COQ6 AND *COQ2* MUTATIONS ASSOCIATED WITH STEROID RESISTANT NEPHROTIC SYNDROME

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INTRODUCTION AND AIMS

Primary CoQ10 deficiency due to molecular defects in any of the genes of the Coenzyme Q biosynthetic pathway (Figure 1) represents a group of rare recessive disorders primarily characterized by neurological and muscular symptoms and occasionally associated with glomerular disease. Identification of causative single-gene mutation may have important therapeutic consequences mainly because of potential reversibility of symptoms. Here we describe atypical clinical presentations associated with pathogenic mutations in two genes of the CoQ10 pathway, i.e. *COQ2* and *COQ6*, in three patients with SRNS.

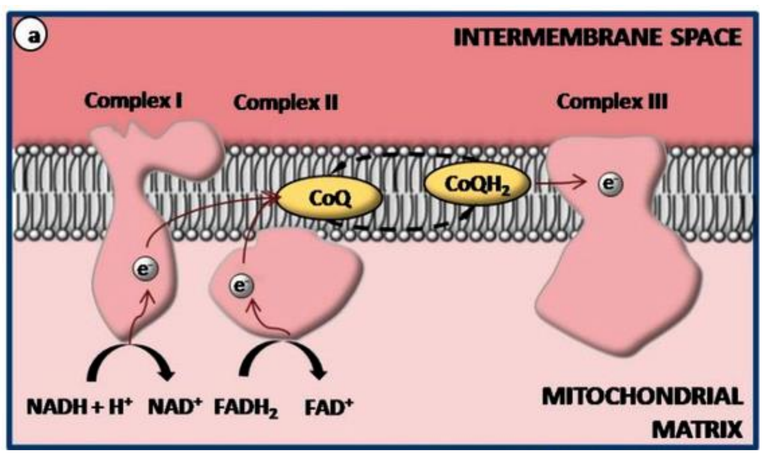

Figure 1. Coenzyme Q biosynthetic pathway

METHODS

We used next-generation sequencing (NGS) to analyze a panel of 29 genes associated with Steroid Resistant and syndromic forms of Nephrotic Syndrome. Target enrichment was performed using an Illumina TruSeq Custom Amplicon panel designed specifically for selected genes. Sequencing was performed on an Illumina MiSeq Desktop Sequencer. The potential pathogenicity of the newly identified missense mutations was evaluated by in silico approaches *(SIFT, Polyphen and Mutation Taster),* comparative analysis in 10 different species (ClustalW) and functional complementation in yeast. All pathogenic mutations were confirmed by Sanger sequencing.

Gene	Accession #	Chromosome
Autosomal Recessive		
ARHGDIA	NM_001185078.1	17
CFH	NM_000186.3	1
COQ2	NM_015697.7	4
COQ6	NM_182476.2	14
CUBN	NM_001081.3	10
DGKE	NM_003647.2	17
EYA1	NM_000503.4	8
LCAT	NM_000229.1	16
LAMB2	NM_002292.3	3
MYO1E	NM_004998.3	15
NPHS1	NM_004646.3	19
NPHS2	NM_014625.2	1
PDSS2	NM_020381.3	6
PLCE1	NM_016341.3	10
PTPRO	NM_030667.2	12
SCARB2	NM_005506.3	4
SMARCAL1	NM_014140.3	2
Autosomal Dominant		
ACTN4	NM_004924.4	19
APOL1	NM_145343.2	22
ARHGAP24	NM_001025616.2	4
CD2AP	NM_012120.2	6
FN1	NM_212482.1	2
INF2	NM_022489.3	14
LMX1B	NM_001174147.1	9
MYH9	NM_002473.4	22
SIX1	NM_005982.3	14
TRPC6	NM_004621.5	11
WT1	NM_024426.4	11
X-Linked		
GLA	NM_000169.2	X

Figure 2. Targeted re-sequencing of 29 SRNS-associated genes by MiSeq (Illumina)

RESULTS

We identified one novel homozygous *COQ2* mutation (c.1169G>C; p.Gly390Ala) in two cousins with adolescent-onset SRNS and mild neurological symptoms from two related Italian families of Southern Italy (Family 1; Figures 3 and 4) and one novel COQ6 mutation (c.782C>T; p.Pro261Leu) in a child with early onset SRNS without deafness and a renal pathology picture of type 1 membranoproliferative lesions associated with C3 deposits (Family 2; Figures 3 and 4). Functional complementation in yeast, in silico approaches and segregation analysis confirmed the pathogenicity of the newly identified changes (Figure 4).

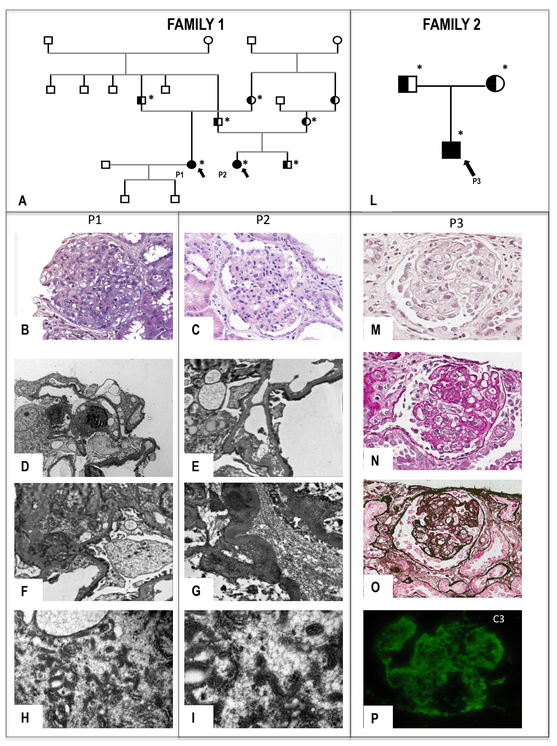

Figure 3. Pedigrees and renal biopsy findings.

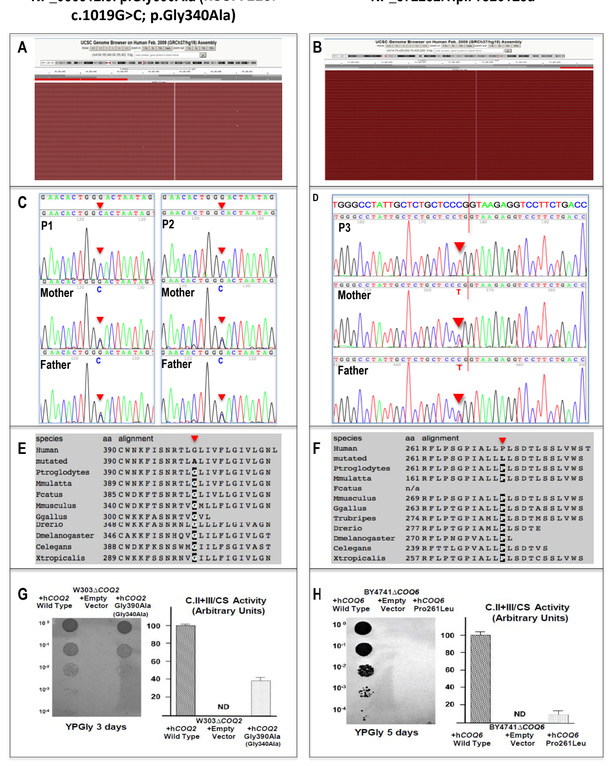

Figure 4. Mutation Analysis.

CONCLUSIONS

Our study provides new leads to gaining a better understanding of clinical variability in primary CoQ10 deficiency because it (1) expands the spectrum of known and functional characterized COQ2 and COQ6 variants and the small number of affected pedigrees so far reported; (2) describes novel possible phenotypes associated with COQ2 and COQ6 changes; and (3) emphasizes the importance of an early molecular diagnosis also in patients with adolescent-onset SRNS or without neurological symptoms to provide effective treatment with CoQ10 and improve or prevent neurological and renal manifestations.

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