Supplementary Figure S4. Decision making strategy to pathogenicity of a variant identified by whole exome sequencing

Autosomal recessive variants

Include homozygous or compound heterozygous alleles as disease causing if:

- Truncating mutation (stop, abrogation of start or stop, obligatory splice, frameshift) **or**
- Missense mutation if a minimum of 4 of 5 of the following criteria were met:
  - Continuously conserved at least among vertebrates (or beyond)
  - Previously reported as disease causing or functional evidence implicating causality
  - Loss of function in human allele is supported by functional data
  - Phenotype correlates with the published phenotype for the gene
  - Predicted deleterious for the protein function (at least in two among three prediction programs (Polyphen (>0.5), SIFT (Del.), Mutation taster (D.C.))

Exclude allele as disease causing if:

- Allele frequency
  - Allele frequency >1% (in EVS server, ExAC, gnomAD, 1000 genomes)
  - If the variant is present >1 homozygously in any individual in any of the publically available databases listed above
- Non segregation
  - if compound heterozygous variants are in cis or if an affected family member is without the variant or an unaffected family members is with the variant

Discussion of genotype-phenotype correlation in a panel of nephro-geneticists followed by review of clinical phenotype with referring physician

Cross reference with the ACMG guidelines (Richards *Genet Med* 2015, 17:405)

Autosomal dominant variants

Include heterozygous alleles as disease causing if:

- Truncating mutation (stop, abrogation of start or stop, obligatory splice, frameshift) **or**
- Missense mutation if a minimum of 4 of 5 of the following criteria were met:
  - Continuously conserved at least among vertebrates (or beyond)
  - Previously reported as disease causing or functional evidence implicating causality
  - Phenotype correlates with the published phenotype for the gene
  - Predicted deleterious for the protein function (at least in two among three prediction programs (Polyphen (>0.5), SIFT (Del.), Mutation taster (D.C.))

Exclude allele as disease causing if:

- Allele Frequency
  - Heterozygous allele frequency >0.1% (in EVS server, ExAC, gnomAD, 1000 genomes)
  - If the variant is present homozygously in any individual in any of the publically available databases listed above
- Non segregation
  - if an affected family member is without the variant
- If an unaffected family member is with the allele consider incomplete penetrance and variable expressivity

Discussion of genotype-phenotype correlation in a panel of nephro-geneticists followed by review of clinical phenotype with referring physician

Cross reference with the ACMG guidelines (Richards *Genet Med* 2015, 17:405)