ESTIMATION OF MODY FREQUENCY AND PREVALENT SUBTYPES IN PEDIATRIC PATIENTS BY TARGETED NGS

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INTRODUCTION:

- Monogenic diabetes: > 30 genes described.
  - DM MODY: 14 subtypes.
  - Neonatal Diabetes.
  - Mitochondrial Diabetes.
- Frequency and prevalence in pediatric patients?.

Materials/Methods

Cohort:

60 patients fulfilling MODY clinical criteria:

- < 25 years.
- AD.
- No obesity.
- Negative autoimmunity.
- Partial beta cell function preservation.

2 ND patients.

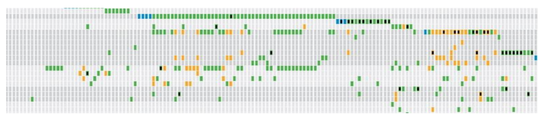
Materials/Methods

Molecular analysis: NGS (MonDIAB_V1):

173 genes:

Glucose homeostasis.

Dysglycemia.

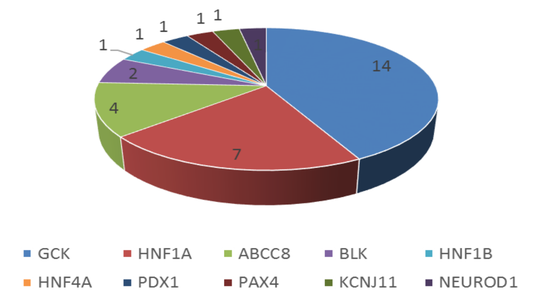


- **Average coverage >100x;**
- **% bases with coverage >20x= >90%;**
- **Variant priorization using VarSeqV2.1.0 (GoldenHelix).**

Results:

- 33 potentially pathogenic heterozygous variants (bioinformatic predictors CADD>20; DANN>0.98).
- In 26/60 (43,3%).

Gene Names	Sequence Ontology (Combined)	HGVS c. (Clinically Relevant)	HGVS p. (Clinically Relevant)	DESCRITO	PHRED Score	Zygosity
GCK	missense_variant	NM_000162.3:c.1340G>A	NP_000153.1:p.Arg447Gln	SI	25.3	Heterozygous
GCK	missense_variant	NM_000162.3:c.683C>T	NP_000153.1:p.Thr228Met	SI+F	28.1	Heterozygous
GCK	missense_variant	NM_000162.3:c.676G>A	NP_000153.1:p.Val226Met	SI+F	29.3	Heterozygous
GCK	stop_gained	NM_000162.3:c.867T>G	NP_000153.1:p.Tyr289Ter	SI	35	Heterozygous
GCK	stop_gained	NM_000162.3:c.1009C>T	NP_000153.1:p.Gln337Ter	SI	44	Heterozygous
GCK	frameshift_variant	NM_000162.3:c.713delT	NP_000153.1:p.Met238Serfs*56	SI	35	Heterozygous
GCK	stop_gained	NM_000162.3:c.1072C>T	NP_000153.1:p.Arg358Ter	SI	36	Heterozygous
HNF4A	missense_variant	NM_175914.4(HNF4A):c.841A>G	p.(Ser281Gly)	NOVEL (ALL:0.0073% - AMR:0.0029% - EAS:0.10%)	23.7	Heterozygous
PAX4	missense_variant	NM_006193.2:c.496C>T	NP_006184.2:p.Arg166Trp	NOVEL (ALL:0.0020% - ASJ:0.010% - NFE:0.0036%)	31	Heterozygous
ABCC8	5_prime_UTR_variant	NM_000352.4:c.-8G>T	?	This variant is known to ClinVar (Oct-2018)	16.9	Heterozygous
GCK	missense_variant	NM_000162.3:c.370G>A	NP_000153.1:p.Asp124Asn	SI	29.3	Heterozygous
ABCC8	missense_variant	NM_000352.4:c.4106C>T	NP_000343.2:p.Ala1369Val	NOVEL (ALL:.0.0024% - AFR:0.013% - EAS:0.012% - NFE:0.0018%)	20.2	Heterozygous
HNF1A	missense_variant	NM_000545.6:c.92G>A	NP_000536.5:p.Gly31Asp	NO (functional -)	22.4	Heterozygous
HNF1A	missense_variant	NM_000545.6:c.686G>A	NP_000536.5:p.Arg229Gln	SI+F	24.8	Heterozygous
NEUROD1	synonymous_variant	NM_002500.4:c.615C>A	NP_002491.2:p.Pro205= (new branching point)	NOVEL (absent from databases)	16.06	Heterozygous
PDX1	missense_variant	NM_000209.3:c.226G>A	NP_000200.1:p.Asp76Asn	NO	24.2	Heterozygous
HNF1A	missense_variant	NM_000545.6:c.1340C>T	NP_000536.5:p.Pro447Leu	SI+F	28.2	Heterozygous
GCK	stop_gained	NM_000162.3:c.556C>T	NP_000153.1:p.Arg186Ter	SI	35	Heterozygous
ABCC8	5_prime_UTR_variant	NM_000352.4:c.-8G>T	?	This variant is known to ClinVar (Oct-2018)	16.9	Heterozygous
HNF1A	initiator_codon_variant	NM_000545.6:c.2T>C	NP_000536.5:p.Met1Thr	NOVEL	24.1	Heterozygous
BLK	missense_variant	NM_001715.2:c.974A>C	NP_001706.2:p.Lys325Thr	NOVEL (not in HGMD)	26	Heterozygous
HNF1A	missense_variant	NM_000545.6:c.521C>T	NP_000536.5:p.Ala174Val	SI	22	Heterozygous
NKX6-2	missense_variant	NM_177400.2:c.541C>G	NP_796374.1:p.Leu181Val	NOVEL (ALL:0.011% - AMR:0.018% - NFE:0.011% - FIN:0.035% - OTH:0.032%)	26.2	Heterozygous
KCNJ11	missense_variant	NM_000525.3:c.149G>A	NP_000516.3:p.Arg50Gln	SI+F	25.1	Heterozygous
GCK	missense_variant	NM_000162.3:c.893T>A	NP_000153.1:p.Met298Lys	SI+F	24	Heterozygous
KCNJ11	missense_variant	NM_000525.3:c.973C>A	NP_000516.3:p.Arg325Ser	NOVEL low MAF (ALL:0.0012% - NFE:0.0027%)	22.1	Heterozygous
HNF1B	missense_variant	NM_000458.3:c.866A>G	NP_000449.1:p.Asn289Ser	NOVEL (absent from databades)	23.6	Heterozygous
GCK	missense_variant	NM_000162.3:c.683C>T	NP_000153.1:p.Thr228Met	SI+F	28.1	Heterozygous
GCK	missense_variant	NM_000162.3:c.563C>A	NP_000153.1:p.Ala188Asp	NOVEL (absent from databases)	32	Heterozygous
ABCC8	missense_variant	NM_000352.4:c.2104C>T	NP_000343.2:p.Arg702Cys	NOVEL (ALL:0.0094% - AMR:0.0060% - SAS:0.013% - NFE:0.015%)	23.9	Heterozygous
HNF1A	missense_variant	NM_000545.6:c.475C>T	NP_000536.5:p.Arg159Trp	SI	25.2	Heterozygous
NR4A3	missense_variant	NM_173200.2:c.806C>G	NP_775292.1:p.Pro269Arg	Not in HGMD	19.38	Heterozygous
GCK	missense_variant	NM_000162.3:c.660C>G	NP_000153.1:p.Cys220Trp	NOVEL (absent from databses)	25	Reference
HNF1A	frameshift_variant	NM_000545.6:c.872dupC	NP_000536.5:p.Gly292Argfs*24	SI	28.5	Heterozygous
GCK	missense_variant	NM_000162.3:c.742G>A	NP_000153.1:p.Glu248Lys	SI+F	24	Heterozygous
BLK	missense_variant	NM_001715.2:c.109C>A	NP_001706.2:p.Pro37Thr	NOVEL (ALL:0.0032% - NFE:0.0067%)	17.39	Heterozygous



- Regarding the prevalent MODY subtypes:
  - **MODY 2 *(GCK)*: 14**/33 **(42,4%):** 4 nonsense, 1 frameshift, and 9 missense variants (2 novel).
  - **MODY 3 *(HNF1A)*: 7**/33 **(21,2%):** 1 frameshift and 6 missense variants (1 non previously described).
  - **MODY 12 *(ABCC8)*:** 4/33 (**12,1%**): 1 proximal promotor variant in 2 patients and 2 missense variants (1 non previously described).
  - **MODY 11 *(BLK)*:** 2/33 **(6,1%):** 2 novel missense variants.
- Regarding 14 MODY subtypes:
  - 5 missense novel variants in:
    - ***HNF1B*** **(MODY 5).**
    - ***HNF4A*** **(MODY 1).**
    - ***PDX1*** **(MODY 4).**
    - ***PAX4*** **(MODY 9).**
    - ***KCNJ11*** **(MODY 13).**
  - 1 novel splicing alteration variant in ***NEUROD1*** **(MODY 6).**
- **Combinations**: **7 cases (26,9%)** apparent **digenic inheritance** (2 relevant MODY genes variants).
  - 3 cases: ***HNF1A*** **(MODY 3) *+ ABCC8* (MODY 12).**
  - ***HNF4A*** **(MODY 1) *+ PAX4* (MODY 9).**
  - ***GCK*** **(MODY 2) *+ ABCC8* (MODY 12).**
  - ***GCK*** **(MODY 2) *+ KCNJ11* (MODY 13).**
  - ***ABCC8*** **(MODY 12) *+ HNF1A* (MODY 3) *+ NR4A3.***

Conclusions:

1. Targeted NGS analysis: Variantes Potentially pathogenic variants in known MODY genes in 43,3% of the examined patients.
2. Up to 26,9% of the patients with relevant variants in MODY genes (11,7% of the examined cohort) presented an apparent digenic inheritance with 2 relevant variants in MODY genes.
3. 56,7% of patients fulfilling MODY clinical criteria examinaded, do not present relevant variants in the known 14 MODY genes: Other genes involved, still remain unknown.