A Novel Mutation in the MC2R Gene in a Two-Year-Old Boy with Adrenal Insufficiency

Sara Al-Khawaga, Basma Haris, Reem Hasnah, Saras Saraswathi, Amira Saeed, Sanaa Sharari, Idris Mohammad, Khalid Hussain

[1]Department of Pediatric Medicine, Division of Endocrinology, Sidra Medicine, Doha, Qatar.
E-mail: khussain@sidra.org

INTRODUCTION

Melanocortin-2 receptor (MC2R) is a member of the G protein-coupled receptor family. Adrenocorticotropic hormone (ACTH) activates; the binding of MC2R and ACTH activates the heterotrimeric G protein complex, and in turn stimulates steroidogenesis. Pathogenic variants in the MC2R gene result in glucocorticoid deficiency-1 (GCCD1), an autosomal recessive disorder in which unresponsiveness to ACTH leads to deficient secretion of cortisol and adrenal C19 androgen precursors. Biochemically serum cortisol levels are low with elevated ACTH. Patients with GCCD1 usually present with failure to thrive, hypoglycemia, recurrent infections, hyperpigmentation, and neurological sequel.

OBJECTIVE(S)

To describe a case of two-year old boy with symptoms of adrenal insufficiency and confirmed novel pathological mutation in the MC2R gene.

CASE REPORT

The patient is a two-years old boy, full term, product of uneventful pregnancy and normal vaginal delivery. He had repeated episodes of neonatal sepsis starting at the age of 2 days. He had recurrent symptoms of failure to thrive, hypoactivity, hypoglycemia, and recurrent infections.

METHODS

Whole Exome Sequence (WES) Analysis was performed using genomic DNA from the patient and his parents, the exonic regions and flanking splice junctions of the genome were captured and sequenced by NextGen sequencing on an illumine system. Reads were aligned to human genome build GRCh37/UCS hg19, and analyzed for sequence variants using Xome Analyzer. Sequence and copy number variants were described according to the Human Genome Society(HGVS) and International System for Human Cytogenetic Nomenclature (ISCN) guidelines, respectively.

RESULTS

His biochemical investigations showed elevated levels of ACTH >1500 (reference 5-60 pg/ml), low levels of cortisol <22 (69-632 nmol/L), low aldosterone 151 pmol/L (reference 194-2579), and hypoglycemia (1.1 mmol/L). WES has identified a p.Leu109Gln (CTG>CAG): c.326 T>A in exon 2 in the MC2R gene.

Investigation	Value	Reference
ACTH	>1500 pg/ml	5-60 pg/ml
Cortisol	<22 nmol/L	69-632 nmol/L
Aldosterone	151 pmol/L	194-2579 pmol/L
Glucose	1.1 mmol/L	5.6 to 6.9 mmol/L

Table 1. Biochemical profile displaying hypoaldosteronism . Elevated levels of ACTH >1500 (reference 5-60 pg/ml), low levels of cortisol and aldosterone 151 pmol/L (reference 194-2579), associated with hypoglycemia.

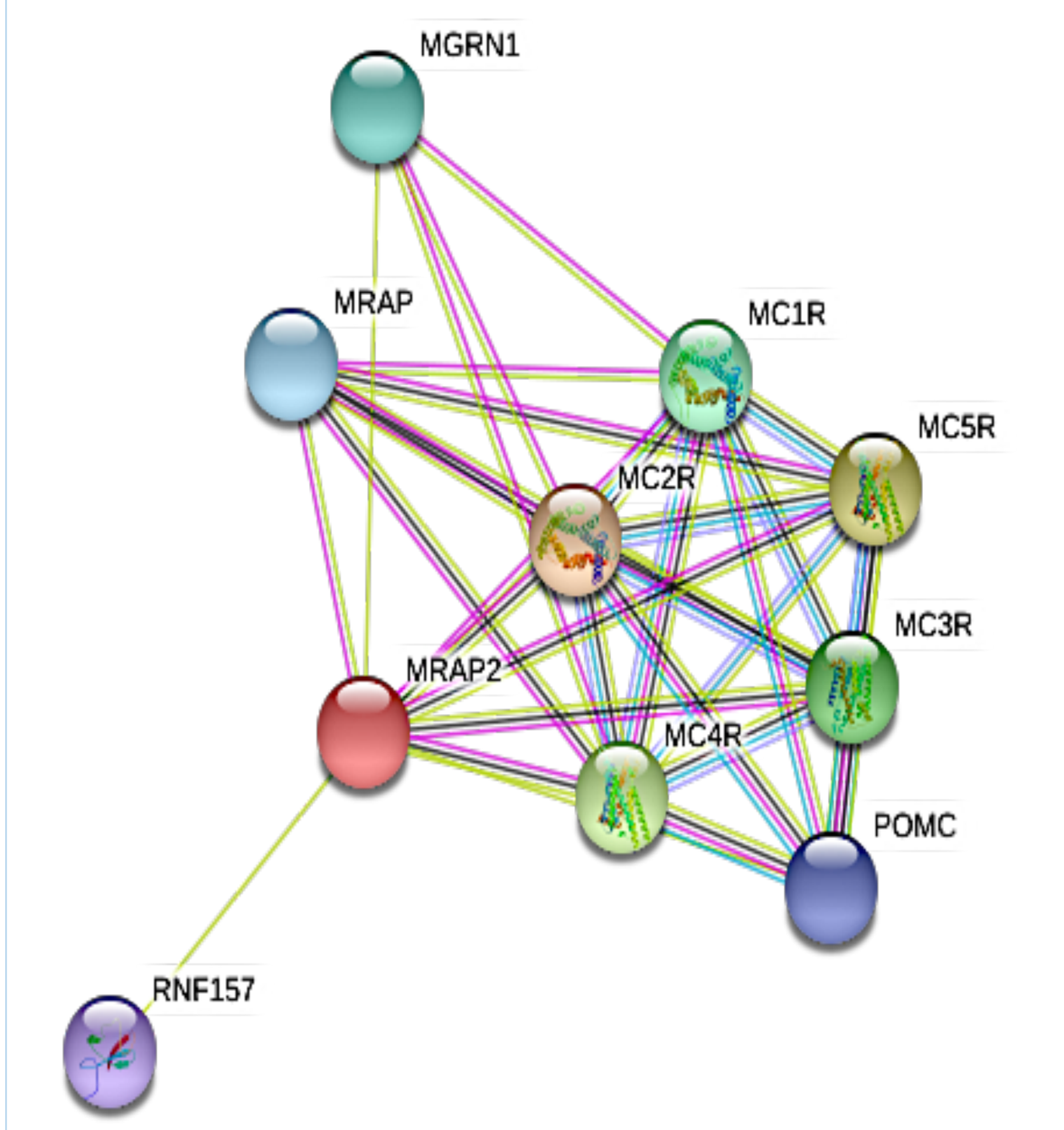

Figure 1. STRING network interaction of MC2R gene.

CONCLUSION

- We report a novel mutation in the MC2R gene leading to severe cortisol deficiency.
- The L109Q variant is a non-conservative amino acid substitution, which is likely to impact secondary protein structure as these residues differ in polarity, charge, size, and/or other properties.
- Further functional analysis will aid in unravelling the molecular mechanism of how the novel mutation leads to adrenal insufficiency.

REFERNCES

1. Lin, L., et al., *Severe loss-of-function mutations in the adrenocorticotropin receptor (ACTHR, MC2R) can be found in patients diagnosed with salt-losing adrenal hypoplasia.* Clin Endocrinol (Oxf), 2007. **66**(2): p. 205-10.
2. Chung, T.T., et al., *The majority of adrenocorticotropin receptor (melanocortin 2 receptor) mutations found in familial glucocorticoid deficiency type 1 lead to defective trafficking of the receptor to the cell surface.* J Clin Endocrinol Metab, 2008. **93**(12): p. 4948-54.
3. Chida, D., et al., *Melanocortin 2 receptor is required for adrenal gland development, steroidogenesis, and neonatal gluconeogenesis.* Proc Natl Acad Sci U S A, 2007. **104**(46): p. 18205-10.