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Importance of omic sciences and artificial intelligence in the classification of clinical significance of new and de novo variants associated with MODY2: Precision medicine

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Abstract

Maturity-Onset Diabetes of the Young (MODY), is a rare and heterogeneous group of genetic disorders characterized by dysfunction of pancreatic beta cells, leading to chronic hyperglycemia. Variants in Glucokinase (GCK) is known as GCK-MODY2. In the ClinVar database, there are 1093 variants reported for the GCK gene, of which 314 are pathogenic and 280 are probably pathogenic. We present a case of a 7-year-old male patient with polyuria, pollakiuria and weight loss. Non-consanguineous parents, mother with DM pregnancy, with paraclinical tests with elevated blood glucose and HB1AC, negative antibodies. Given the clinical and paraclinical suspicion of MODY, a targeted study was requested, whole exome sequencing + variants number of copies (CNV) analysis using Next Generation Sequencing (NGS) of genes related to MODY type diabetes. Finding in this a nucleotide variant was identified c.1022G>A in heterozygosity in exon 8 of the GCK gene (NM_033507.3). At the protein level it produces the missense change from a Serine to an Asparagine at amino acid 341 (p.Ser341Asn).

The heterozygous variant in the GCK gene, generates the change of a guanine for an adenine in position 1022 of the cDNA, in exon 8 of the gene (c.1022G>A) and that at the protein level produces the missense change of a Serine by an Asparagine at amino acid 341 (p.Ser341Asn). The GCK gene encodes the GCK enzyme, which is involved in insulin secretion and glucose homeostasis. Deleterious genetic variants for gene expression produce hyperglycemia and other complications related to the pathophysiological-molecular mechanism.

The variant identified in this case is located at a splice site and has not been reported in National Center for Biotechnology Information (NCBI); Medical Genomics (MedGen); the human gene mutation database (HGMD); Online Mendelian Inheritance in Man (OMIM), 1000 Genomes Project,

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Keywords: MODY; Genetic testing; Genotype-phenotype correlations; Diabetes; Omic sciences.

Exome Aggregation Consortium (ExAc), Leiden Open Variation Database (LOVD3); Ensemble, the Genome Aggregation Database (gnomAD), ClinGen, Database of Genomic Variants (DBV), but high-performance bioinformatics algorithms (MetaScore, and Individuals predict a deleterious effect, as do biological bases, genomic annotations, proteomics, molecular bases, protein structure and function, functional studies, use of artificial intelligence tools (GenAI, VarChat, Alphafold, Mastermind, Alliance of Genome Resources Version: 7.1.0) and according to Richards, et al. Standards and guidelines for the interpretation of sequence variants, American College of Medical Genetics and Genomics, Association for Molecular Pathology, ClinGen, and use of pipeline-algorithms, this variant is classified as effect pathogenic (Ia), evidence: PVS1, PS3, PM5, PM6, PP3, PM2, PP2. Reason for establishing genotype/endotype/phenotype correlation, with related ontological platforms: Human Phenotype Ontology (HPO), OMIM, Gene Ontology (GO); ORPHANET; in a patient without a related family history, which confers *a de novo inheritance mechanism*. The early identification of this disease through clinical suspicion and carrying out multimodal studies that include omics techniques and artificial intelligence, use of pipeline-algorithms and following current recommendations on interpretation of clinical significance of variants, allows us to make precise diagnoses, establish targeted treatments, genetic counseling, monitoring, prognosis, approaching precision, personalized, predictive, preventive, participatory, proactive medicine with a view to being used at the population level (Medicine 7P).

Introduction

Diabetes mellitus of early onset in youth, known as MODY (for its acronym for Maturity-Onset Diabetes of the Young), is a rare, heterogeneous group of genetic disorders characterized by dysfunction of pancreatic beta cells, leading to chronic hyperglycemia. It results from one or more defects in a single gene or chromosomal locus [1].

The disease can be inherited within families as a dominant, recessive or non-Mendelian trait or can present as a spontaneous case due to a de *novo variant*. Unlike Diabetes Mellitus Type 1 and Type 2, which are polygenic and multifactorial [2].

About 1-6% of patients with juvenile diabetes have MODY type diabetes. This is a genetically and clinically heterogeneous entity [3]. At least 14 MODY types have been identified (these include: PDX1, HNF1B, HNF1 A, HNF4A, GCK, NEUROD1, KLF11, CEL, PAX4, INS, APPLI1, BLK, ABCC8 and KCNJ11 (Table 1). The three most common forms of MODY are caused by variants in the HNF4A, GCK, and HNF1A genes, and make up the majority of all MODY cases [4]. Both HNF4A and HNF1A encode transcription factors that promote this process of genes involved in the pancreas, beta cell development and insulin production, while GCK encodes glucokinase, the enzyme that catalyzes the phosphorylation of glucose and, therefore, it is important for detecting blood glucose levels in the pancreatic beta cell. So far, at least 14 genes associated with MODY have been identified.

Adjusted from: Younis H, Ha SE, Jorgensen BG, Verma A, Ro S. Maturity-Onset Diabetes of the Young: Mutations, Physiological Consequences, and Treatment Options. J Pers Med. 2022; 12(11): 1762. Published 2022 Oct 25. doi:10.3390/jpm12111762

Furthermore, the diagnosis of a familial index case could lead to the identification of other affected or carrier family members and may indicate possible extrapancreatic complications in affected individuals [5]. Confirmed molecular diagnosis has important implications for clinical management, disease prognosis, and genetic counseling. However, it is estimated that more than 80% of MODY patients are undiagnosed or misdiagnosed as type 1 or type 2 diabetes [6].

14 MODY subtypes have been identified of which the subtype caused by Glucokinase (GCK) is called GCK-MODY (MODY2) and represents between 10% and 60% of all MODY patients [7]. People with GCK-MODY can be differentiated from those with type 1 diabetes, as hyperglycemia is less severe, pancreatic autoantibodies are rare, and C-peptide is not low. People with GCK-MODY tend to be less obese and less hyperglycemic than people with early-onset type 2 diabetes.

The GCK enzyme is involved in insulin secretion and glucose homeostasis. Regulates glucose levels by catalyzing the first step of glycolysis: the phosphorylation of glucose to form glucose-6-phosphate. Glucose phosphorylation is the rate-limiting step of insulin secretion in pancreatic β cells and glycogen synthesis in liver cells and therefore these processes are regulated by GCK activity [8].

Glucokinase deficiency arising from variants in both alleles, whether homozygous or compound heterozygous, prevents beta cells from secreting insulin in response to hyperglycemia [2]. Heterozygous activating variants of the GCK gene cause congenital hyperinsulinism, while the phenotype of inactivating GCK variants is Diabetes Mellitus (DM). GCK variants most frequently alter glucokinase kinetics. Inactivating variants (MODY)

Table 1: Genes associated with MODY.

Gene	OMIM # / Designation	Pathophysiology	Clinical significance	Treatment
HNF4A	125850 /MODY1	Progressive decrease in insulin secretion β-cell dysfunction Worsening of glucose control Low levels of apolipoproteins and triglycerides Neonatal hypoglycemia	Mild hyperglycemia	Sulfonylureas, insulin
GCK	125851/ MODY2	Higher glucose threshold for insulin release Glucose-sensing defects β-cell dysfunction Mild hyperglycemia (HbA1c 7.3-7.5%)	Mild hyperglycemia	Treatment is unnecessary
HNF1A	600496/ MODY3	Insufficient glucose-mediated insulin secretion β-cell dysfunction Low renal glucose threshold	Neonatal hyperglycemia	Sulphonylureas (additional meglitinides, GLP-1 RA, SGLT-2 inhibitors), insulin
PDX1	606392/ MODY4	β-cell dysfunction Impaired glucose-mediated insulin secretion Mild form of diabetes Overweight/obesity in some patients	Neonatal hyperglycemia	Sulphonylureas , insulin, metformin, dipeptidyl peptidase-4 inhibitors
HNF1B	137920 / MODY5	β-cell dysfunction Decreased insulin secretion with progressive worsening of glucose control Genitourinary malformations	kidney disease Diabetic ketosis Glomerulocystic kidney disease	Sulfonylurea, repaglinide, GLP-1 RA, insulin
NEUROD1	606394/ MODY6	β-cell dysfunction Insulinopenia or insulin resistance Different degrees of hyperglycemia	Adult onset (mid-20s)	Insulin
KLF11	610508 / MODY7	Decreased glucose sensitivity of β-cells Decreased sensitivity to insulin Mild hyperglycemia	Pancreatic malignancy	Insulin
CEL	609812 / MODY8	Impaired endocrine Exocrine pancreatic insufficiency (dysfunction of the mature acinar cell)	Adult onset (36 years) Hyperglycemia	Oral anti-hypoglycemic agents / insulin
PAX4	612225/ MODY9	β-cell dysfunction Progressive hyperglycemia Occurrences of ketoacidosis	Nephrological diseases	Oral anti-hypoglycemic agents / insulin
INS	613370 / MODY10	Hyperglycemia β-cell dysfunction	Neonatal hyperglycemia	Insulin
BLK	613375 / MODY11	Hyperglycemia β-cell dysfunction Affected insulin secretion	Neonatal hyperglycemia obesity	Oral anti-hypoglycemic agents / insulin
ABCC8	600509 / MODY12	Impaired insulin secretion ATP-sensitive potassium channel dysfunction	Kidney diabetes	Insulin, sulfonylureas
KCNJ11	616329 / MODY13	Impaired insulin secretion ATP-sensitive potassium channel dysfunction	Kidney diabetes Neonatal diabetes	Sulfonylureas
APPL1	616511 / MODY14	Impaired glucose-mediated insulin secretion Hyperglycemia Reduced beta cell survival	Wolfram or DIDMOAD syndrome	Oral anti-hypoglycemic agents / insulin

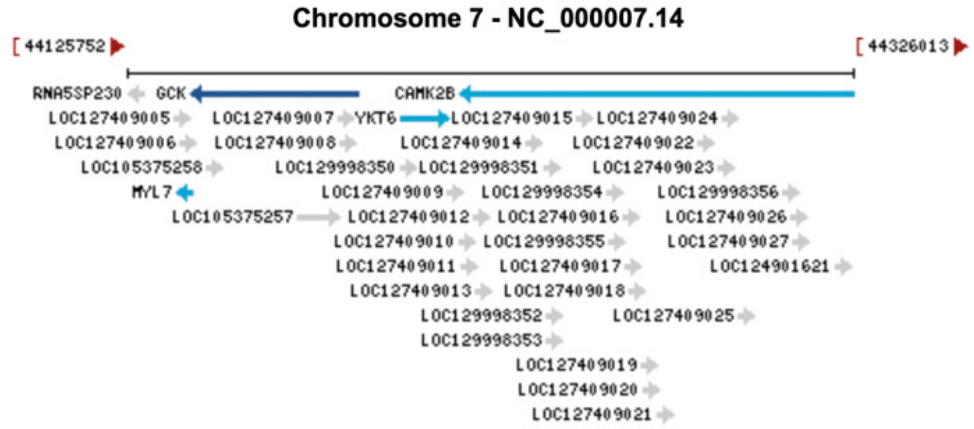

Figure 1: GCK gene cDNA 15 exons, located at 7p13.

Taken from: https://www.ncbi.nlm.nih.gov/gene/2645

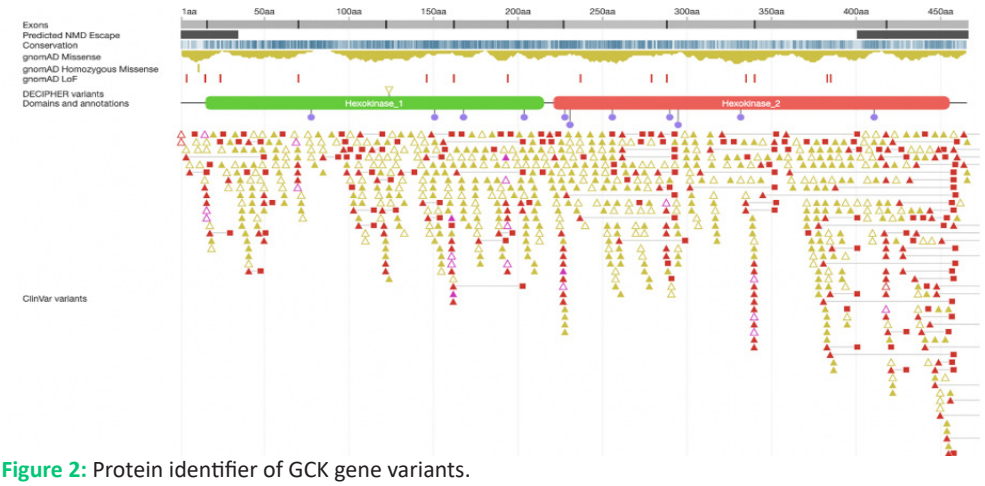

Figure 2: Protein identifier of GCK gene variants.

Taken from: www. deciphergenomics.org/gene/GCK/overview/protein-genomic-info.

usually decrease the affinity of glucokinase for glucose. The catalytic efficiency of glucokinase for ATP (ATP Km) and the Hill coefficient increase or decrease and the maximum specific activity (K cat) decreases [9].

However, unlike type 1 and 2 diabetes (T1D and T2D) or other MODYs, patients with GCK-MODY generally have a favorable prognosis without the need for antidiabetic treatment. Furthermore, patients with GCK-MODY rarely suffer cardiovascular complications with the same risks as healthy non-diabetic people [7].

The GCK gene encoding the enzyme glucokinase is located on chromosome [7]. Two major transcripts are transcribed from two organ-specific promoters. The neuroendocrine promoter constitutively active in endocrine cells of the pancreas, brain, pituitary, adrenal, and enteroendocrine cells. On the other hand, the downstream promoter that controls the expression of the GCK gene in the liver (HEP-GCK promoter) is insulin-dependent and gives rise to the transcript NM_033507.3 9. (See Figure 1).

In ClinVar, there are 1093 variants reported for the GCK gene, of which 314 are classified clinically significant as pathogenic and 280 as probably pathogenic (Consulted on May 2024) (See Figure 2). The most frequent type of variant is missense.

The early identification of this disease is by clinical suspicion and carrying out multimodal studies that include Omics techniques and artificial intelligence, use of pipeline-algorithms and following current recommendations. On interpretation of clinical significance of variants, allows us to make precise diagnoses, establish targeted treatments, genetic counseling, monitoring, prognosis, approaching precision, personalized, predictive, preventive, participatory, proactive medicine with a view to being used at the population level (medicine 7p).

Materials and methods

A clinical case is presented of a 7-year-old male patient without any relevant medical history who consulted for 3 months of polyuria, pollakiuria and weight loss. Non-consanguineous parents with no known family history of carbohydrate disorder, with initial paraclinics with elevated blood glucose and HB1AC, negative antibodies (Table 2).

He did not present with an acute crisis such as ketoacidosis or diabetic coma. Family history: non-consanguineous parents, mother diagnosed with DM during pregnancy. No family history of known genetic diseases. At the physical examination, the patient's weight was 27 kg, height 135 cm, BMI 17 (Indices with Z score WHO P/E: 0.05, T/E: 0.86, BMI/E: -0.64), without clinical evidence of insulin resistance or syndromic phenotype.

Given the clinical and paraclinical suspicion of diabetes Mellitus of Early Onset in Youth (MODY), and the importance of the phenotype/endotype/genotype correlation, a directed study was requested, whole exome sequencing + Variants Number of Copies (CNV) analysis using Next Generation Sequencing (NGS) of specific genes related to MODY type diabetes.

Results

The study carried out on the patient was aimed at identifying variants included in exonic regions or splicing regions (at least 20 bp), insertions and small deletions. This analysis allowed the identification of exonic deletions and duplications and variants involving large regions of the gene.

The genes evaluated were ABCC8, AGPAT2, AKT2, ALMS1, APOE, APPL1, AR, ARL6, ATM, BLK, BSCL2, CAV1, CDKN1C, CDKN2A, CEL, CFTR, CIDEC, CISD2, CP, DCAF17, DNAJC3, EIF2AK3, ENPP1, FOXP3, FXN, G6PC2, GATA4, GATA6, GCK, GLIS3, GLUD1, GNAS, GPIHBP1, HADH, HAMP, HFE, HMGA2, HNF1A, HNF1B, HNF4A, IER3IP1, IL2RA, INS, INSR, KCNJ11, KLF11, KRAS, LEP, LEPR, LIPC, LMNA, LRBA, MC4R, MKKS, MLXIPL, MNX1, NEUROD1, NEUROG3, NKX2-2, PAX4, PAX6, PCBD1, PCNT, PCSK1, PDX1, PIK3R1, PLAGL1, PLIN1, POLD1, POMC, PPARG, PPP1R3A, PTF1A, RFX6, SHH, SLC19A2, SLC29A3, SLC2A1, SLC2A2, SPINK1, STAT1, STAT3, TP53, TRMT10A, UCP2, WFS1, ZBTB20, ZFP57.

The variants identified that were classified as benign, had an allele frequency greater than or equal to 1%, and result in a synonymous amino acid change or occur in 5' or 3' untranslated regions. Variants with a depth greater than 20X, high allelic radius were reported and those with other characteristics that did not meet the minimum technical thresholds were discarded. Pathogenic and probably pathogenic variants were confirmed by Sanger sequencing.

The identified variants are evaluated and interpreted taking into account the parameters recommended by the American College guidelines of Medical Genetics (ACMG) for the classification of variants (Richards et al. 2015) and its updates according to the Association for Molecular Pathology (AMP); ClinGen (clinicalgenome.org), including information and consultation of clinical, exomic, genomic, population, phylogenic databases, use of in silico predictors, search for experimental studies, functionality, omics sciences, protein structural and functional studies, use of artificial intelligence, in order to classify the significance of the variant found. Finally, the association of the identified variants with the syndromes described in OMIM, MONDO, Orphanet, human phenotype is evaluated. Ontology - HPO and in the scientific literature, and the clinical association with the phenotype described in the patient.

The study reported a heterozygous variant in the GCK gene that generates the change of a guanine for an adenine in position 1022 of the cDNA, in exon 8 of the gene (c.1022G>A) and that at the protein level produces the change missense from a Serine to an Asparagine at amino acid 341 (p.Ser 341Asn) (Figure 2). The identified variant has not been reported in databases has not been reported in National Center for Biotechnology Information (NCBI); Medical Genomics (MedGen); The Human Gene Mutation Database (HMGD); Online Mendelian Inheritance in Man (OMIM), 1000 Genomes Project, Exome Aggregation Consortium (ExAc), Leiden Open Variation Database (LOVD3); Ensembl, The Genome Aggregation Database (GnomAD v 4.0), ClinGen, Database of Genomic Variants (DVG).

Table 2: Patient paraclinics.

Paraclinical	Result	Reference value
Pre Glucose	111 mg/ dL	<100 mg/ dL
Post Glucose	1110.8 mg/ dL	<140 mg/ dL
HB1AC	6.9%	<6.4%
Acs Anti-Insulin	4.99%	<8.2%
Acs Anti Pancreatic Islets	1/4	<2
Acs glutamic acid decarboxylase (GAD)	0.1 IU/ mL	<1.0 UI /m:
C Peptide	0.92 ng/ mL	1.1 - 4.4 ng/ mL
Basal Insulin	4.37 uIU / mL	2.6 - 24.5 uIU / mL

Own elaboration. Source patient medical history.

Variant reported in ClinVar with 2 entries with conflict of interest classification - VUS (RCV001903778) and the other as Likely pathogenic (Nov 1, 2022) related to MODY (RCV003329421) single submitter (Invitae Variant Classification Sherloc (09022015)). Frequencies exomes: not found (cov: 39.3); genomes: not found (cov: 31.7) 1 publication for rs1376631949 (April 2024). Functional consequence Help effect on RNA splicing function Variation; dbSNP rs1376631949, Frequency A=0.000004 (1/242076, GnomAD_exome), Missense Variant LOC105375258: 2KB Upstream Variant.

With predictors in silico: Meta Score: MetaRNN with prediction Pathogenic Moderate score 0.8483, dbNSFP version 4.7); BayesDel addAF (Uncertain addAF score 0.1448 dbNSFP version 4.7); BayesDel noAF (Uncertain noAF score -0.0298 dbNSFP version 4.7); MetaLR (Uncertain score 0.8158 dbNSFP version 4.7); MetaSVM (Uncertain score 0.5226 dbNSFP version 4.7); REVEL (Uncertain score 0.513 dbNSFP version 4.7); Individual Predictions: dbscSNV (Pathogenic Strong ADA score 0.9999 version v1.1); M-CAP (Moderate Pathogenic score 0.6921 dbNSFP version 4.7); SIFT4G (Benign Moderate score 0.164, 0.207, 0.164, 0.168, 0.2 dbNSFP version 4.7); MaxEntScan (Pathogenic Supporting score 5.2709 version 5-Apr-2023); PrimateAI (Pathogenic Supporting score 0.8178 dbNSFP version 4.7); EIGEN (Benign Supporting raw coding 0.005254 dbNSFP version 4.7); EIGEN PC (Benign Supporting PC raw coding score 0.07205 dbNSFP version 4.7); Mutation assessor (Benign Supporting score 1.67 dbNSFP version 4.7); PROVIDE (Benign Supporting score -1.52, -1.56, -1.53, -1.76 dbNSFP version 4.7); SIFT (Benign Supporting score 0.09, 0.098, 0.107, 0.1 dbNSFP version 4.7); BLOSUM (Uncertain score 0 version BLOSUM100); DANN (Uncertain score 0.9927); DEOGEN2 (Uncertain score 0.622 dbNSFP version 4.7); FATHMM (Uncertain score -4 dbNSFP version 4.7); FATHMM-MKL (Uncertain coding score 0.9189 dbNSFP version 4.7); FATHMM-XF (Uncertain coding score 0.8089 dbNSFP version 4.7); LIST-S2 (Uncertain score 0.8551, 0.8575, 0.8603, 0.906 dbNSFP version 4.7); LRT (Uncertain score 0.000165 dbNSFP version 4.7); MutationTaster (Uncertain score 0.9999 dbNSFP version 4.7); MutPred Uncertain score 0.57 dbNSFP version 4.7); MVP (Uncertain score 0.9113, 0.9113, 0.9113, 0.9113, 0.9113 dbNSFP version 4.7). In-Silico Predictors classification PP3: Pathogenic look and strong.

Discussion

MODY is a rare, familial, clinically and genetically heterogeneous form of diabetes characterized by young age of onset (generally 10-45 years) with maintenance of endogenous insulin production, lack of pancreatic beta-cell autoimmunity, absence of obesity and insulin resistance and extra-pancreatic manifestations in some subtypes. Also known as MODY, Mason type diabetes, Mason-type diabetes, maturity onset diabetes of the young, maturity-onset diabetes of the young, maturity-onset diabetes of the young (disease), MONDO:0018911, OMIM:606391, Orphanet: 552.

MODY type diabetes is characterized by the onset of hyperglycemia at an early age (classically before the age of 25). It presents impaired insulin secretion with minimal or no defects in insulin action (in the absence of coexisting obesity). It is inherited in an autosomal dominant pattern with abnormalities in at least 14 genes on different chromosomes identified to date [10] (Table 1).

The gene GCK glucokinase [Homo sapiens (human)], ID: 2645, Primary source HGNC:HGNC:4195, Ensembl: ENSG00000106633, MIM: 138079; Alliance Genome: HGNC:4195, Gene type: protein coding, Also known as GK; GLK; HK4; HHF3; HKIV; HXKP; LGLK; MODY2; PNDM1; FGQTL3, encodes a member of the hexokinase family of proteins. Hexokinases phosphorylate glucose to produce glucose-6-phosphate, the first step in most glucose metabolism pathways. In contrast to other forms of hexokinase, this enzyme is not inhibited by its product glucose-6-phosphate but remains active while glucose is abundant. The use of multiple promoters and alternative splicing of this gene resulted in distinct protein isoforms that exhibit tissue-specific expression in the pancreas and liver. In the pancreas, this enzyme plays a role in glucose-stimulated insulin secretion, while in the liver, this enzyme is important in glucose uptake and conversion to glycogen. Variants in this gene that alter enzyme activity have been associated with multiple types of diabetes and hyperinsulinemic hypoglycemia.

According to UNIPROT (https://www.uniprot.org/), this Glucokinase protein contains 42 amino acids, Proteomes Identifier: UP000005640, Family & Domains Phylogenomics databases: GeneTree ENSGT00950000182787.

The gene variant GCK, NM_000162.5(GCK):c. 1019G>A (p.Ser340Asn), Variation ID: 1405403 Accession: VCV001405403.4, Type and length single nucleotide variant, 1 bp, Location Cytogenetic: 7p13 7: 44146463 (GRCh38); 7: 44186062 (GRCh37), it is a germline variant. HGVS Nucleotide NM_000162. 5:c. 1019G>A (Matched Annotation from NCBI and Canonical SPDI: NC_000007.14:44146462:C:T.

This genomic variant results in a missense variant at the codon level, leading to the substitution of serine for an asparagine at amino acid 341, designated pSer341Asn. This single nucleotide change involves a substitution of a Guanine (G) for an Adenine (A) at nucleotide position 1022 of the coding sequence. This variant is located in the last amino acid of exon 8 and is part of the splice site. According to the splice site algorithms, it is expected that this variant will generate the loss of the splice donor site, which results in an inactivating variant of the GCK gene and, as a consequence, glucose levels are not regulated.

Since GCK-MODY is an autosomal dominant disease, 50% of offspring are at risk of inheriting the variant. Although the vast majority of people with GCK-MODY have inherited the GCK variant from a parent, several people with de novo GCK variant have been reported [14,15,1,16]. Although these are rare, the patient described presents a de novo variant, given that his family members had no history of early-onset diabetes. It is difficult to determine how many variants are de novo, as asymptomatic parents are often not tested, but one systematic study found 4% (6 of 150), suggesting they may be more common than previously thought [17]. The reported patient had early-onset hyperglycemia without the presence of obesity or clinical signs of insulin resistance. Paraclinical tests not suggestive of type 1 or type 2 DM; who was ruled out exocrine disease of the pancreas. He did not present with acute attacks, which suggests the presence of monogenic diabetes.

The diagnosis of monogenic forms is essential, since type 1 or type 2 diabetes can be misdiagnosed, leading to suboptimal, even potentially harmful, treatment plans and delays in the diagnosis of other family members 10. People with HNF4A-MODY and HNF1A-MODY can be treated effectively with sulfonylurea. However, patients with HNF1B- MODY generally do not respond to sulfonylurea treatment and often require insulin injections several times a day [4]. With a defined and precise diagnosis, it is possible to implement and start targeted treatments, improving the patient's glycemic control and reducing the use of insulin. As well as what was reported by Altmutair [4]. Where they describe the efficacy of once-weekly GLP-1RA (semaglutide) in patients with a complete deletion of the HNF1B gene (HNF1B-MODY). In contrast, most patients with GCK-MODY do not require treatment.

In the reported cases, patients consulted due to hyperglycemia as a finding in routine health check-ups, asymptomatic and stable over time, without ketoacidotic complications, and not requiring drug treatment [4,11,12]. Which agrees with the reported clinical picture of the patient, given that the patient does not present with an acute crisis type ketoacidosis or hyperosmolar state, which is why he benefited from the precise genetic diagnosis to guide the diagnosis. Glucokinase structure are inactivating variants that result in GCK-MODY. However, there are also polymorphisms without phenotype and activating variants that affect the coding region and cause hypoglycemia [9].

Recently, Kuznetsova et al. (April 2024) published in the journal PLOS ONE that developed an automated pipeline for collecting and harmonizing data on genetic variants to monogenic diabetes. They translated variant genetic sequences into protein sequences accounting for all protein isoforms and their variants. This allows researchers to consolidate information on variant genes and proteins linked to monogenic diabetes and facilitates their study using proteomics or structural biology. Our open and flexible implementation using Jupyter notebooks enables tailoring and modifying the pipeline and its application to other rare diseases, thereby giving more pathogenicity support in the variant reported in our case.

Additionally, a search for this variant was carried out in artificial intelligence assistants. According to the first variant wizard GenAI genetics, VarChat, the genomic variant c.1022G>A in the GCK gene results in the amino acid substitution of serine to asparagine at position 341 of the glucokinase protein (p.Ser 341Asn). This variant is cataloged in the dbSNP database with the reference rs1376631949. The GCK gene encodes for the enzyme glucokinase, which plays a crucial role in glucose homeostasis by acting as a glucose sensor in the pancreas and regulating insulin secretion. Glucokinase also functions in the liver to facilitate glycogen synthesis and glycolysis in response to increased glucose levels.

The specific variant c.1022G>A, p.Ser 341Asn, rs1376631949 is not directly discussed in the provided papers, and therefore, no direct clinical associations or functional studies from these sources can be attributed to this variant. However, the GCK gene has been extensively studied, and variants within this gene are known to cause a spectrum of conditions related to glucose metabolism, including maturity-onset diabetes of the young type 2 (MODY2) and Persistent Hyperinsulinemic Hypoglycemia of Infancy (PHHI).

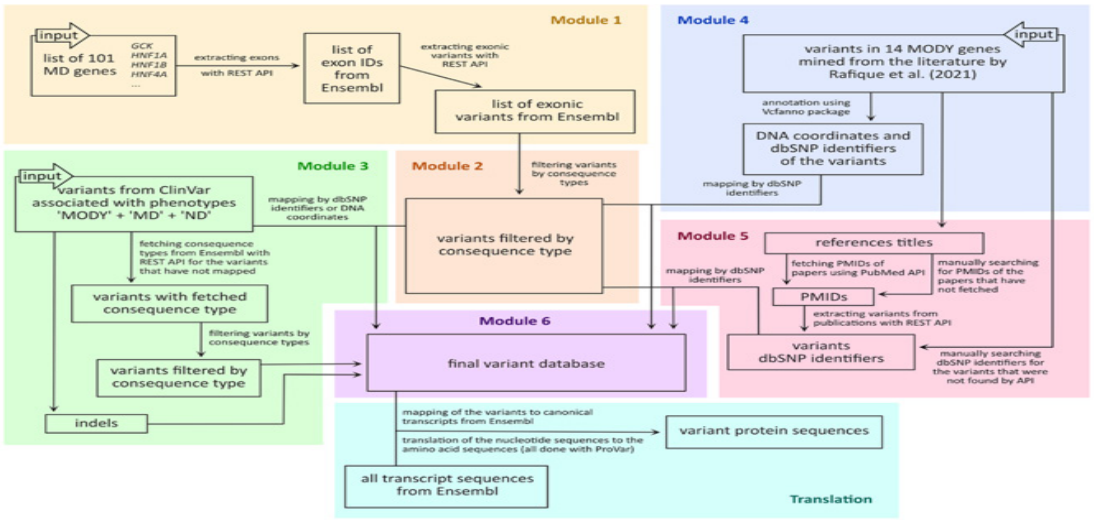

Figure 3: General architecture of the pipeline [18].

Taken f Taken from: https://swissmodel.expasy.org/repository/uniprot/A0A8C8KJG0?csm=A4A56D45E1D8F2B6rom: https://swissmodel.expasy.org/repository/uniprot/A0A8C8KJG0?csm=A4A56D45E1D8F2B6

In ClinVar, the variant rs1376631949 has been submitted with conflicting interpretations of pathogenicity. One submission classifies it as pathogenic, while another indicates a conflict regarding its interpretation. This discrepancy may arise from differences in the evidence used to assess the variant, such as family studies, functional assays, or population frequency data. The pathogenicity of a variant can be influenced by its impact on protein function, its conservation across species, and its prevalence in affected versus control populations. In summary, the c.1022G>A, p.Ser 341Asn, rs1376631949 variant in the GCK gene is a missense change with conflicting interpretations of its clinical significance.

Given the role of GCK in glucose regulation, variants that affect its function can be associated with disorders such as MODY2 or PHHI. The clinical presentation of individuals with GCK variants can vary, and the pathogenicity of specific variants may depend on additional genetic, environmental, or lifestyle factors.

In the context of genetic counseling and clinical decision-making, the presence of the c.1022G>A, p.Ser 341Asn variant in the GCK gene warrants careful consideration. Functional studies, segregation analysis, and a thorough evaluation of the patient's clinical phenotype may provide further insights into the relevance of this variant.

Minigene showed effect on RNA splicing: complex alteration with 3 transcripts. 1/ deletion of the last 8 bp of exon 8 (r.1012_1019del, p.Val 338Argfs*118); 2/ retention of the first 17 bp of intron 8 (r.1019_1020delins18, p.Ser340Lysfs*19); 3/ skipping of exon 8 (r.864_1019del, p.Tyr289_Ser340del).

In accordance with various genomic intelligence platform as Mastermind only report about this variant he data from NM_033507. 3:c. 1022G>A (p.Ser341Asn).

Conflicting interpretations of pathogenicity and refers to ClinVar.

Write down that p.S341N variant found 4 times in the supplemental data for the article File: pone.0300350.s002.csv, the what is Bioinformatics pipeline for the systematic mining genomic and proteomic variation linked to rare diseases: The example of monogenic diabetes (Figure 3).

Module 1: Extract variants from Ensembl affecting genes linked to monogenic diabetes. Module 2: filter variant by consequence on the protein. Module 3: extract variants from ClinVar affecting genes linked to monogenic diabetes. Modules 4 and Module 5: extract the variants from the literature using the mining by Rafique et al. Module 6: consolidate the variants in a single table. Translation: produces the possible variant protein sequences. MODY-maturity-onset diabetes of the young, MD-monogenic diabetes, ND-neonatal diabetes, API-application programming interface, PMID-identifiers of scientific publications from the PubMed database, dbSNP identifiers-identifiers of the genomic variants from the dbSNP database, that start from "rs". And it becomes one more tool for confirmation of pathogenic behavior of the clinical case variant.

According to Alliance of Genome Resources Version: 7.1.0, (https://www.alliancegenome.org/) reports for source rs1376631949, (GRCh38)7:44146463C>A(Homo sapiens) Allele/Variant: Genes: GCK (Hsa), Synonyms: Not Available, Variant Type: SNP, Molecular Consequence: splice_region_variant , missense_variant, non_coding_transcript_exon_variant, intron_variant , Diseases: MODY2, Variant Name: (GRCh 38)7:44146463 C>A, Symbol: rs1376631949, Name: rs1376631949, Source: rs1376631949.

According to Human Phenotype Ontology (HPO) the GCK gene NCBIGene: 2645, Synonyms: FGQTL3, GK, GLK, HHF3, HK4, HKIV, HXKP, LGLK, MODY2, PNDM1. This gene encodes a member of the hexokinase family of proteins. Hexokinases phosphorylate glucose to produce glucose-6-phosphate, the first step in most glucose metabolism pathways. In contrast to other forms of hexokinase, this enzyme is not inhibited by its product glucose-6-phosphate but remains active while glucose is abundant. The use of multiple promoters and alternative splicing of this gene resulted in distinct protein isoforms that exhibit tissue-specific expression in the pancreas and liver. In the pancreas, this enzyme plays a role in glucose-stimulated insulin secretion, while in the liver, this enzyme is important in glucose uptake and conversion to glycogen. Mutations in this gene that alter enzyme activity have been associated with multiple types of diabetes and hyperinsulinemic hypoglycemia.

It has 80 term associations, with 7 disease associations: OR-

PHA: 552 (MODY); OMIM:602485 (Hyperinsulinemic hypoglycemia, familial, 3); ORPHA:99885 (Isolated permanent neonatal diabetes mellitus); OMIM:606176 (Diabetes mellitus, permanent neonatal 1); ORPHA:79299 (Congenital glucokinase-related hyperinsulinism); OMIM:125851(Maturity-onset diabetes of the young, type II).

Conclusion

Given the role of GCK in glucose regulation, variants that affect its function can be associated with disorders such as MODY2 or PHHI. The clinical presentation of individuals with GCK variants can vary, and the pathogenicity of specific variants may depend on additional genetic, environmental, or lifestyle factors.

In the context of genetic counseling and clinical decision-making, the presence of the c.1022G>A, p.Ser 341Asn variant in the GCK gene warrants careful consideration.

Minigene showed effect on RNA splicing: complex alteration with 3 transcripts. 1/ deletion of the last 8 bp of exon 8 (r.1012_1019del, p.Val 338Argfs*118); 2/ retention of the first 17 bp of intron 8 (r.1019_1020delins18, p.Ser340Lysfs*19); 3/ skipping of exon 8 (r.864_1019del, p.Tyr289_Ser340del). The variant identified in this case is located at a splice site and has not been reported in National Center for Biotechnology Information (NCBI) databases; Medical Genomics (MedGen); The human gene mutation database (HGMD); Online Mendelian Inheritance in Man (OMIM), 1000 Genomes Project, Exome Aggregation Consortium (ExAc), Leiden Open Variation Database (LOVD3); Ensembl, The Genome Aggregation Database (GnomAD), ClinGen, Database of Genomic Variants (DGV), and given the ultra-rare population frequency of Este variant with only 2 entries in ClinVar; with conflict of interpretation and in dbSNP, but high-performance bioinformatics algorithms (MetaScore, and Individuals predict a deleterious effect-PP3), as well as biological bases, genomic annotations, proteomics, molecular bases, protein structure and function, functional studies, use of artificial intelligence tools (GenAI, VarChat, Alphafold, Mastermind, Alliance of Genome Resources Version: 7.1.0,) and according to Richards, et al. Standards and guidelines for the interpretation of sequence variants. 2015, American College of Medical Genetics and Genomics, Association for Molecular Pathology, ClinGen, and use of algorithms - pipeline, this variant is classified as effect pathogenic (Ia), evidence: PVS1, PS3, PM5, PM6, PP3, PM2, PP2; Reason for establishing genotype/ endotype /phenotype correlation, with related ontological platforms: Human Phenotype Ontology (HPO), Online Mendelian Inheritance in Man (OMIM); Gene Ontology (GO); ORPHANET; in a patient without a related family history of MODY, which confers a de novo inheritance mechanism. The early identification of this disease through clinical history, complete physical examination and performance of multimodal studies that include Omics techniques and artificial intelligence, use of pipeline-algorithms and following current recommendations on interpretation of clinical significance of variants, allows us to carry out precise diagnoses, establish targeted treatments, genetic counseling, monitoring, prognosis, approaching precision, personalized, predictive, preventive, participatory, proactive medicine with a view to being used at the population level (Medicine 7P).

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