FOUNDER EFFECT AND THE CLINICAL AND MOLECULAR CHARACTERISTICS IN A COHORT OF CLASSICAL AND NON-CLASSICAL CONGENITAL LIPOID ADRENAL HYPERPLASIA (CLAH) DUE TO STAR MUTATIONS

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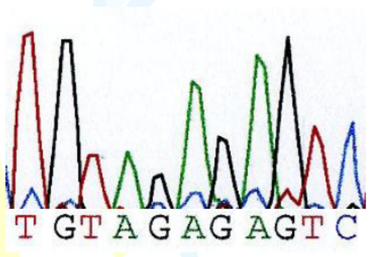
Background: Classical and non-classical congenital lipoid adrenal hyperplasia (CLAH) are extremely rare condition caused by mutations in Steroidogenic Acute Regulatory Protein (*StAR*). The degree of enzyme activity impairment determines the clinical phenotypes.

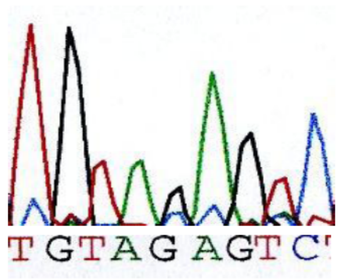
Objective and hypotheses: To identify the genetic cause of primary adrenal insufficiency in a cohort of patients from 13 unrelated families with classical and non-classical CLAH, to correlate genotype to phenotype and to identify a possible founder effect of these mutations.

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 Addissonian 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:



Normal

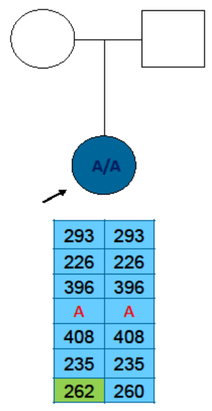


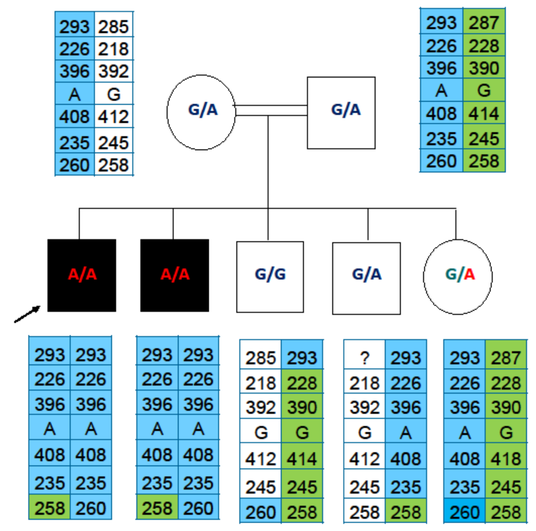
c.201_202delCT

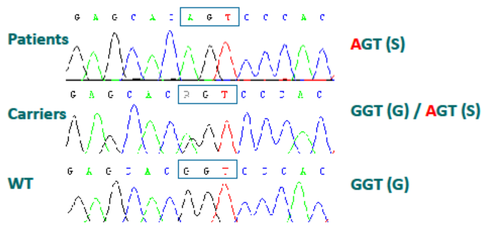
Mutations result. c.201_202delCT is a deletion of one pair in exon 3. This deletion creates a stop codon resulting in a truncated 68 amino acid protein, which eliminates key functional domains of the protein. *A genetic founder effect of the c.201_201delCT mutation* in StAR protein is the cause of most 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 premarital and prenatal counseling implications.

Family pedigree and founder effect:







Sample	A0	A1	A2	A3	A4	A5	A6	A7	A8	A9	A10	A11	A12	A13	A14	A15	A16	A17/A18	Normal
Testesterone (nmol/liter)	NA	<0.1	<0.1	0.16	0.027	<0.01	0.43	<0.69	<0.69	<0.69	UD	UD	<0.1	NA	NA	<0.1	<0.35	0.1	<2.45 nmol/liter
Testesterone (60 minutes) (nmol/liter)	NA	<0.1	NA	NA	0.029	<0.01	0.38	<0.69	<0.69	<0.69	UD	UD	UD	NA	NA	<0.1	<0.35	NA	
Δ4 (nmol/liter)	<1.4	NA	0.3	0.9	0.4	NA	1	<0.35	<0.35	<0.35	UD	UD	0.45	0.07	NA	<0.1	0.2	<0.35	0.052-0.63 µmol/liter
Δ4 (60 minutes) (nmol/liter)	NA	NA	<0.1	NA	NA	NA	1.1	<0.35	<0.35	<0.35	UD	UD	UD	NA	NA	<0.1	0.2	<0.35	
DHEAS (µmol/liter)	<0.2	6	<0.1	<0.1	<0.1	<2	<2	<0.41	<0.41	<0.41	UD	UD	<0.27	0.0009	NA	<0.1	<0.05	<0.41	180-700 nmol/liter
DHEAS (60 minutes) (µmol/liter)	NA	4.8	<0.1	NA	<0.1	<2	<2	<0.41	<0.41	<0.41	UD	UD	UD	NA	NA	<0.1	<0.05	NA	
Aldosterone (pmol/liter)	<25 pg/ml	NA	238	NA	NA	NA	NA	<138	<138	UD	UD	199	<45	NA	NA	NA	NA	325	
Hyperpigmentation	Present	Present	Present	present	None	present	None	Present	Present	Present	present	Present	Present	Present	Present	Present	Present	Present	
Neurological Symptoms	Seizures	None	Seizures	None	Seizures, Hypotonia	Seizure	Seizures, Hypotonia	None	None	None	None	None	None	Supratentorial white matter lesions	Chiari-I	None	None	Seiures	
Present Age (years)	12.5	3 years 10 months	8	6	6 years 4 months	2 years 6 months	Died	13	7	3	1	6	1.7	14.5	10.2	6 years	9 yrs	9-15 years	
Height (cm)	146			110	118		NA	148.3	113	88	66.2	106	82.4	146.1	132.6				
Height percentile (%)	25	50	50	25	50	50	NA	8th	7th	10th	<3rd	6th	46th	1st	15th	50			
Target Height Percentile (%)							NA	6th	6th	6th	6th	50th	23rd	25th	25th				

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Hyperpigmentation	Present	Present	Present	present	None	present	None	Present	Present	Present	present	Present	Present	Present	Present	Present	Present	Present	
Neurological Symptoms	Seizures	None	Seizures	None	Seizures, Hypotonia	Seizure	Seizures, Hypotonia	None	None	None	None	None	None	Supratentorial white matter lesions	Chiari-I	None	None	Seiures	
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Height percentile (%)	25	50	50	25	50	50	NA	8th	7th	10th	<3rd	6th	46th	1st	15th	50			
Target Height Percentile (%)							NA	6th	6th	6th	6th	50th	23rd	25th	25th				

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.

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Adrenals and HPA Axis

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