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Population modelling depicts the mutational burden of NPHS2 (podocin) nephropathy and reveals an undiagnosed adult-onset genetic cohort

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TRAVERE THERAPEUTICS

GeneScape

natera

INTRODUCTION

- Disease burden often underestimated in rare disease like monogenic nephrotic syndrome (NS) (or focal segmental glomerulosclerosis, FSGS)
- NPHS2 mutations are the commonest cause of **childhood NS/FSGS**
- NPHS2 nephropathy is autosomal recessive, but this is complicated by **hypomorphic variant R229Q, which is only pathogenic when inherited in trans with specific alleles**
  - R229Q compound heterozygotes result in adult onset FSGS

AIM

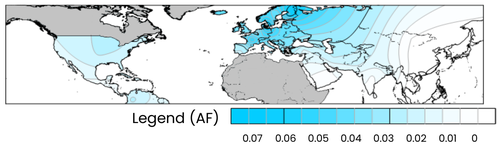
To estimate pathogenic genotype frequencies of *NPHS2* in US, UK, Europe and Japan by population modelling of large, diverse genetic cohorts

METHOD

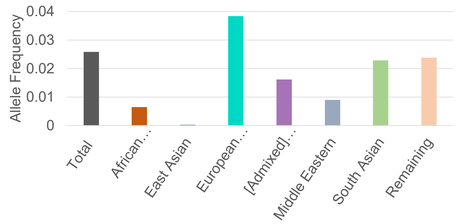
- Over 1.2 million genomes from five databases (NIH TopMed, NIH 'All of US', UK Biobank, gnomAD, TogoVAR) were included for population modelling
- NPHS2 variant pathogenicity was classified by ACMG guidelines and cross-referenced with ClinVAR
- Genotypes were assigned to phenotypic groups of slow, intermediate or rapidly progressing disease
- Modelled frequencies were compared to a clinical cohort (US patients genotyped on Natera Renasight) and the DUPLEX FSGS study

RESULTS

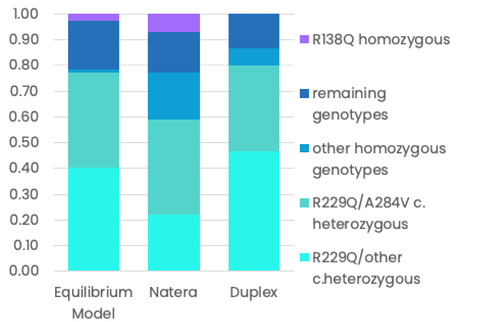
Distribution of R229Q across the Northern Hemisphere



Distribution of R229Q in biogeographical ancestry super groups within the US

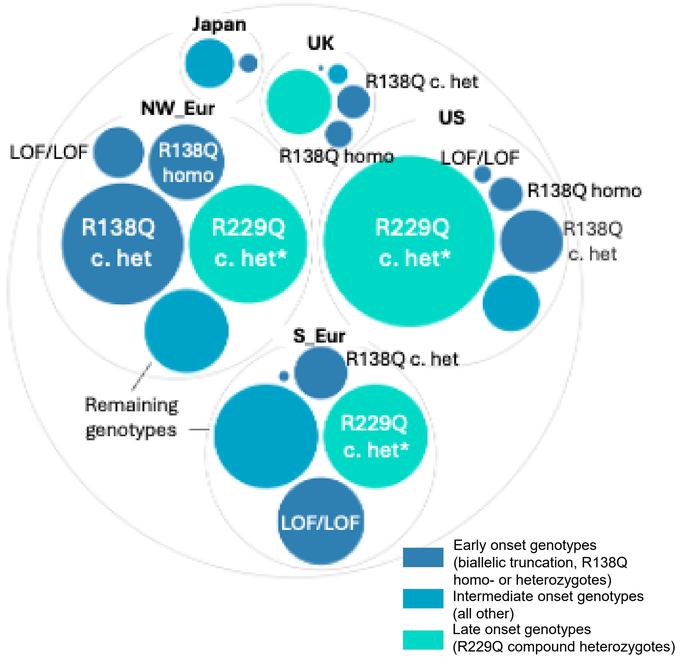


Expected vs. Observed Genotypes

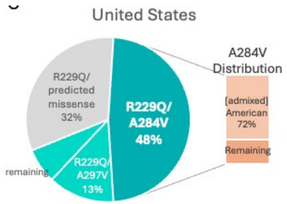


	Natera Renasight™	Duplex (NCT03493685)
About	Commercial renal gene panel in the US	International FSGS trial (patients above age 8 years)
Number of patients	92,984	371
Number of NPHS2 patients	67	15

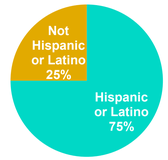
Genotype Frequencies



R229Q compound heterozygous distribution in Equilibrium model



Ethnicity distribution in A284V patients (Natera cohort)



CONCLUSIONS

- **Larger than expected R229Q mutational burden (particularly in the UK and US), associated with late/ adult-onset FSGS, confirmed with patient data.**
- Confirms R138Q distribution in Europe
- **We recommend NPHS2 genetic screening in adult FSGS patients in the UK and US**, to avoid unnecessary immunosuppression and inform planning for transplant

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