

# **A genotype-to-phenotype approach suggests under-reporting of single nucleotide variants in Nephrocystin-1 (*NPHP1*) related disease (UK 100,000 Genomes Project).**

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# SUPPLEMENTARY INFORMATION

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**Supplementary Table 1 - Twenty six additional variants in *NPHP1* from twenty four participants that are not overtly consistent with autosomal recessive inheritance or are recessive with intronic variants or otherwise predicted benign.** Dark blue background indicates homozygous variants and pale blue indicates heterozygous variants; t = in-trans, c = in-cis. Chr:Position, chromosome and position of 5' base of variant in Homo sapiens (human) genome assembly GRCh38; Ref, reference allele; Alt, alternative allele; Consequence, Consequence of the variant (del = deletion, sg = stop gained variant, ns = non-synonymous, int = intronic); Amino acid, amino acid change; gnomAD frequency, gnomAD genome v3.0 allele frequency (all populations); CADD phred, Combined Annotation Dependent Depletion score (phred scale) version 1.6; Clinvar, Clinical significance according to Clinvar (B = benign, P = pathogenic, VUS = variant of uncertain significance, CI = conflicting interpretations of pathogenicity); ACMG, Assessment of pathogenicity after application of American College of Medical Genetics and Genomics and the Association for Molecular Pathology guidelines for the interpretation of sequence variant (P = pathogenic, VUS= variant of uncertain significance).



**Supplementary Table 2. Predicted interactions found in NPHP1 wild-type and R683W models using BioLuminate.**

| Residues                           | Distance(A) | Specific Interactions              | #HB | #Salt Bridges | #Pi Stacking | #Disulfides | #vdW Clash |
|------------------------------------|-------------|------------------------------------|-----|---------------|--------------|-------------|------------|
| <b>R683 (wild-type, A:Arg 683)</b> |             |                                    |     |               |              |             |            |
| A:Ala 682                          | 1.3         |                                    | 0   | 0             | 0            | 0           | 0          |
| A:Val 686                          | 2.7         |                                    | 0   | 0             | 0            | 0           | 0          |
| A:Thr 681                          | 3.3         |                                    | 0   | 0             | 0            | 0           | 0          |
| A:Lys 685                          | 3.2         |                                    | 0   | 0             | 0            | 0           | 0          |
| A:Trp 684                          | 1.3         |                                    | 0   | 0             | 0            | 0           | 0          |
| A:Pro 670                          | 1.9         | 1x hb to A:Pro 670                 | 1   | 0             | 0            | 0           | 0          |
| A:Glu 680                          | 2.7         |                                    | 0   | 0             | 0            | 0           | 0          |
| A:Thr 679                          | 2.0         | 1x hb to A:Thr 679                 | 1   | 0             | 0            | 0           | 0          |
| A:Leu 669                          | 2.2         |                                    | 0   | 0             | 0            | 0           | 0          |
| A:Ile 687                          | 2.0         | 1x hb to A:Ile 687                 | 1   | 0             | 0            | 0           | 0          |
| A:Asp 621                          | 2.0         | 2x hb, 1x salt bridge to A:Asp 621 | 2   | 1             | 0            | 0           | 0          |
| A:Phe 672                          | 2.3         |                                    | 0   | 0             | 0            | 0           | 0          |
| A:Gln 619                          | 2.0         | 1x hb to A:Gln 619                 | 1   | 0             | 0            | 0           | 0          |
| A:Pro 671                          | 3.0         |                                    | 0   | 0             | 0            | 0           | 0          |
| A:Val 622                          | 2.4         |                                    | 0   | 0             | 0            | 0           | 0          |
| A:Arg 673                          | 3.8         |                                    | 0   | 0             | 0            | 0           | 0          |
| <b>R683W (A:Trp 683)</b>           |             |                                    |     |               |              |             |            |
| A:Ala 682                          | 1.3         |                                    | 0   | 0             | 0            | 0           | 0          |
| A:Thr 681                          | 3.2         |                                    | 0   | 0             | 0            | 0           | 0          |
| A:Lys 685                          | 3.1         |                                    | 0   | 0             | 0            | 0           | 0          |
| A:Trp 684                          | 1.3         |                                    | 0   | 0             | 0            | 0           | 0          |
| A:Pro 670                          | 2.4         |                                    | 0   | 0             | 0            | 0           | 0          |
| A:Glu 680                          | 2.6         |                                    | 0   | 0             | 0            | 0           | 0          |
| A:Thr 679                          | 1.8         | 1x hb to A:Thr 679                 | 1   | 0             | 0            | 0           | 0          |
| A:Val 686                          | 2.6         |                                    | 0   | 0             | 0            | 0           | 0          |
| A:Leu 669                          | 2.3         |                                    | 0   | 0             | 0            | 0           | 0          |
| A:Ile 687                          | 1.7         | 1x hb, 1x clash to A:Ile 687       | 1   | 0             | 0            | 0           | 1          |
| A:Asp 621                          | 2.6         |                                    | 0   | 0             | 0            | 0           | 0          |
| A:Val 622                          | 2.0         |                                    | 0   | 0             | 0            | 0           | 0          |
| A:Phe 672                          | 2.4         |                                    | 0   | 0             | 0            | 0           | 0          |
| A:Pro 671                          | 2.4         |                                    | 0   | 0             | 0            | 0           | 0          |
| A:Gln 619                          | 2.4         |                                    | 0   | 0             | 0            | 0           | 0          |

**Supplementary Table 3. Distribution on missense mutation on the NPHP1 protein model, and their predicted effect in the structure.**

[illegible]