GENETICS

INF2 mutations often implicated in autosomal dominant focal segmental glomerulosclerosis

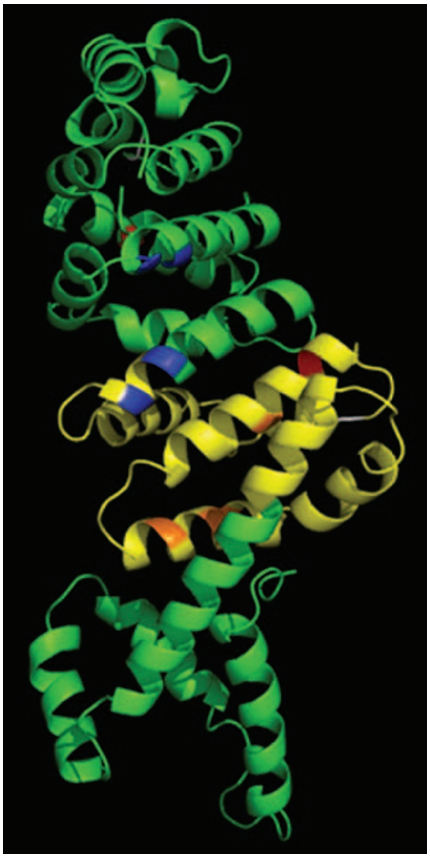
Mutations in the *INF2* gene, which encodes a member of the formin family of actin-regulating proteins, cause a high proportion of cases of autosomal dominant focal segmental glomerulosclerosis (FSGS), according to a study published in the *Journal of the American Society of Nephrology*.

Most cases of inherited FSGS occurring in childhood display an autosomal recessive type of inheritance. However, *ACTN4* and *TRPC6* genes have been shown to be implicated in the rare autosomal dominant forms of the disease occurring in juveniles and adults, accounting for about 4% and 6% of familial FSGS, respectively.

An article by Elizabeth Brown and colleagues published in *Nature Genetics* in 2010 reported the identification of nine independent missense mutations in *INF2* that were found to segregate with autosomal dominant FSGS in 11 unrelated families. These researchers hypothesized that individuals with disease-associated *INF2* mutations have a defect in actin-mediated podocyte structural maintenance and repair.

As Brown *et al.*'s finding had not been confirmed by other studies, and because the role of *INF2* mutations in sporadic cases of FSGS was unknown, Olivia Boyer *et al.* decided to look further into the prevalence of *INF2* mutations in FSGS. These researchers screened 54 families (78 patients) with a glomerular proteinuric disorder that seemed to show an autosomal dominant mode of inheritance. Mutations in *ACTN4* and *TRPC6* were excluded in all cases.

"Given the occurrence of incomplete penetrance in autosomal dominant FSGS cases and the reports of neomutation in *ACTN4*-, *TRPC6*- and *INF2*-related FSGS, we also searched for *INF2* mutations in 84 sporadic cases of FSGS," notes Boyer. No differences were observed between familial and sporadic cases in terms of ethnicity, histology or clinical presentation.



© 3D model of INF2–DID. Image courtesy of Olivia Boyer, Hôpital Necker-Enfants Malade, Paris, France.

Among familial cases, proteinuria occurred at a median age of 20.5 years (range 2–52 years), and FSGS was documented in at least one affected family member in 80% of families. The researchers found seven missense *INF2* mutations in nine families (28 patients), a detection rate of 16.7%. Median age at proteinuria onset was higher in patients with *INF2* mutations than in those without (27 years versus 15.5 years; $P = 0.026$).

Only one patient with sporadic FSGS (who presented with proteinuria and FSGS lesions at 15 years of age) was found to have a known *INF2* mutation (p.R218Q). Complete data from the patient's apparently healthy parents were not available to determine whether this patient had a *de novo* mutation or whether this patient was a familial case with low penetrance and variable expressivity.

Boyer *et al.* found that all variants of the *INF2* mutation were localized in exons 2 and 4 and caused nonconservative changes in highly conserved amino acids of the N-terminal diaphanous inhibitory domain (DID) of INF2, a region that interacts with the C-terminal diaphanous autoregulatory domain (DAD), competing for actin monomer binding and inhibiting depolymerization. Six of the seven distinct altered residues were found to localize to an INF2 region corresponding to an mDia1 DID subdomain that is reported to co-immunoprecipitate with IQ motif-containing GTPase-activating protein (IQGAP1), which is known to interact with the podocyte proteins nephrin and PLCε1.

The results of this study confirm that *INF2* mutations are responsible for a high proportion of autosomal dominant cases of FSGS, greater than the proportion of cases caused by mutations in *ACTN4* or *TRPC6*. The authors recommend that screening for *INF2* mutations, at least in exons 2 to 4, should be strongly considered in patients with an autosomal dominant history of FSGS. "Although *INF2* is the major known gene associated with autosomal dominant FSGS, it explains only 12–17% of cases, suggesting the implication of other podocyte genes, yet to be identified," notes Boyer. "Therefore, our group continues to look for new genes involved in familial proteinuric disorders."

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Original article Boyer, O. *et al.* Mutations in *INF2* are a major cause of autosomal dominant focal segmental glomerulosclerosis. *J. Am. Soc. Nephrol.* **22**, 239–245 (2011)

Further reading Brown, E. J. *et al.* Mutations in the formin gene *INF2* cause focal segmental glomerulosclerosis. *Nat. Genet.* **42**, 72–76 (2010)