ASSOCIATION OF FOCAL AND SEGMENTAL GLOMERULOSCLEROSIS AND CHARCOT-MARIE-TOOTH DISEASE: IDENTIFICATION OF A NEW MUTATION IN INVERTED FORMIN 2-GENE

L.-Y. Mani[1], D. Sidler[1], R. Campait[2], B. Vogt[1], C. Antignac[2,3]

[1]University clinic for Nephrology, Hypertension and clinical pharmacology, University Hospital Bern, Switzerland
[2]Department of Genetics and [3]Laboratory of Hereditary Kidney Diseases, Imagine Institute (Inserm U1163), Paris, France

OBJECTIVES

We report the case of an adult patient having received a kidney transplant during childhood for focal and segmental glomerulosclerosis (FSGS) diagnosed with Charcot-Marie-Tooth (CMT) disease. A heterozygous mutation of the Inverted formin-2 (*INF2*)-gene (1) was identified that has not been described yet, occurring in the gene region where mutations with the identical context were found recently(2).

METHODS

A 43-year old female patient is regularly followed since kidney transplantation at the age of 17 years for end stage renal disease (ESRD) due to FSGS with an uncomplicated clinical evolution.
Nephrotic-range proteinuria was first detected during medical school screening at age 15, associated with impaired renal function and arterial hypertension. Renal biopsy at the age of 16 years was consistent with a FSGS lesion. Kidney disease progressed rapidly during a short treatment course of ciclosporin and steroids and reached a terminal level at age 16 with initiation of chronic hemodialysis.
In addition, the patient suffered from hereditary motor and sensory neuropathy type I (CMT disease) diagnosed at the age of nine years; electromyoneurogram showed slowed nerve conduction velocities of N. peroneus; a sural nerve biopsy at the age of nine years revealed marked reduction in myelinized nerve fibers and the presence of mast cells; genetic testing was not performed. The phenotype included stumbling and falls since the age of three years and progressive distal muscle weakness of upper and lower extremities leading to foot (pes equinovarus and cavus) and hand deformities requiring repeated orthopedic interventions.
Symmetric sensorineural hearing loss at 2000 Hz was diagnosed at age 19 leading to bilateral treated deafness since the age of 38 years.
Familial history revealed no cases in family members; there are no siblings or offspring of the index case.
Review of the native kidney biopsy with performance of electron microscopy confirmed FSGS lesion, not otherwise specified (NOS)-variant.
In the clinical context of FSGS associated with CMT disease, a mutation in the *INF2* gene was suspected.

RESULTS

Direct sequencing of exons 2 and 3 of the *INF2* gene revealed a heterozygous in frame deletion of 9 base pairs (c.367_375del) in exon 2 that leads to a protein lacking three amino acids at position 123-125 (p.Gly123_Val125). This mutation has not been described previously and localizes in the gene region where mutations in cases with the association of CMT disease and FSGS were recently reported (N-terminal diaphanous-inhibitory domain, second and third armadillo repeats; exon 2, nucleotides 300-500).

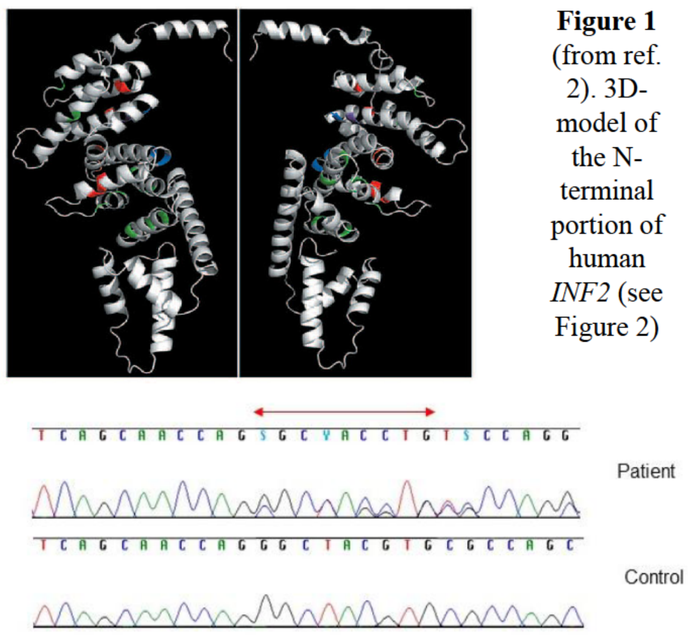

Figure 1 (from ref. 2). 3D-model of the N-terminal portion of human *INF2* (see Figure 2)

Figure 3 Chromatogram *INF2* protein of the index patient. Heterozygous mutation c.367_375del in exon 2 leading to lack of 3 amino acids (p.Gly123_Val125)

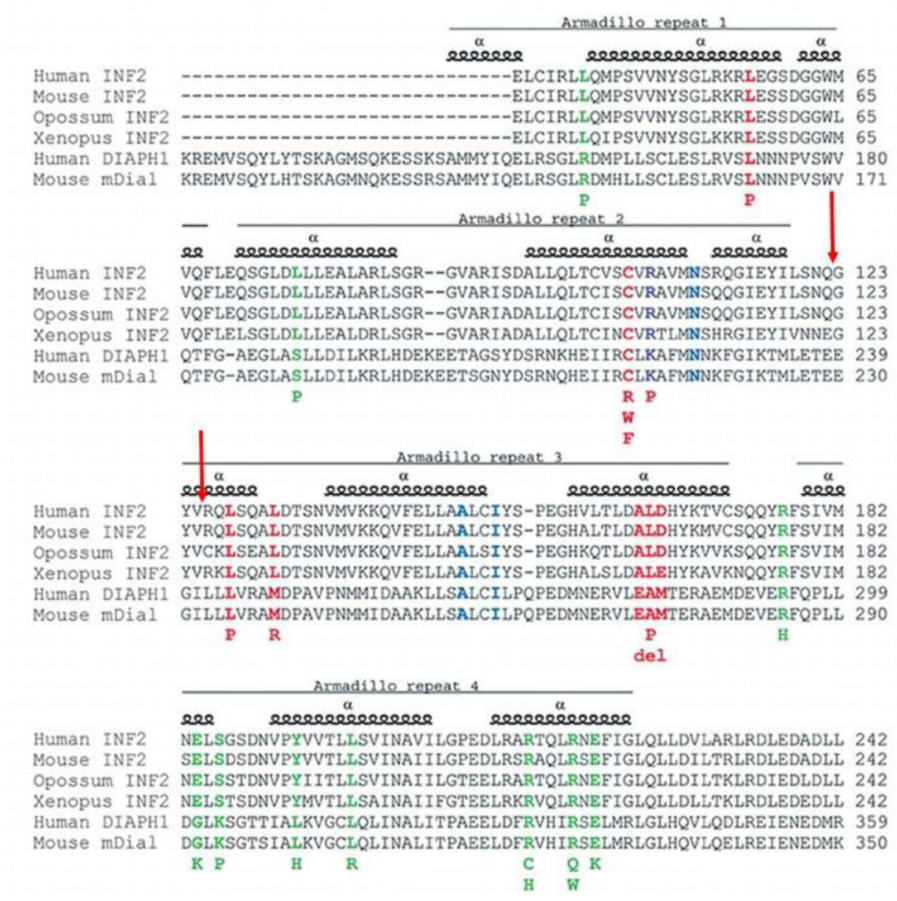

Figure 2 (adapted from ref. 2). C-terminal sequence of *INF2*, *INF2*-like and DIAPH1 (diaphanous-related protein 1) proteins from different species showing amino acid substitutions in different conditions. Red arrows indicate the zone where the mutation in our patient was identified. Red and purple letters= substitutions in patients with FSGS and CMT disease in the cited study. Green letters= substitutions in patients with FSGS alone. Blue letters=residues important for DID (diaphanous-inhibitory domain)-DAD (diaphanous autoregulatory domain) interactions.

CONCLUSIONS

We identified a new heterozygous likely spontaneous mutation in the *INF2* gene. As localized in the gene region where mutations leading to this phenotype have been described until now, it is most likely to explain the renal and neurological presentation in this patient. It can however not be excluded that the mutation found is merely responsible for the renal phenotype as genetic testing for classical genes for CMT disease has not been performed.

REFERENCES:

1.Brown EJ, Schlöndorff JS, Becker DJ et al. Mutations in the formin gene INF2 cause focal segmental glomerulosclerosis. Nat Genet 2010;42:72-6
2.Boyer O, Nevo F, Plaisier E et al. INF2 mutations in Charcot-Marie-Tooth disease with glomerulopathy. N Engl J Med. 2011 Dec 22;365(25):2377-88

DOI: 10.3252/pso.eu.51era.2014