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Whole Exome Sequencing Reveals Potential Genetic Contributors to Monogenic Diabetes Mellitus in Trinidad

Akili Joseph, Winston Elibox and Rajini Haraksingh

Department of Life Sciences, Faulty of Science and Technology, The University of the West Indies, St. Augustine

akili.mata@my.uwi.edu

Abstract

Background & Objective:

Diabetes Mellitus (DM) in Trinidad and Tobago (TT)

- Prevalence rate of 14.5%
- DM mortality rate in TT is 14% compared to 11.3% globally.
- East-Indians residing mainly in Trinidad and account for 34.6% of population in TT, have a disproportionately higher rate of DM relative to other ethnicities.
- Alludes to a possible founder effect as this population has tripled (~468,524 persons) since its first introduction (~148,000 persons) to Trinidad in 1845.
- Prevalence of monogenic DM is 1-5% globally but unknown in Trinidad.
- East-Indian population presents a unique and understudied group for the elucidation of novel genetic variants that may contribute to DM.
- We seek to curate a cohort of DNA samples from diabetic patients and to identify known and novel variants that are associated with monogenic DM.

Design & Methods:

- DM patients across Trinidad were consented, interviewed, and DNA was isolated.
- Families with a Mendelian inheritance pattern were identified, and whole exome sequencing (WES) conducted.
- Variants identified by bioinformatic analysis were first screened in family members and then in DM cohort.
- Based on the results, a targeted next generation sequencing (NGS) based diagnostic panel specific for this population will be designed.

Results & Conclusion:

- 400 DM samples were collected, 3 were selected for family studies so far.
- 16 variants likely to contribute to the DM phenotype were identified so far.
- Analysis and screening of additional families are in progress.
- We expect that there are novel genetic contributors to monogenic DM as only one (within *PDX1*) of the 16 identified variants has been previously linked to this phenotype.

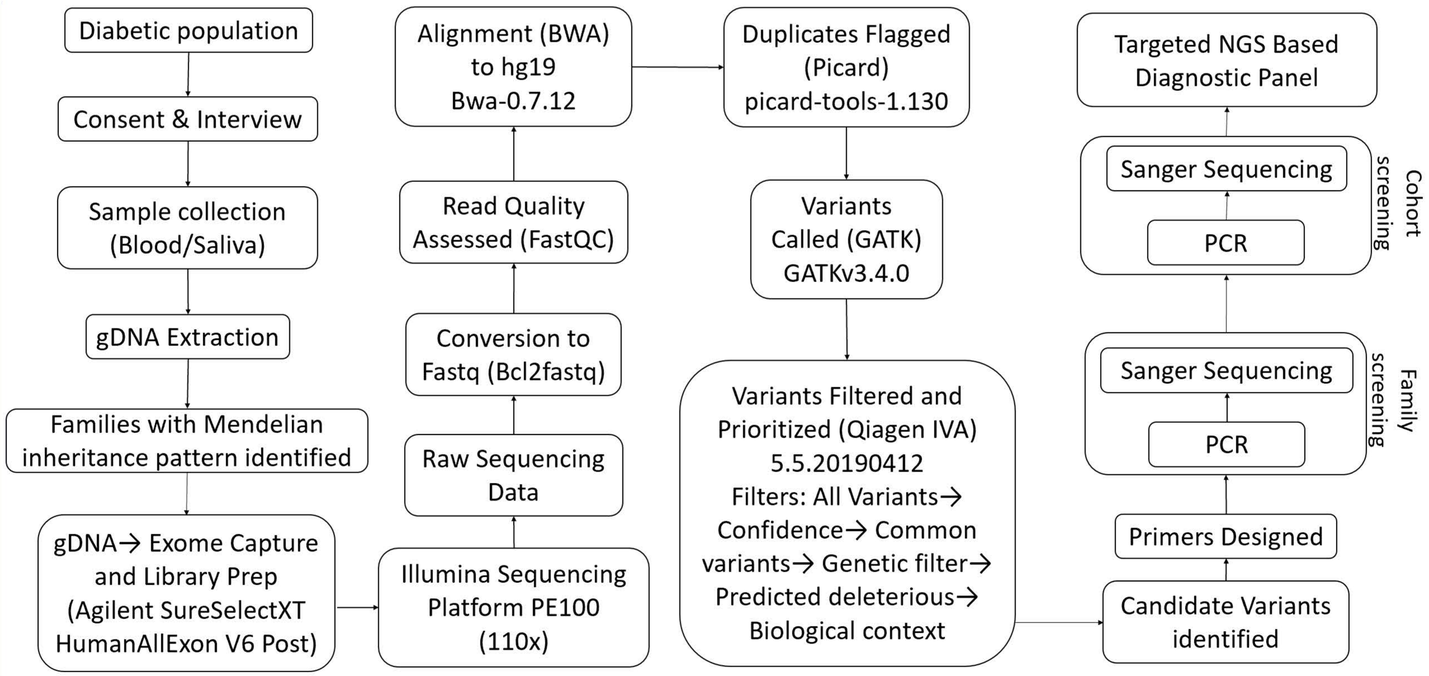

Figure 1: Methodology Flowchart and Variant Analysis. Summary of methodology from participant enrollment to NGS based diagnostic panel.

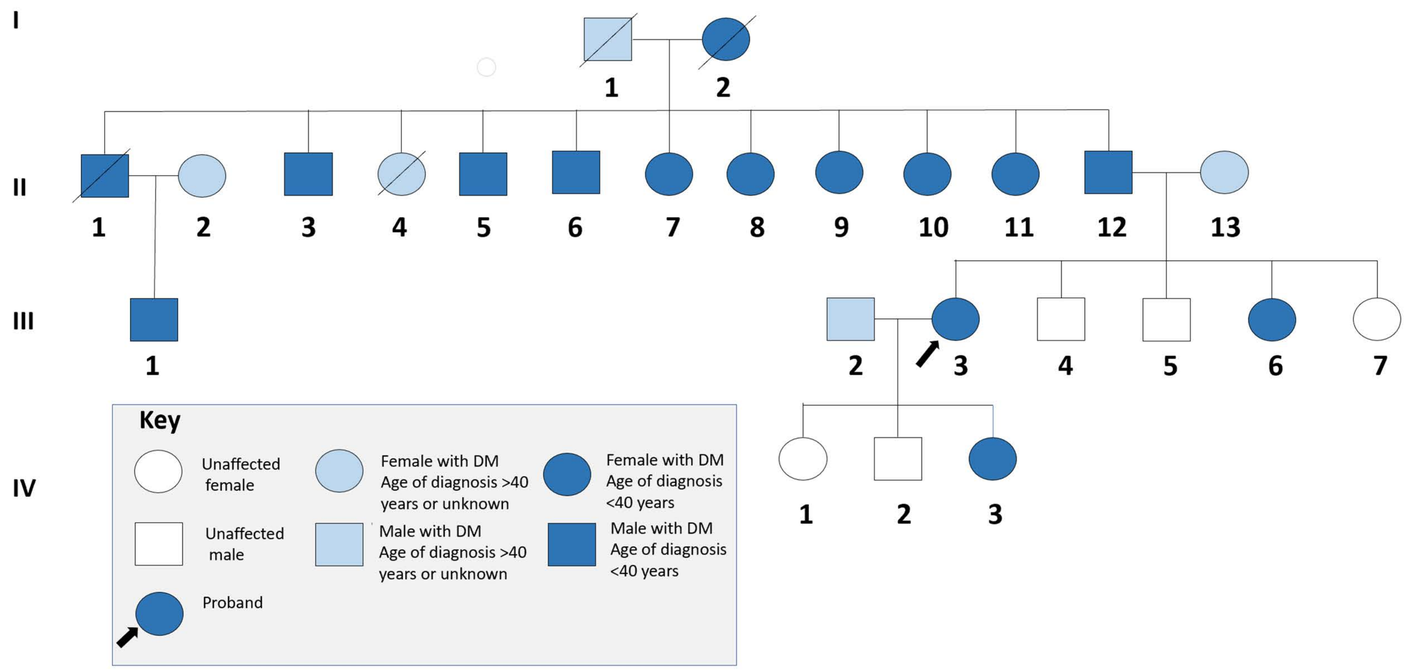

Figure 2: Pedigree of one selected family. Multiple cases of Type 2 DM were reported in this pedigree. However, multiple persons were diagnosed at <40 years of age (including one at 11 years old) despite not showing the usual risk factors associated with Type 2DM.

Gene	Variant
PDX1	c.670G>A
ACAD9	c.2452A>G
POU2F1	c.1201A>G
FCRL1	c.625A>G
POMC	c.706C>G
ALMS1	c.10245C>G c.10699A>G
ZFHX3	c.518C>G
RP5-991G20	
NLRP3	c.592G>A
ORM1	c.338A>G
RFX6	c.130dupA c.1927C>T
TCF7L2	c.1279C>G
CBS/CBSL	c.1327C>T
NOCL2	c.1700G>C

Figure 3 (above): List of genes in which candidate variants were found for the 3 families studied. Those highlighted in green were identified in pedigree in Figure 2.

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