Assessing the Clinical Relevance of Genetic Variants Associated with Chronic Kidney Disease in Hispanic/Latino Individuals

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BACKGROUND

- **Genetic variants play a significant role in the development of Chronic Kidney Disease (CKD)**
  →Hispanic/Latino individuals are **disproportionately underrepresented in CKD research**
- The Trans-Omics for Precision Medicine (TOPMed) program provides **Whole Genome Sequencing Data + Phenotypic Profiles for >10,000 Hispanic/Latino Individuals**
- Proband: **40 y.o. Puerto Rican male** with **hypertension** and **eGFR 88**. **Serum creatinine 1.41**. **Highest uACR 1681. No diabetes**.
  →**eGFR consistent** with **stage 2 CKD** (mild kidney damage)
  →**uACR consistent** with **Albuminuria category A3** (severly increased)

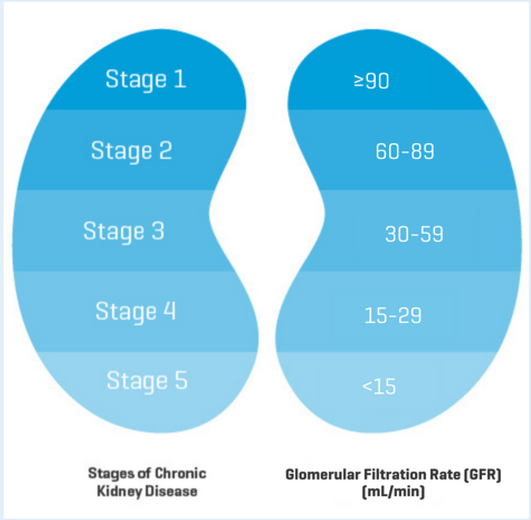

Figure 1. Stages of Chronic Kidney Disease and corresponding GFR levels.

RESEARCH OBJECTIVES

- **Improve understanding of clinical relevance of genetic variants in CKD**
- **To address the CKD research disparity gap in the Latino/Hispanic population subset**
- **Identify potential targets for precision medicine treatment for individuals with unique genetic underpinnings**

METHODS

I. Data Acquisition

- **TOPMed cohort** (WGS + Phenotypic Data)
- Select Hispanic/Latino individuals with **Confirmed CKD**
  →Subset of 47 Genomes

II. Variant Analysis

- **WGS data processed** by GENYSIS Core
- **Correlated variants** with detailed clinical phenotype data
- Sifted through literature to **examine overlapping phenotypic profiles**

III. Classification

- Apply **ACMG/AMP Guidelines**
- Classify Variants as **B, LB, P, LP, or VUS**
  →Perform targeted analysis on VUS'

RESULTS

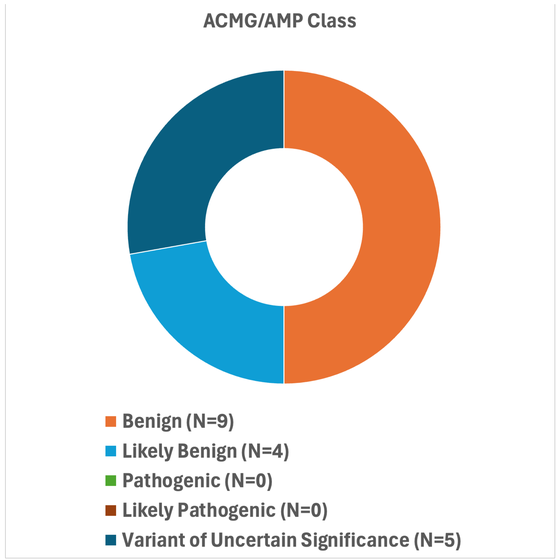

Figure 2. Distribution of identified variants by ACMG/AMP classification.

Initial analysis of 18 genetic variants revealed:

- The majority of variants, **13 (72%)**, were classified as **Benign (B) or Likely Benign (LB)**.
- The remaining **5 (28%)** variants were classified as **Variants of Uncertain Significance (VUS)**.
  →1 rare variant in *SCNN1G* gene associated with Liddle Syndrome (NM_001039.4:c.1676C>G; p.Ser559Cys)
- No variants were classified as **Likely Pathogenic (LP)** or **Pathogenic (P)**.

GENE OVERVIEW

- The *SCNN1G* gene is comprised of **13 exons** and encodes a **649 amino acid aa** protein
- The protein is one of the three pore-forming subunits of the heterotrimeric **Epithelial Sodium Channel (ENaC)**, a critical regulator of **sodium balance** and **fluid homeostasis**
- Protein expression is localized primarily to the **kidney**
- The gene is located on **Chromosome 16 (16p12.2)**
- It is localized within 400kb of the *SCNN1B* gene, which is also implicated in **Liddle Syndrome**

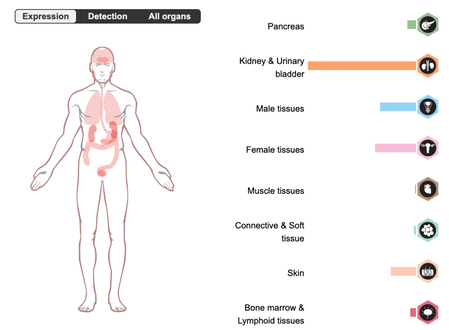

Figure 3. Tissue-specific expression map of the *SCNN1G* gene. Dark red regions indicate higher protein expression, predominantly in the kidney.

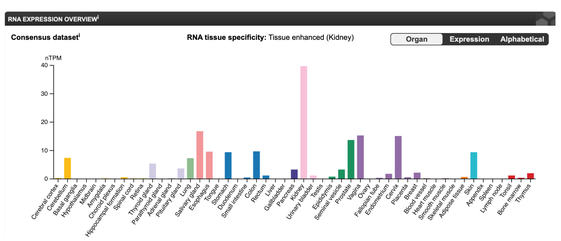

Figure 4. Tissue-specific RNA expression of *SCNN1G gene.*

DISCUSSION

- **Proband presents hypertension** which is **consistent with Liddle Syndrome**
  →Low plasma renin activity and low plasma aldosterone levels needed for confirmation of Liddle Syndrome
- **Novel genetic variant SCNN1G has conflicting evidence**
  →Low in-silico predictor score (REVEL=0.282; BP4)
  →Located in **exon 13** which encodes the **γ subunit of the ENaC**
  →Missense variants in this region are associated with **gain-of-function mutations** seen in **Liddle Syndrome**

REFERENCES

Granhøj, J., Nøhr, T. K., Hinrichs, G. R., Rasmussen, M., & Svenningsen, P. (2024). Reverse Phenotypes of Patients with Genetically Confirmed Liddle Syndrome. *Clinical journal of the American Society of Nephrology : CJASN, 19*(5), 610–619. https://doi.org/10.2215/CJN.0000000000000430

Stage 4 Chronic kidney Disease (CKD). (n.d.). My Kidney Journey. https://my.mykidneyjourney.com/en-my/chronic-kidney-disease/ckd-stage-4

Allele Registry. (n.d.). https://reg.clinicalgenome.org/redmine/projects/registry/genboree_registry/allele?hgvsOrDescriptor=NC_000016.10:g.23215195C%3EG

Clinical Synopsis -#618114 - LIDDLE SYNDROME 2; LIDLS2 (2018). https://omim.org/clinicalSynopsis/618114