Non-coding and mitochondrial DNA variants are disease causing for 1 in 20 patients with monogenic diabetes

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Introduction and Study Aim

- Most cases of diagnosed diabetes have multifactorial etiologies, but 1% to 4% are caused by variants in one of several diabetes-related genes.[1]
- Monogenic diabetes encompasses neonatal diabetes, mature onset diabetes of the young (MODY), and other syndromic presentations.
- Most multi-gene panel testing historically performed for this indication has not included analysis of intronic regions or the mitochondrial genes.
- In this study, we retrospectively assessed the diagnostic utility of next-generation sequencing (NGS) multi-gene panel tests containing both nuclear and mitochondrial genes and coverage of disease-associated non-coding variants

Methods

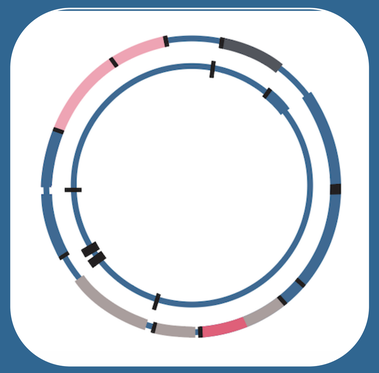
- Clinical reports of 507 patients with an indication of suspected monogenic diabetes who underwent NGS panel testing were examined (Table). Panel testing included sequence and copy number variant (CNV) analyses from a clinically validated exome assay targeting coding exons (+/- 20 bp from the intron/exon boundary) of up to 30 nuclear genes and up to 72 disease-associated non-coding variants.
- Almost 40% of patient tests (199/507) included mitochondrial genome analysis (mtDNA; 37 genes) as well.
- Variant interpretation was performed using modified ACMG/AMP guidelines. A molecular diagnosis was defined as the identification of pathogenic or likely pathogenic variants consistent with the patient's reported phenotype and known associated disease inheritance.

Results

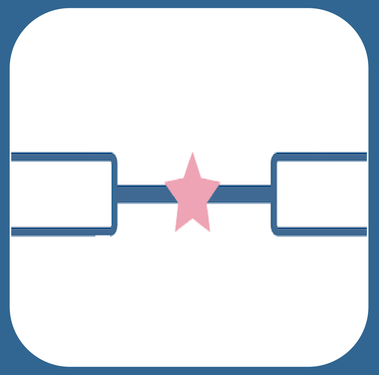
- Almost 25% (126/507) of patients received a molecular diagnosis in one of 11 genes associated with monogenic diabetes (Table, Figure).
- One molecular diagnosis was a targeted likely pathogenic non-coding variant, *INS* NM_000207.3:c.-152C>G, identified as homozygous in the patient.
- The pathogenic *MT-TL1* m.3243A>G mitochondrial variant, associated with maternally inherited diabetes and deafness (MIDD) syndrome, was the molecular diagnosis in ~5% (6/126) of patients with diagnostic findings. Age at testing range was 22 to 64 years and heteroplasmy levels in blood ranged from 5.2% to 48.0%. Two of these patients had hearing loss and most (5/6) reported a maternal family history of diabetes +/- hearing loss and/or macular dystrophy.
- Of note, diagnostic CNVs were reported in 10 patients, including two recurrent copy-number losses: a single-exon deletion in *GCK* (n=3) and a >1 Mb multigenic deletion involving *HNF1B* (n=7).

In this cohort of 507 patients with suspected monogenic diabetes, ~25% (126/507) of patients received a molecular diagnosis.

For 1 in 20 patients with confirmed monogenic diabetes, the causative variant was found in the:



Mitochondrial genome (n=6)



Non-coding space (n=1)

Category	# in total cohort	% of total cohort (n=507)	# in dx cohort	% of dx cohort (n=126)	Dx yield by category
Age range at testing					
Infants and children (newborn-age 10)	89	17.6%	28	22.2%	**28/89 31.5%**
Puberty (ages 11-19)	96	18.9%	30	23.8%	**30/96 31.3%**
Young adults (ages 20-40)	198	39.1%	52	41.3%	**52/198 26.3%**
Adults (ages 40- 75)	124	24.5%	16	12.7%	**16/124 12.9%**
Sex					
Male	222	43.8%	46	36.5%	**46/222 20.7%**
Female	285	56.2%	80	63.5%	**80/285 28.1%**
Panel					
MODY	387	76.3%	102	81.0%	**102/387 26.4%**
Monogenic diabetes	120	23.7%	24	19.0%	**24/119 20.2%**

Table. Patient cohort demographics and diagnostic yield by demographic category. Dx= diagnostic, MODY= mature onset diabetes of the young

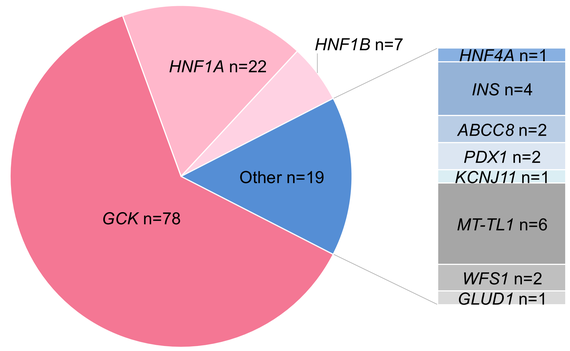


Figure. Most (84%) molecular diagnoses were explained by variants in the 3 genes associated with MODY in which a molecular diagnosis can help guide treatment: *GCK* (61.9%), *HNF1A* (17.5%), and *HNF1B* (5.6%). Also represented in this figure are the diagnostic variants identified in less common genes associated with MODY or neonatal diabetes (*HNF4A, ABCC8, KCNJ11, INS, PDX1*) or syndromic presentations involving diabetes (*GLUD1, WFS1, MT-TL1*).

Conclusion

NGS panel testing that includes mitochondrial genome analysis and targeted sequencing of disease-causing non-coding variants resulted in molecular diagnoses for almost 25% of patients with suspected monogenic diabetes.

References

1. McDonald TJ, Ellard S. Maturity onset diabetes of the young: identification and diagnosis. *Ann Clin Biochem*. 2013;50:403.

Conflict of interest statement: All authors are employed by Blueprint Genetics.

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