Novel CYP11A1 mutations in 15 patients (13 families) with variable clinical presentations

Claire Goursaud1, Florence Roucher-Boulé1, Delphine Mallet-Motak1, Raja Brauner1, Claire-Lise Gay1, Ane Mercedes Garcia1, Anne Lienhardt-Roussie1, Farida Jannene1, Maryam Razzaghzay2, Yves Morel1

1Hospices Civils de Lyon, Laboratoire d’Endocrinologie Moléculaire et Maladies Rares, Lyon-Bron, France; 2Faculté ophtalmologique Adolphe de Rothschild and Université Paris Descartes, Paris, France; CHU Hospices Civils de Lyon, Service d’Endocrinologie Pédiatrique, Lyon-Bron, France; 3Centro medico Orinoco, Endocrinología Pediatria, Ciudad Guayana, Bolivar, Venezuela; 4Hôpital de la mare et de l’enfant, Département de pédiatrie médicale, Limoges, France; 5CHU Ibn Roch, Hôpital d’enfants, unité d’Endocrinologie/Diabétologie et Gynécologie de l’Enfant et de l’adolescent, Casablanca, Morocco; 6Metabolic Disorders Research Center, Endocrinology and Metabolism Molecular-Cellular Sciences Institute and Hazrat Aliaashir Children’s Hospital, Iran University of Medical Sciences, Tehran, Iran

BACKGROUND

The side chain cleavage enzyme (CYP11A1) catalyzes the conversion of cholesterol to pregnenolone, the first rate-limiting step of steroidogenesis. CYP11A1 mutations are associated with primary adrenal insufficiency (PAI) and, in 46,XY patients, Disorders of Sex Development (DSD). 35 patients (27 families) have been previously reported in the literature including 15 intermediate forms documented:
- Six 46,XY patients with normal male external genitalia, including 5 homozygous for p.R451W
- Five 46,XY patients with partial DSD (micropenis, hypospadias...)
- Four 46,XX patients with late onset of PAI (≥ 18 months)

We report 15 patients (13 families) with 15 CYP11A1 mutations (10 new ones) and variable clinical presentations.

METHODS

- Sanger sequencing: selective amplification by PCR followed by conventional dideoxy sequencing of exons and the exon-intron boundaries on a ABI-3730XL and compared to the human genome (GRCh37/hg19) using SeqScape® software v3 (Life Technologies, CA, USA)
- 57 genes analyzed including AAAS, AIRE, CITED2, CYP11A1, MC2R, MCM4, MRAP, NNT, NR0B1, NR5A1, PBX1, PRDX3, STAR, TXNRD2
- In silico studies: predictive software, sequences alignment (between species and steroidogenesis CYP) using Clustal omega and Genedoc, molecular modelling using Swiss-PdbViewer

RESULTS

Diagnosis based on:
- SW (10 patients):
  - 1 patient 46,XY (2) without DSD homozygous for a mutation reported in similar cases: p.R451W
  - 2 patients 46,XX (8, 11) with PAI diagnosed in the first year of life (one day and 7 months) compound heterozygous for p.G1338R/p.L170Vfs*30 and p.R396G/p.R465Q
  - 2 patients 46,XX (5, 9) with late onset of PAI (> 3 years) with p.R120Q, p.E314K, p.R465W mutations
- Familial history (3 patients)
- 1 patient 46,XY DSD with complete female phenotype (6b) compound heterozygous for p.R120X and p.A2275S

CONCLUSION

The incidence of CYP11A1 mutations (33%) is high in our cohort of patients with first step of steroidogenesis deficiency (STAR and CYP11A1 gene). Diagnosis is based on SW in approximately 67% of cases. For some mutations, in silico studies seem to predict good genotype-phenotype correlation. Our patient without DSD is homozygous for p.R451W, mutation found in 5 patients 46,XY with the same phenotype. Intermediate forms are at risk to be misdiagnosed because the phenotype overlaps with other causes of PAI. This emphasizes the utility of MPS allowing the study of many causative genes simultaneously. Further studies should be done to explore these dissociated forms.