

A UNIQUE CASE OF DUAL OPPPOSING PATHOLOGIES

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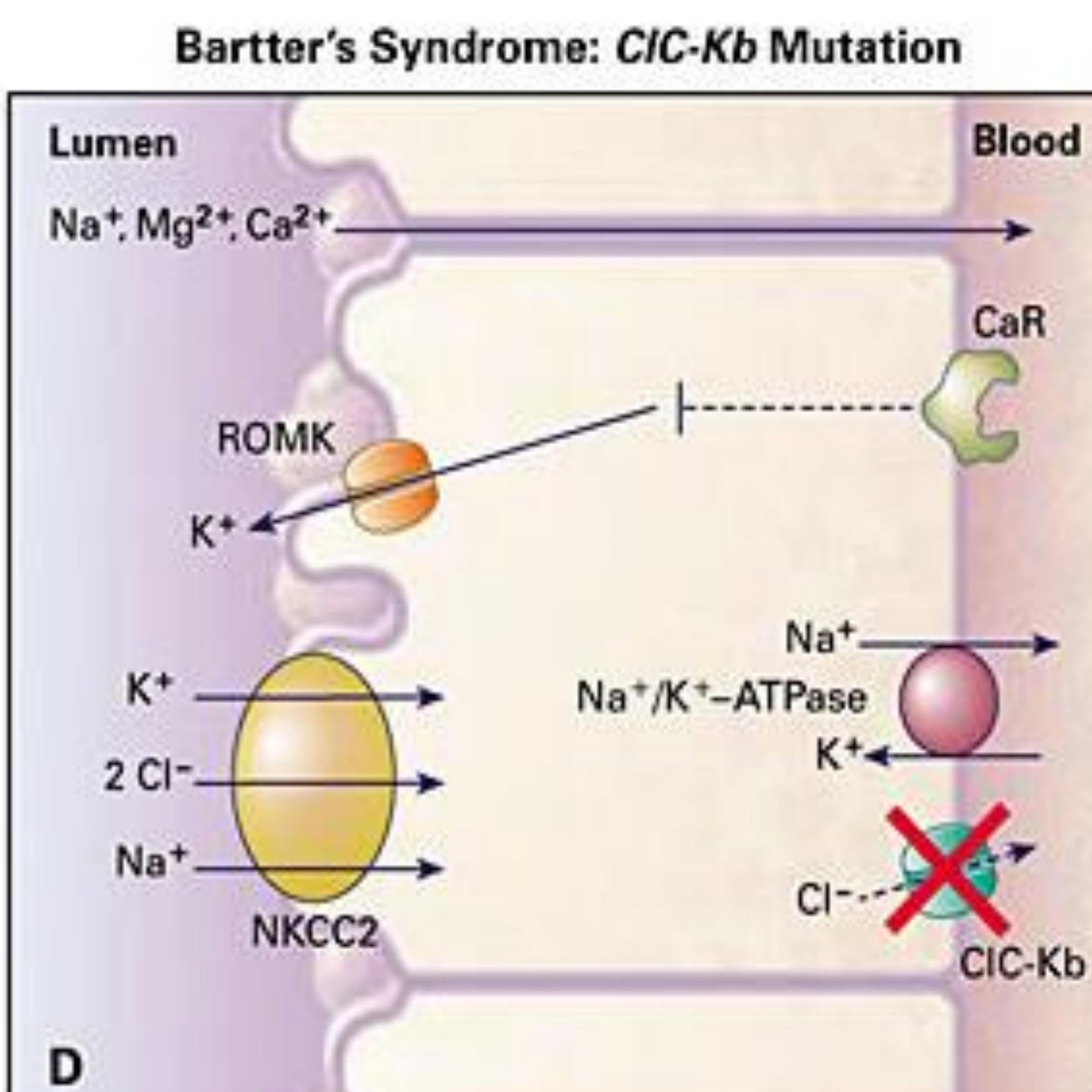


BACKGROUND

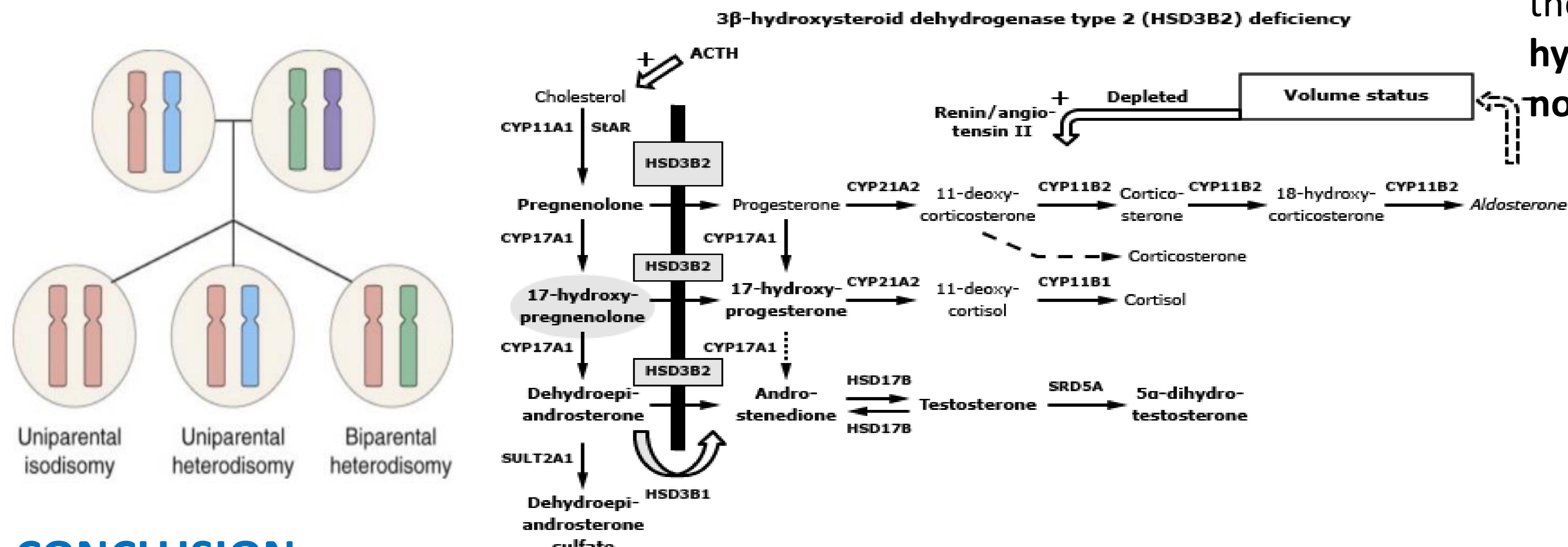
We present a patient with co-existence of two rare conditions 3 β -Hydroxysteroid dehydrogenase type 2 deficiency (HSD3B2) the rarest form of Congenital Adrenal Hyperplasia (CAH) and Bartter's Syndrome (hypokalaemic alkalosis secondary to hyperaldosteronism).

CASE REPORT

A female infant (46XX) born at 34/40 weeks weighing 2.67Kg to non-consanguineous parents presented on day four of life with significant weight loss. Subsequent investigations revealed hyponatraemia (Na:126mmol/L), hypochloraemia (Cl:87mmol/l), metabolic alkalosis, elevated levels of 17-hydroxyprogesterone >110nmol/L(normal<5.7), ACTH: 553ng/l(10-50) and renin:2,206mU/L (5.4-30). Urine steroid profile suggested HSD3B2 deficiency, confirmed by the identification of a homozygous *HSD3B2* mutation c.745C>T, p. Arg249*. Genitalia were normal with no virilisation. She was started on hydrocortisone, fludrocortisone and sodium chloride. Renin levels remained >2,000 mU/L, with presence of hypochloraemic alkalosis. She developed a persistent Hypokalaemia (as low as 2.1 mmol/l) even after temporarily stopping the fludrocortisone and an underlying renal tubulopathy was suspected. Bartter's type 3 was established by identification of a homozygous *CLCKNB* deletion. The co-existence of two rare recessive conditions due to homozygous mutations raised the possibility of uniparental isodisomy. A SNP microarray analysis confirmed 2 segments of homozygosity on chromosome 1 of maternal ancestry, encompassing both *HSD3B2* and *CLCKNB*.



Bartter's syndrome results from an inability to reabsorb NaCl in the thick ascending loop of Henle. This leads to a secondary hyperactivity of the renin-angiotensin-aldosterone system. High levels of aldosterone enhance K⁺ and H⁺ exchange for Na⁺ in the collecting duct. Giving the cardinal features of hypokalaemic hypochloraemic metabolic alkalosis with normotensive hyperaldosteronism.



CONCLUSION

- Uniparental isodisomy, the presence of two identical copies of a given genomic region inherited from one parent results from an error in meiosis. It predisposes to recessive diseases, as each heterozygous variant of that parent in the genomic region will be present in homozygous state in the child. Thus, identification of a homozygous rare mutation in an offspring of non-consanguineous parents should raise suspicion of this condition, especially if the phenotype is unusual, potentially encompassing more than one disorder.
- Despite identifying the genetic cause for the hypokalaemic alkalosis (Bartter's syndrome) the biochemical fingerprint of hyperaldosteronism, it remains unexplained how this has arisen in a child with CAH (hypoaldosteronism) and challenges our current understanding of mineralocorticoid-mediated effects in the renal collecting duct.