

VARIED PRESENTATION OF SIX PATIENTS WITH CYP11A1 MUTATIONS

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Introduction

Mutations in the side chain cleavage enzyme, (*CYP11A1*), like those in the steroidogenic acute regulatory protein, (*STAR*) cause lipoid congenital adrenal hyperplasia (CLAH) manifesting with adrenal and gonadal insufficiencies along with derangements of the renin/angiotensin system. Increased adrenal size is usually a feature of *STAR* but not of *CYP11A1* mutation. Milder forms presenting without all of these features have also been described and the presentation can sometimes mimic that of isolated or Familial Glucocorticoid Deficiency (FGD). We present six patients, from four families with varying clinical pictures who have *CYP11A1* mutations discovered by whole exome sequencing.

Clinical presentations

Patients 1 & 2 are sisters with ACTH resistance, having high ACTH levels, low glucocorticoids and no response to exogenous ACTH. They had no achalasia or alacrima and were described as pale compared to other family members, they were treated with glucocorticoids alone and were given an atypical, non-pigmented FGD diagnosis. Patients 3 & 4 have FGD and subclinical hypothyroidism, two of their siblings (Figure 1;II:1 & II:3) died in childhood aged 6 and 4. The patients are adult now and patient 4 (II:6) has suffered 3 miscarriages. Patient 5 presented with adrenal failure in early life with mineralocorticoid and glucocorticoid deficiency. She was said to have had big adrenals in the neonatal period and was given a diagnosis of lipoid adrenal hyperplasia. Patient 6 had a salt wasting early neonatal history and was hyperpigmented in infancy. He was treated as a case of Addison's disease all through his childhood to account for his infantile hypoglycaemia and hyponatraemic convulsions (despite normal renin and aldosterone levels). Before that he was thought to have had ketotic hypoglycaemia. In young adulthood he has normal renin/aldosterone levels and is off fludrocortisone. He remains well without mineralocorticoid replacement and has fully developed puberty.

Objective & Methods

To find the genetic cause of adrenal insufficiency whole exome sequencing was undertaken on genomic DNA of the patients. Variants in the seven genes known to cause Familial Glucocorticoid Deficiency or non-classical congenital lipoid adrenal hyperplasia; *MC2R*, *MRAP*, *STAR*, *CYP11A1*, *NNT*, *MCM4* and *TXNRD2*, were assessed for causality. Further analysis of genomic DNA and cDNA was performed by PCR/RT-PCR followed by automated Sanger sequencing.

Results

The mutations in *CYP11A1* were as follows; patients 1&2 had a homozygous A359V mutation in exon 6, the parents and an unaffected sibling were heterozygous for the change (Figure 1A). Patients 3&4 had compound heterozygous mutations I279Yfs*9 and *122Rext*68, DNA of other family members was unavailable for analysis (Figure 1B). Patient 5 was compound heterozygous for R120Q in exon 2 and Q395K in exon 7, the R120Q was inherited from her father, Q395K from her mother (Figure 1C). Finally patient 6 was compound heterozygous for E314K and an exon5/intron5 splice site mutation, the E314K came from his mother and the splice mutation from his father, an unaffected sister inherited only the splice mutation (Figure 1D). The A359V and I279Yfs*9 mutations have been previously reported and in homozygosity shown to cause severe cases of CLAH^{1,2}, all other variants were novel, with the exception of the E314K (aka rs6161 with a minor allele frequency 0.001).

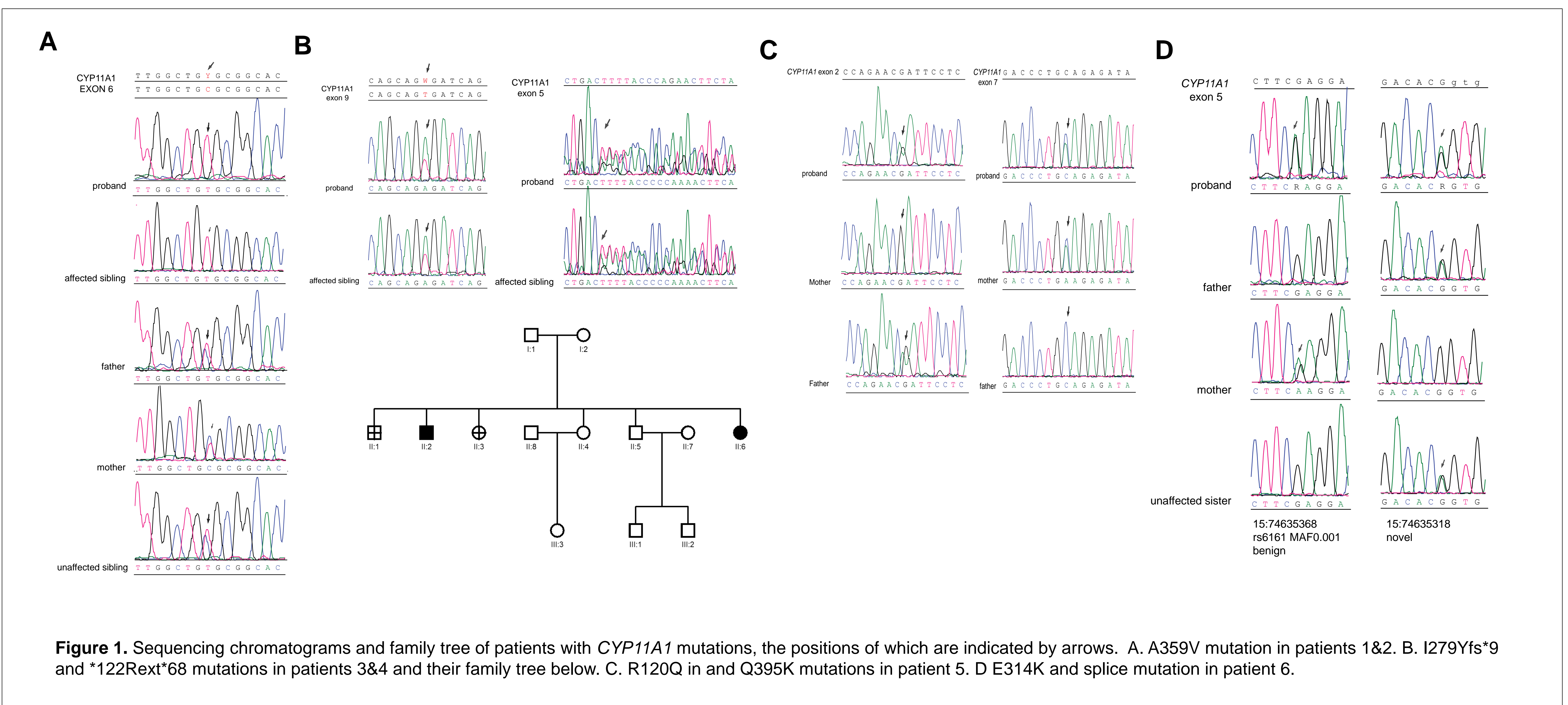


Figure 1. Sequencing chromatograms and family tree of patients with *CYP11A1* mutations, the positions of which are indicated by arrows. A. A359V mutation in patients 1&2. B. I279Yfs*9 and *122Rext*68 mutations in patients 3&4 and their family tree below. C. R120Q in and Q395K mutations in patient 5. D. E314K and splice mutation in patient 6.

Conclusions

The presentation of these patients with *CYP11A1* varied between cases, ranging from a patient with neonatal salt wasting/adrenal crisis and large adrenals to a pair of non-pigmented sisters aged 2 and 4y at diagnosis who are on glucocorticoid replacement alone. The A359V and I279Yfs*9 have been documented to cause CLAH in homozygosity so it is interesting that the patients (1,2,3 and 4) described here have milder phenotypes. For 3 & 4 this may be the consequence compound heterozygosity with the stop codon loss (122Rext*68) on the other allele. The effect of this is uncertain but since both siblings carry the two mutations it seems likely that this is the cause of their adrenal failure. The R120Q and E395K seen in patient 5, who was diagnosed as possible lipoid adrenal hyperplasia, have not previously been described. The E314K mutation is predicted to be benign but has a minor allele frequency of 0.001 and this in combination with a putative splice site variant at the end of exon 5 may result in the relatively mild phenotype of this patient. Whole exome sequencing revealed the nature of the underlying defect in each patient to be mutation(s) in *CYP11A1*, the gene encoding the first enzyme in the steroidogenic pathway, converting cholesterol into pregnenolone. These cases emphasize the utility of whole exome sequencing as a tool for improved diagnosis and therefore patient management in the endocrine clinic.

References

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