MISSPLICING DUE TO A SILENT EXONIC SUBSTITUTION IN THE T-BOX TRANSCRIPTION FACTOR TBX19 RESULTING IN ISOLATED ACTH DEFICIENCY

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INTRODUCTION

Congenital isolated ACTH deficiency (IAD) → low plasma ACTH and serum cortisol with preserved function of all other pituitary hormones.

TBX19 is a T-box transcription factor involved in the terminal differentiation of pituitary POMC expressing cells (Figure 1). Of the 25 TBX19 mutations associated with IAD, most are missense but 5 have been described to affect splicing.²

CLINICAL CASE

We report a neonate of Romanian origin, who presented at 15 hours of life with respiratory arrest and hypoglycaemia. Over the following 2 weeks recurrent hypoglycaemia was documented.

On examination → normal male genitalia and no hyperpigmentation

Biochemical investigations:

→ Undetectable serum cortisol (cortisol <1 μg/dl; NR 7.8-26.2) and
→ Inappropriate plasma ACTH levels (22.1 pg/ml; NR 4.7-48.8)

He responded to hydrocortisone treatment and continues on replacement. He has a healthy sister who is 30 months older. However, there is a family history of adrenal disease as his aunt (mother’s sister) has been on hydrocortisone treatment since 18 months of age with a diagnosis of suspected IAD.

METHODS & RESULTS

DNA → analysed by a HaloPlex next-generation sequencing array targeting genes for adrenal insufficiency & variants → filtered by Ingenuity Variant Analysis (Figure 2).

The effect of the novel mutation was assessed by an in vitro splicing assay, pT01 exonTrap cloning vector (Mobitec), comparing wild type and mutant heterologous minigenes.

The mutation results in aberrant splicing of exon 2, giving rise to a mutant mRNA transcript whereas the wild-type vector spliced exon 2 normally (Figure 4a-c, 5).

CONCLUSION

We have identified a translationally silent TBX19 mutation causing aberrant splicing as the likely cause of isolated ACTH deficiency in the patient. Most mRNA transcripts are aberrantly spliced leading to a truncated, non-functional protein in keeping with the complete loss of cortisol production and early presentation in the patient.

Table 1. Details of TBX19 variant found in the proband.

<table>
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<tr>
<th>Chromosome</th>
<th>Position</th>
<th>Reference allele</th>
<th>Allele</th>
<th>Gene region</th>
<th>Gene symbol</th>
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<tbody>
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<td>'G'</td>
<td>'A'</td>
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<td>TBX19</td>
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</tbody>
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A novel, homoygous, extremely rare, synonymous variant p.Thr96= was found in exon 2 of the TBX19 gene (Figure 3; Table 1).