A retrospective study of monogenic diabetes in two population health studies

Alexandre Bolze[1] , Simon White[1], Elizabeth T. Cirulli[1], Lavania Sharma[1], Karen A. Schlauch[2,3], Gai Elhanan[2,3], Joseph J. Grzymski[2,3], Nicole L. Washington[1], James T. Lu[1]

[1]Helix, San Mateo, CA, USA [2] Desert Research Insitute, Reno, NV, USA [3] Renown Institute for Health Innovation, Reno, NV, USA

Introduction

- Monogenic Diabetes accounts for 1 - 2% of all diabetes cases[1,2].
- Majority of monogenic diabetes caused by heterozygous loss-of-function variants in *GCK*, *HNF1A* & *HNF4A* [2].
- Sequencing *GCK*, *HNF1A* and *HNF4A* in T2D patients allows for better treatment (insulin is not necessary for these patients)[1,2].
- The clinical importance of identifying a pathogenic variant in an asymptomatic individual is not known because few studies have been conducted in the general population.
- In a large 'unselected' cohort, we aimed to:
  - Calculate the prevalence of carriers of monogenic diabetes pathogenic variants.
  - Assess the clinical impact of being a carrier.

- Participants: 20K (Healthy NV Project) + 50K (UK Biobank)
- Data: Exome + EHR + vitals + lab results for all.

Clinical impact

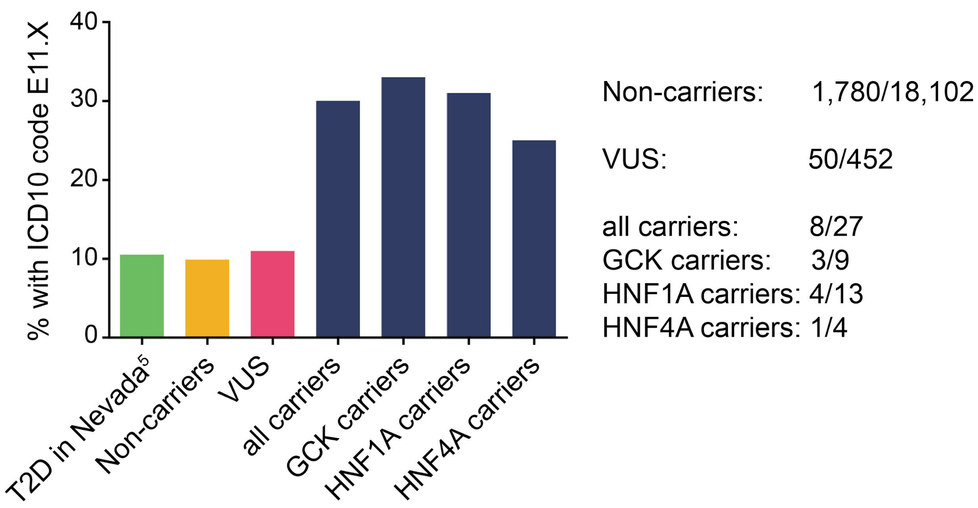

Figure 1: Absolute risk of being diagnosed with T2D in HNP.
Type 2 Diabetes diagnosis was assessed as having at least one ICD10 code starting by E11 in the EHR. Basic characteristics of the carriers: sex:{19 F, 8M}; age:{mean: 52 yo, median: 53 yo, 8 < 40 yo, 3 < 30 yo}.

In a small sample size group, carriers of P/LP in *GCK*, *HNF1A* or *HNF4A* had a **~30%** chance of being diagnosed with T2D.

Prevalence of carriers in the population

Healthy NV Project℠

	Variant type	counts in *GCK*	counts in *HNF1A*	counts in *HNF4A*
Analytical filter	All	1,291	1,124	1,936
	high quality	608	714	869
Vep filter	NS or FS	0	10	6
	splice	1	1	0
	missense	41	149	80
	unknown	1	10	6
Interpretation	VUS	34	122	68
	P / LP	**7**	**9**	**4**

Table 1: Filtering and interpretation of variants.
Vep annotation based on the most severe consequence. NS: nonsense, FS: frameshift. As a control, we looked at numbers of putative loss-of-function variants in gnomAD[3]: o/e(*GCK*) = 0.19, o/e(*HNF1A*) = 0.14, o/e(*HNF4A*) = 0.26. The higher number for *HNF1A* may be the result of looking at impact across all *HNF1A* transcripts.
Interpretation was based on a combination of ClinVar, Varsome ACMG interpretation[4], and a final manual review for variants with conflicting interpretations. 27 individuals carried one of the 20 P/LP variants.

0.15% (27 of 18,581) of participants in the Healthy NV Project carry a P/LP variant in *GCK*, *HNF1A* or *HNF4A*.

Meta-analysis HNP + UK Biobank

rank	gene	P-meta	P-UKBB	P-HNP
1	*GCK*	1.16E-09	4.00E-05	4.80E-08
...	...	...	...	...
283	*HNF4A*	0.0134	0.012	0.66
7,942	*HNF1A*	0.485	0.54	0.023

Table 2: Result of gene-burden tests for T2D in the 2 cohorts.
Results of this experiment were analyzed to assess the association of these 3 genes with EHR entries of diabetes.
17,570 genes tested. *GCK* was ranked as top gene. Coding model: (nonsynonymous in canonical transcript) AND (polyphen and SIFT not benign). MAF < 0.1% in each gnomAD population and these cohorts. BOLT-LMM for HNP- and UKB- only tests. Meta-analysis with PLINK.

More details in BioRxiv[6]
+
Liz Cirulli's talk:
Thursday 10AM, session 40: "Genome-wide rare variant analysis for thousands of phenotypes in 70,000+ exomes"
+
ukb.research.helix.com

Discussion

- Difficult to interpret variants. **Large number of VUS**
- **Need larger cohort** to draw conclusions on absolute and relative risk of carrying a pathogenic variant for monogenic diabetes
- Main questions:
  - **Why is only a fraction of carriers diagnosed with diabetes?**
  - What can be done to help carriers avoid diabetes?

1. Donath et al., *BMC Medicine* 17(1): 132, 2019
2. Naylor et al., "Maturity-Onset Diabetes of the Young Overview", *Gene Reviews*, 2018
3. gnomad.broadinstitute.org/ (accessed 2019/10/10)
4. varsome.com (accessed 2019/10/06)
5. www.americashealthrankings.org/explore/annual/measure/Diabetes/state/NV (accessed 2019/10/10)
6. Cirulli et al., "Genome wide rare variant analysis for thousands of phenotypes in 54,000+ exomes", *BioRxiv*, 2019.