Novel genetic changes in Autosomal Dominant, Primary Macronodular Adrenal Hyperplasia associated with hypercortisolism and giant adrenals

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OBJECTIVES

- Primary macronodular adrenal hyperplasia (PMAH) is a rare cause of adrenal hypercortisolism.
- A family with Autosomal Dominant PMAH with adrenal hypercortisolism was studied. Aberrant receptors studies were negative.
- ARMC5 has been associated with PMAH and adrenal tumors(1,2).
- cAMP-dependent protein kinase A (PKA) signaling is the major activator of cortisol secretion in the adrenal cortex and mutations in PDE11A4 has been associated with PMAH(3).
- The aim of this study was to reveal the genetic basis of ADPMAH studying PDE11A4 and ARMC5 genes.

METHODS

- Bilateral adrenalectomy was performed. The adrenal weight was 470 gr. Clinical evaluation of the family (Fig 1) was carried out including biochemical, hormonal and imaging studies (CT/MRI).
- DNA was extracted from lymphocytes and sequencing of PDE11A4 and ARMC5 genes was performed in the index case. Screening for the found mutations was done in the family.
- Immunohistochemical studies for PDE11A4 and ARMC5 in the adrenal tissue of the index patient was performed.

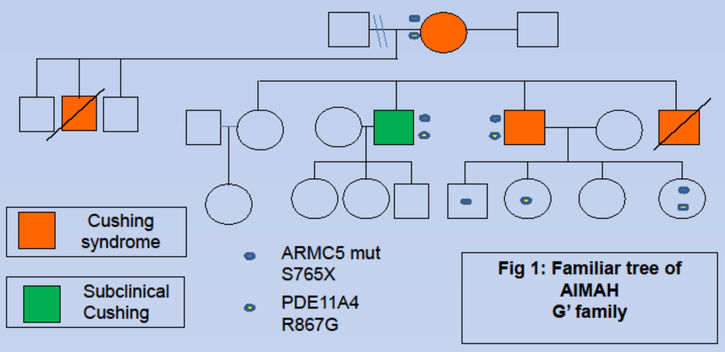
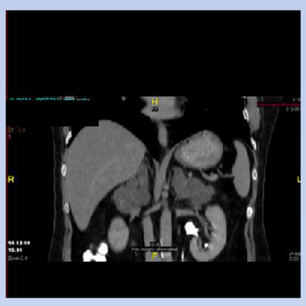


Fig 1: Familiar tree of AIMAH G' family



Adrenal CT of the index case

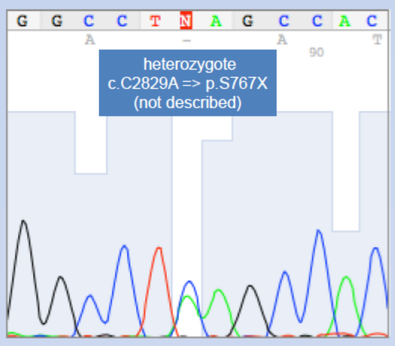
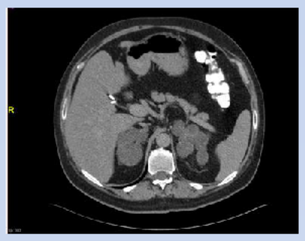


Fig.2. ARMC5 mutation



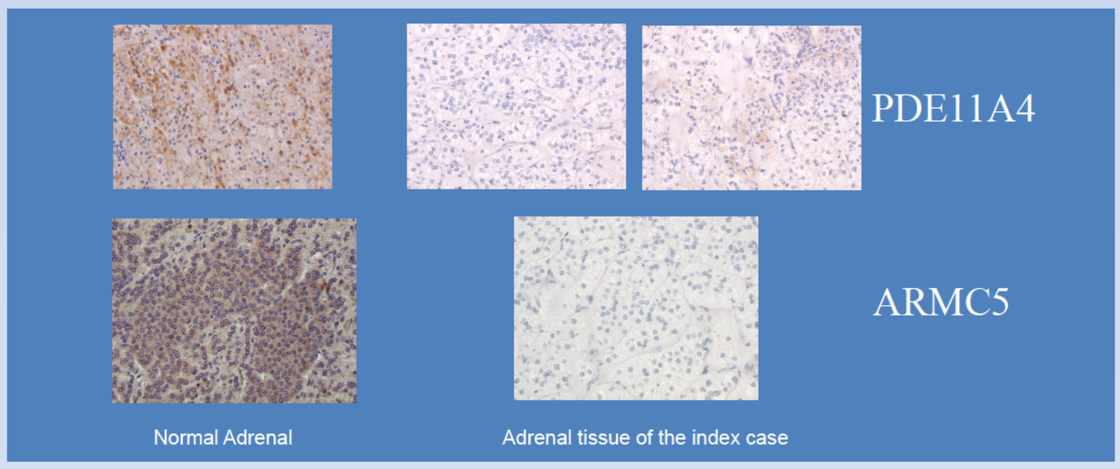
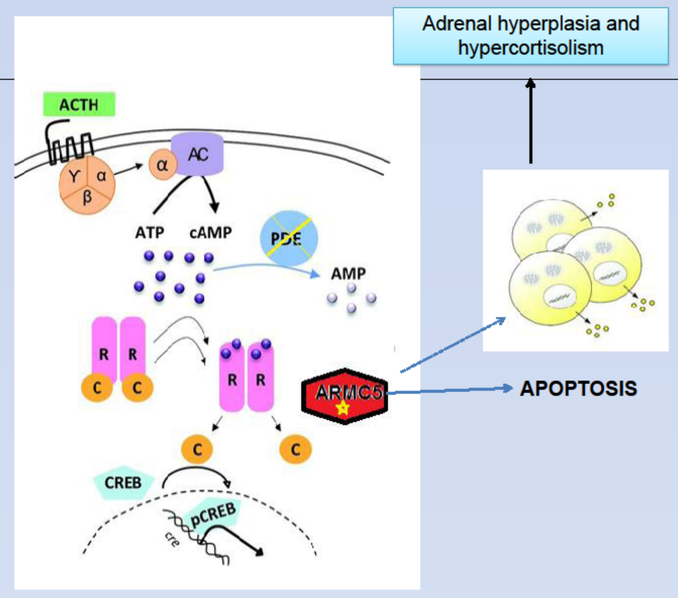


Fig. 3 Immunostaining studies of adrenal tissue

RESULTS

- A germline heterozygote rare variant of PDE11A4 R867G (2-3% frequency in general population) was found(4) as well as a novel germline heterozygote mutation of ARMC5 mutation (Fig 2).
- Adrenal protein expression of PDE11A4 and ARMC5 in the adrenal gland of the index case was very low (Fig 3).
- All the patients with hypercortisolism harbor both ARMC5 and PDE11A4 mutations.
- Young patients with one or both mutations had a normal HPA axis and the adrenal glands had a normal appearance per MRI.



CONCLUSIONS

- A family with ADPMAH causing giant adrenal hyperplasia associated with a novel mutation in ARMC5 in conjunction with PDE11A4 mutation, causing low protein expression is reported.
- Coexistence of PDE11A4 variant in all three affected individuals may indicate a phenotype modifier role.
- Because clinical and biochemical abnormalities appear during adulthood, young phenotypically normal mutation carriers may be at risk of developing clinical disease in the future

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