Background: Classical and non-classical congenital lipoid adrenal hyperplasia (CLAH) are extremely rare condition caused by mutations in Steroidogenic Acute Regulatory Protein (STAR). The degree of enzyme activity impairment determines the clinical phenotypes.

Objective and hypotheses: To identify the genetic cause of primary adrenal insufficiency in a cohort of patients from 13 unrelated families with classical and non-classical CLAH, to correlate genotype to phenotype and to identify a possible founder effect of these mutations.

Results: All (n=15) affected individuals with classical CLAH in Israel and the Palestinian territories had the same N-terminal c.201_202delCT mutation due to a founder effect and presented neonatally with severe Addisonian crisis and XY-DSD (in cases of XY karyotype) responding well to full replacement therapy. Three patients with non-classical CLAH had the G221S mutation (novel in the homozygous state), again with a founder effect. These patients presented during early childhood with addisonian crisis during a severe infection requiring just glucocorticoid replacement therapy. Characterization of the pubertal development in XX and XY patients of this cohort is underway.

Mutations result:

Mutations result c.201_202delCT is a deletion of one pair in exon 3. This deletion creates a stop codon resulting in a truncated 68 amino acid protein, which eliminates key functional domains of the protein. A genetic founder effect of the c.201_201delCT mutation in STAR protein is the cause of most described Palestinian cases of CLAH.

A genetic founder effect of the c.201_201delCT mutation in STAR protein is the cause of most described Palestinian cases of CLAH. This has significant premartial and prenatal counseling implications.

Conclusions

- Classical and non-classical CLAH due to StAR mutations are extremely rare but are significantly more common in the Palestinian population, given the founder effect of the 2 mutations characterized here.
- The different clinical phenotype of patients with classical and non-classical reflects the degree of StAR protein dysfunction caused by these mutations.
- To our knowledge, this is one of the largest cohorts studying the clinical and molecular characteristics of CLAH patients. The actual prevalence of mutations in the StAR gene in the general Palestinian population remains to be determined.