JUVENILE NEPHRONOPHTHISIS DUE TO *NPHP1* HOMOZYGOUS DELETION REVEALED BY WHOLE EXOME SEQUENCING

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INTRODUCTION

Renal failure is a major cause of morbidity and mortality worldwide and revealing a potential genetic background is essential for the patients' management and families' counselling.

- **Nephronophthisis** (NPH) is an autosomal recessive nephropathy with chronic tubulointerstitial involvement, which represents the leading cause of end-stage renal disease (ESRD) in children and adolescents.

- With regard to the age of onset for ESRD, three clinical variants have been described:
  - Infantile
  - Juvenile
  - Adolescent

- Genetic diagnosis can be established using molecular genetic testing by sequence analysis of a multigene panel including NPH-related genes and other ciliopathy or renal disease-related genes of interest as well as gene targeted deletion-duplication analysis.

MATERIALS AND METHODS

A 17-year-old female with tubulointerstitial nephritis was referred for whole exome sequencing (WES). WES was performed on DNA extracted from peripheral blood, using Twist's Human Exome Core-v2 kit (Twist Bioscience). Following preparations according to the manufacturer's protocol, libraries were sequenced on an Illumina NextSeq-500 genetic analyzer. Data processing, variant calling and pre-classification were conducted by SOPHiA DDM® bioinformatics pipelines. Multiplex Ligation-dependent Probe Amplification (MLPA) was performed (P387-C1, Coffalyser net, MRC-HOLLAND) to further confirm results.

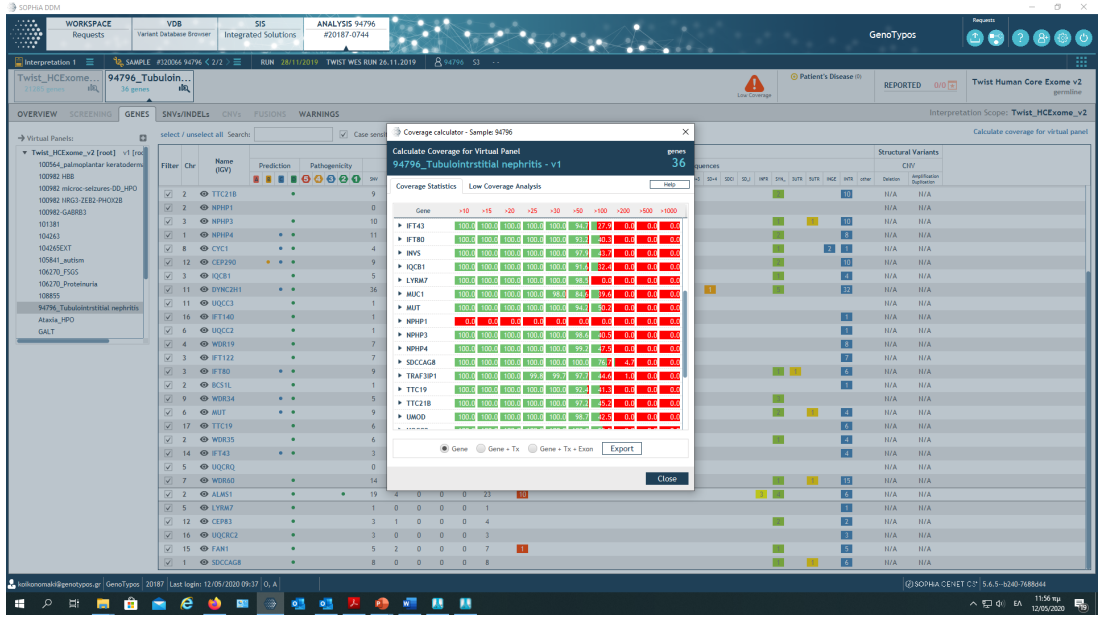
GENES ANALYZED

ALMS1, BCS1L, CEP120, CEP164, CEP290, CEP83, CYC1, DYNC2H1, FAN1, IFT122, IFT140, IFT172, IFT43, IFT80, INVS, IQCB1, LYRM7, MUC1, MUT, NPHP1, NPHP3, NPHP4, SDCCAG8, TRAF3IP1, TTC19, TTC21B, UMOD, UQCC2, UQCC3, UQCRB, UQCRC2, UQCRQ, WDR19, WDR34, WDR35, WDR60

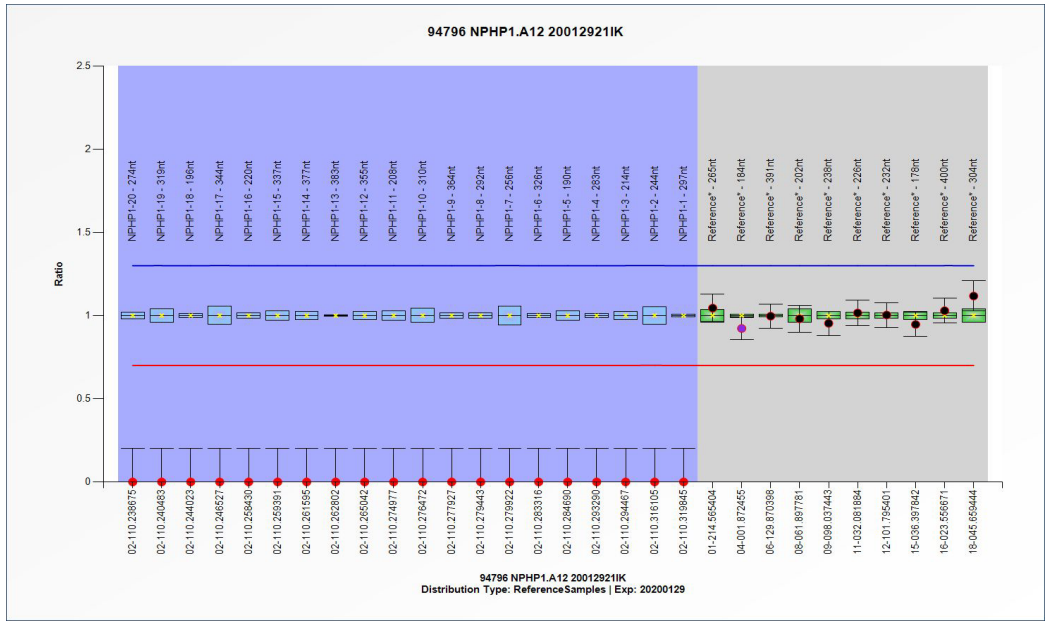
RESULTS

No pathogenic/likely pathogenic SNVs/Indels were detected, related to the phenotype. Gene coverage analysis revealed a homozygous *NPHP1* whole gene deletion, subsequently confirmed by MLPA. Deletions including at least *NPHP1* are associated with Juveline nephronophthisis, which is in concordance with the phenotype. Parental DNA MLPA analyses revealed *NPHP1* heterozygous deletions in both, whereas the proband's sister was completely normal thus, substantiating inheritance and further guiding the selection of the appropriate family member for possible kidney transplantation.

NGS ANALYSIS – *NPHP1* COVERAGE CALCULATION



MLPA ANALYSIS of *NPHP1* gene



DISCUSSION

Optimization in WES protocols allows greater confidence in calling copy number variations. By applying this approach, definite diagnosis of the nephropathy was achieved, otherwise challenging with traditional methods. Whole exome sequencing permits a large number of genes investigated, for different types of variants, establishing diagnosis and leading to accurate and timely decisions for the patient's and families' healthcare.