either sex 3βHSD2 deficiency.
- Spared mineralocorticoid function and unmutilated genitalia in females may lead to midadipose and subcutaneous fat deposition.
- The effect of 3βHSD2 mutation on body composition in children with 3βHSD2 deficiency is complex and variable.
- The role of REG3 in the pathogenesis of adrenal androgen excess needs to be elucidated.
- The correct diagnosis of 3βHSD2 deficiency is not only essential for the proper clinical management in infancy and childhood but also for the surveillance of gonadal function and fertility of the patients in later life.