REVIEW

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Genetic Landscape and Diagnostic Challenges of MODY: A Comprehensive Review of Etiology, Subtypes, and Future Perspectives

MODY'nin Genetik Yapısı ve Tanısal Zorlukları: Etiyoloji, Alt Tipler ve Gelecek Perspektiflerine Kapsamlı Bir Bakış

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ABSTRACT

Maturity-onset diabetes of the young (MODY) is a monogenic, autosomal-dominant form of diabetes. Because of the phenotypic overlap with other types of diabetes, MODY remains difficult for clinicians to diagnose; many cases are misdiagnosed as type 1 or type 2 diabetes, and more than three-quarters of cases remain undetected. Significant progress has been made in elucidating the intricate molecular pathways and diverse etiologies of MODY, facilitated by next-generation sequencing techniques. In this review, we provide a comprehensive overview of the pathogenesis, subtypes, associated genes, and mutations of MODY, as well as current genetic testing methods, treatment strategies, and future perspectives.

Keywords: MODY, next-generation sequencing (NGS), *GCK, HNF4A, PDX1*

ÖZ

Genç yaşta başlayan olgunluk tipi diyabet (MODY), monogenik, otozomal dominant kalıtsal bir diyabet türüdür. MODY tanısı, birçok vakanın tip 1 veya tip 2 diyabet olarak yanlış teşhis edilmesi ve diğer diyabet türleriyle fenotipik örtüşme nedeniyle vakaların dörtte üçünden fazlasının teşhis edilememesi nedeniyle klinisyenler için hala bir zorluk olmaya devam etmektedir. Yeni nesil dizileme yöntemleri, MODY'nin karmaşık moleküler mekanizmalarının ve heterojen etiyolojisinin anlaşılmasında büyük ilerlemeler sağlamıştır. Bu derlemede, MODY'nin patogenezi, alt tipleri, ilişkili genleri ve mutasyonlarının yanı sıra mevcut genetik test yöntemleri, tedavi stratejileri ve geleceğe yönelik perspektifler hakkında kapsamlı bir genel bakış sunuyoruz.

Anahtar Kelimeler: MODY, yeni nesil dizileme (NGS), *GCK, HNF4A, PDX1*

Introduction

Maturity-onset diabetes of the young (MODY) is a monogenic, autosomal dominant (AD) form of diabetes caused by pancreatic beta-cell dysfunction and is not insulin dependent (1). Genetic mutations cause loss of exocrine pancreatic function and deterioration of β-cells (2). In this AD hereditary disease, 63% of carriers develop diabetes before age 25, and 96% before age 55. This shows that the disease primarily occurs before age 25 (3). MODY can be misclassified as type 1 diabetes because it typically presents at or before age 25. Similarly, it can be misclassified as type

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2 diabetes because it coexists with overweight or obesity. However, MODY is a different type of diabetes (4). While type 1 diabetes is an autoimmune disease, MODY is not an autoimmune disease. While type 2 diabetes is characterized by insulin resistance, MODY is characterized by a defect in insulin production (5). While type 1 and type 2 diabetes are polygenic, MODY is a monogenic form of diabetes caused by a variation in a single gene (4). MODY is much rarer than type 1 and type 2 diabetes. Approximately 1–5% of patients with diabetes have MODY (6). Due to its rarity and confusion with other types of diabetes, many misdiagnoses occur (7). Since it is an AD hereditary disease, clinicians' ability to make the correct molecular diagnosis, the development of new techniques, advances in genetic testing, and easier access to genetic tests are all essential for accurate diagnosis (8). In addition, MODY can be diagnosed with up to 100% sensitivity using direct sequencing (9). In most cases, molecular genetic tests should be performed before starting specific treatments (10). Next-generation sequencing (NGS), including whole-exome sequencing (WES) and whole-genome sequencing (WGS), has made great strides in elucidating the complex molecular mechanisms and heterogeneous etiology of MODY (11). Fourteen subtypes of MODY have been identified, and they differ in several respects. Some features (such as glycemic phenotype) can even vary within the same pedigree (12). Therefore, a family history of diabetes, particularly the presence of family members with diabetes aged 25 years or younger, is an important criterion for diagnosing MODY. Responses to treatment and clinical course vary among MODY subtypes. H*epatocyte nuclear factor 1-alpha (HNF1A)*-MODY (MODY3), *GCK*-MODY (MODY2), *hepatocyte nuclear factor 4-alpha (HNF4A)* -MODY (MODY1), *hepatocyte nuclear factor 1-beta (HNF1B)*-MODY (MODY5), and *ABCC8*-MODY (MODY12) are the most prevalent of these. *NEUROD1*-MODY (MODY6), *IPF1/PDX1*-MODY (MODY4), and *INS*-MODY (MODY10) are less common subtypes. Since then, several alleged variants of MODY, including APPL1 (MODY14), PAX4 (MODY9), KLF11 (MODY7), and BLK (MODY11), have been disqualified as genuine MODY (13). Therefore, MODY subtypes should be genetically characterized and distinguished. Each subtype is defined by the gene that harbors the causative mutation, and variant–phenotype relationships exist among these genes (14). Making these distinctions is essential for the clinical picture and for the correct treatment.

Genetic Basis of MODY

As understanding of the underlying causes of MODY has improved, many subtypes have been identified. The most common subtypes are caused by mutations in the genes *HNF1A*, *GCK*, *HNF4A*, and hepatocyte nuclear *HNF1B* (15). *HNF* genes play an important role in liver development and function. However, these genes' pancreatic activities are affected in MODY. The *GCK* gene plays a role in glucose-stimulated insulin secretion in the pancreas, while also contributing to glucose uptake and the conversion of glucose to glycogen in the liver. Compared with *GCK*-MODY, *HNF1A*-MODY presents with more characteristic phenotypes (such as polyuria, polydipsia, and weight loss) (16). The *HNF1B* gene encodes a member of the homeodomain-containing nuclear transcription factor superfamily, which regulates the organogenesis of the pancreas, liver, genitourinary system, kidney, intestine, and lungs. Therefore, it is characterized by a wide spectrum. Management of *HNF1B*-MODY includes intensive insulin therapy during the early period, whereas *HNF1A*-MODY can be managed with a low-carbohydrate diet. The genes commonly mutated in MODY generally affect the insulin-producing β-cells of the pancreas. In particular, the *HNF4A* and *HNF1A* genes play a vital role in β-cell production. The *HNF4A* and *HNF1A* genes encode transcription factors that regulate genes involved in insulin secretion. Because these genes play a role in the regulation of insulin secretion, a mutation leads to loss of function and deterioration of β-cells (16). Specific inherited gene variants cause MODY to manifest differently. Understanding the effects of genetic variants is critical to clinical interpretation. For example, individuals with *HNF1A* and *HNF4A* gene variants show increased sensitivity to sulfonylureas, a class of insulin-stimulating drugs. More accurate results can be obtained with treatments that take this effect into account (17). Since the correct diagnosis, prognosis, and management of MODY are of critical importance, genotype-phenotype relationships should be investigated. Further studies are needed to investigate the pathogenetic effects of non-genetic regulators (18).

Diagnostic Approach to MODY

MODY is suspected based on three main features: (1) a strong family history of diabetes of any type, with affected relatives presenting between the second and fifth decades; (2) onset of diabetes usually before the age of 25; (3) clinical features inconsistent with type 1 diabetes (insulin independence or a low insulin requirement, absence of antibodies to pancreatic antigens, and preserved β-cell function with persistently detectable C-peptide despite hyperglycemia) or with type 2 diabetes (absence of insulin resistance, obesity, and acanthosis nigricans) (19). Some extra-pancreatic features that can be used to suspect MODY subtypes include macrosomia and neonatal hypoglycemia in *HNF4A*-MODY, renal cysts in *HNF1B*-MODY, and stable, non-progressive, mild hyperglycemia in *GCK*-MODY. This is because MODY comprises 14 subtypes, each characterized

by distinct gene variants, patterns of hyperglycemia, and other features (20).

Because of phenotypic overlap with other types of diabetes, MODY remains difficult for clinicians to diagnose; many cases are misdiagnosed as type 1 or type 2 diabetes, and more than 80% go undetected. As misdiagnosis can lead to inadequate treatment, the focus must be on correct diagnosis to ensure a stronger link to clinically important treatment benefits, such as a more precise prognosis of complication risk, appropriate genetic counseling for family members—especially children—and, most importantly, it directs the choice of the most appropriate treatment. The etiology of the disease determines the appropriate course of treatment, but only molecular genetic testing can verify this. Molecular genetic testing in patients is essential to establish the diagnosis of MODY, define the subtype, anticipate the clinical course, and guide treatment options. Significant has been made in deciphering the complex molecular pathways and heterogeneous etiology of monogenic diabetes (including MODY), with the advent of current technologies such as NGS that include targeted gene panels, WES, and WGS. Accurate diagnosis of MODY leads to treatment adjustments across its three subtypes. For most *GCK*-MODY patients, pharmacological treatment is typically unnecessary, though a low glycemic index diet may be advised. In contrast, patients with *HNF1A*-MODY and *HNF4A*-MODY can achieve optimal glycemic control using sulfonylureas instead of insulin. Consequently, diagnosing MODY can significantly alter care pathways, reduce or even eliminate treatment burdens for individuals, and decrease costs for both patients and society. Despite this, only a handful of studies have explored the cost-effectiveness of MODY screening. Findings suggest that genetic testing for a carefully selected population of young patients with diabetes aged 25–40 years holds promise as a cost-effective intervention in high-income countries (21). Testing is increasing globally, with most developed countries offering at least one academic, health-service, or commercial laboratory for testing. While some regions face resource limitations, it's essential to identify target populations for molecular genetic testing to enhance detection rates. Various algorithms are available to assist in molecular diagnosis by using clinical and laboratory parameters to identify candidates. One example is the MODY probability calculator developed by Exeter University, which proved useful and showed good discriminatory ability with an optimal probability cut-off of 36% in a Portuguese cohort (22).

MODY is a heterogeneous group of monogenic forms of diabetes. Although it was initially defined as a clinical syndrome of early-onset diabetes, subtypes caused by specific gene mutations have emerged as distinct pathological entities. Furthermore, strict adherence to classical criteria for screening for MODY mutations results in poor sensitivity, which hampers effective screening strategies. Some researchers have explored various clinical biomarkers to improve the accuracy of candidate selection for molecular diagnosis. Although molecular diagnosis has become more accessible, there is a pressing need for improved clinical screening strategies for monogenic diabetes. These enhancements would improve identification of candidates for molecular diagnosis and optimize cost-effectiveness. Direct sequencing and NGS techniques can detect mutations in the MODY gene with approximately 100% sensitivity. When clinical characteristics point to specific gene mutations, such as mild fasting hyperglycemia (for *GCK* gene mutations), diabetes linked to renal cysts (for *HNF1B* mutations), or pancreatic cysts and exocrine pancreatic dysfunction (for CEL mutations), phenotype-based targeted gene testing may be performed in addition to NGS. To identify affected family members and provide genetic counseling, a precise diagnosis of MODY is necessary. Genetic testing for the same mutation should be offered to diabetic relatives in all forms of MODY, as they may also benefit from treatment (23).

Technologies in Genetic Diagnosis

When considering testing, casting a wider net may be desirable, as additional subtypes and phenotypic connections among them are being reported. Genetic testing remains the definitive method for confirming monogenic forms of diabetes. Traditionally, Sanger sequencing has been considered the gold standard for molecular genetic testing of human disorders. This method involves determining the nucleotide sequence of specific genes and comparing it to reference sequences. However, Sanger sequencing has limitations. For instance, it cannot detect large genetic rearrangements such as the complete deletion of the *HNF1B* gene, a common cause of renal cysts and diabetes (RCAD). Additionally, it does not reliably identify certain variants of mitochondrial DNA associated with mitochondrial diabetes. The emergence of NGS technologies is transforming MODY diagnostics by enabling massively parallel DNA sequencing. Targeted NGS (tNGS) is particularly noteworthy, as it facilitates the simultaneous analysis of multiple gene sequences (24). This tNGS approach not only increases the diagnostic yield simply by testing more genes but also identifies patients with rare syndromic forms of diabetes whose diagnosis was not suspected.

When a MODY patient does not exhibit sufficiently clear clinical features, in-depth genomic screening, such as WES or WGS, can be the most effective genetic testing

option. In exome sequencing, selecting specific genes for testing is unnecessary, allowing detection of MODY-related genes that targeted gene sequencing may miss. This advantage makes exome sequencing particularly valuable in cases where targeted approaches are ineffective due to ambiguous clinical presentations. Similarly, WGS offers even broader coverage than exome sequencing, as it analyzes the entire genome, including non-coding regions that might harbor relevant variants. WGS can identify mutations not only in known MODY genes but also in regulatory elements and intronic regions, potentially unveiling novel pathogenic variants. In cases where exome and targeted gene sequencing are insufficient, WGS serves as a powerful diagnostic tool that provides a comprehensive genetic overview and clarifies ambiguous cases (25). Single-nucleotide variants (SNVs) and small insertion, deletion, and duplication variants are detected by sequencing, while partial and complete gene deletions, which represent a small percentage of all mutations in MODY genes, are detected by copy-number variant (CNV) analysis. CNVs are large-scale deletions or duplications of DNA, ranging in size from approximately 50 to 1,000,000 base pairs. Historically, CNVs were difficult to detect using Sanger sequencing or early tNGS panels because of limitations in identifying DNA dosage changes and the small size of CNVs, often requiring adjunct methods such as microarray-based genomic hybridization or multiplex ligation-dependent probe amplification (MLPA), which increased costs and labor. However, new bioinformatics techniques like tNGS now leverage raw NGS data to predict CNV presence more efficiently (26). MODY subtypes, types of genetic tests, and corresponding genotype–phenotype information are illustrated in Figure 1.

Chromosomal microarray analysis (CMA) is also a genomic technique that allows for high-resolution detection of CNVs, including whole-gene deletions or duplications, and has become an important adjunct to sequence-based testing in suspected cases of MODY. In patients with a clinical phenotype consistent with MODY but whose sequencing panel (targeting SNVs and small indels) is negative, CMA can identify structural rearrangements in genes such as *HNF1B* (MODY5) or other genes where exon- or gene-level deletions are known to occur. For example, a heterozygous deletion on chromosome 17q12—which includes *HNF1B*—was detected by microarray analysis in a patient with early-onset diabetes and renal and urinary anomalies after NGS panels failed to detect a mutation (27). Clinical laboratory guidelines for MODY genetic testing recommend that when panel sequencing is negative but clinical suspicion remains high—particularly for genes known to exhibit gene-dosage alterations such as *HNF1A*, *HNF4A*, *GCK*, and *HNF1B*—deletion/duplication analysis (via MLPA or CMA) should be considered (28). In this way, microarray analysis improves diagnostic yield, ensures that structural variants are not overlooked, and contributes to more accurate subtype assignment and tailored management for MODY patients. MODY 1 results from missense mutations in the *HNF4A* gene, while MODY 2 is caused by point mutations in the *GCK* gene. MODY 3 arises from variants in the *HNF1A* gene, including missense, nonsense, and splicing mutations, as well as in-frame amino acid deletions, insertions, duplications, and whole-gene deletions. MODY 5, on the other hand, is associated with *HNF1B* whole-gene deletions or other structural variants and linked to RCAD syndrome.

Challenges in Genetic Diagnosis

In the era of NGS, clinicians frequently encounter variants of unknown significance (VUS) in genetic testing. VUS may be reclassified over time as genetic knowledge grows. We have limited data on the optimal approach to VUS in MODY (29). With a proper diagnosis and treatment of MODY, switching from injections to oral hypoglycemic medications or to lifestyle changes alone can greatly enhance a patient's quality of life. Insulin treatment may be less necessary if the diagnosis is made early. Clinical prediction models may make it easier to identify which individuals will benefit from molecular genetic testing. To categorize the variants that cause MODY, reporting novel variants and their associated symptoms is crucial. Routine genetic testing in suspected cases will expand existing understanding (30). Using four cohorts from diverse settings, It has been demonstrated that pathogenic variants in the three MODY-associated genes are relatively common in the population. In clinically selected individuals, pathogenic variants in *HNF1A* and *HNF4A* are associated with the highest risk of diabetes; however, in clinically unselected individuals, their risk is significantly reduced. It was demonstrated that the features of the environment in which the variants were discovered, rather than the types of variants, were responsible for this decreased risk. Unexpectedly, the penetrance of pathogenic *GCK* variants was comparable across cohorts despite differences in their environments.

Studies show that pathogenic variants in common MODY genes are not ultra-rare and often display reduced penetrance when found incidentally. Genetic counseling should consider the setting, family history, and health status. An exception is *GCK*-MODY, which shows near-complete penetrance across contexts, supporting its inclusion in the ACMG secondary gene list to prevent unnecessary treatment (31). Experiences with genetic testing in other conditions demonstrate the importance of understanding personal experiences with chronic illness and lay beliefs

about inheritance. Health professionals should explore how individuals with MODY perceive their health and diabetes, as family beliefs shape the meaning of genetic information. Without addressing these views, families may dismiss the results. Using simple language or visuals can improve understanding. Clarifying motivations for predictive testing helps manage expectations and concerns during genetic counseling (32).

Clinical Implications of Genetic Diagnosis

First, diabetes diagnosed before six months of age is frequently caused by mutations in genes encoding components of the ATP-sensitive potassium channel: the sulfonylurea receptor 1 subunits or the inward-rectifier potassium channel (Kir6.2). Treatment with high-dose sulfonylureas, compared with insulin, can improve glycemic control. Second, individuals who have modest, stable fasting hyperglycemia, especially in young people, may have a glucokinase mutation and may do not need special care. Thirdly, low-dose sulfonylureas can be used to treat people with familial young-onset diabetes who do not meet the diagnostic criteria for type 1 or type 2 diabetes, because these individuals may harbour mutations in the transcription factors HNF-1A or HNF-4A. Finally, patients with extrapancreatic features, such as renal disease or deafness, usually require early insulin therapy (33). Accurate genetic diagnoses are crucial because they frequently result in improved diabetes management and allow predictive genetic testing of their asymptomatic relatives. Reducing the risk of diabetes-related complications later in life requires early diagnosis and adequate treatment (34).

During the first decade of life, patients with MODY1 exhibit relatively normal glucose tolerance. Testing and subsequent diagnosis are typically predicated on unintentional hyperglycemia detected during concurrent illness or family screening. Due to hormonal changes that result in insulin resistance and disruption of glucose regulation, glucose intolerance typically manifests during adolescence or in early adulthood. Patients should be managed with a low-carbohydrate diet at diagnosis and during the early stages of the disease, when their blood glucose and glycated hemoglobin levels are still within the "non-diabetic" range. Sulfonylureas

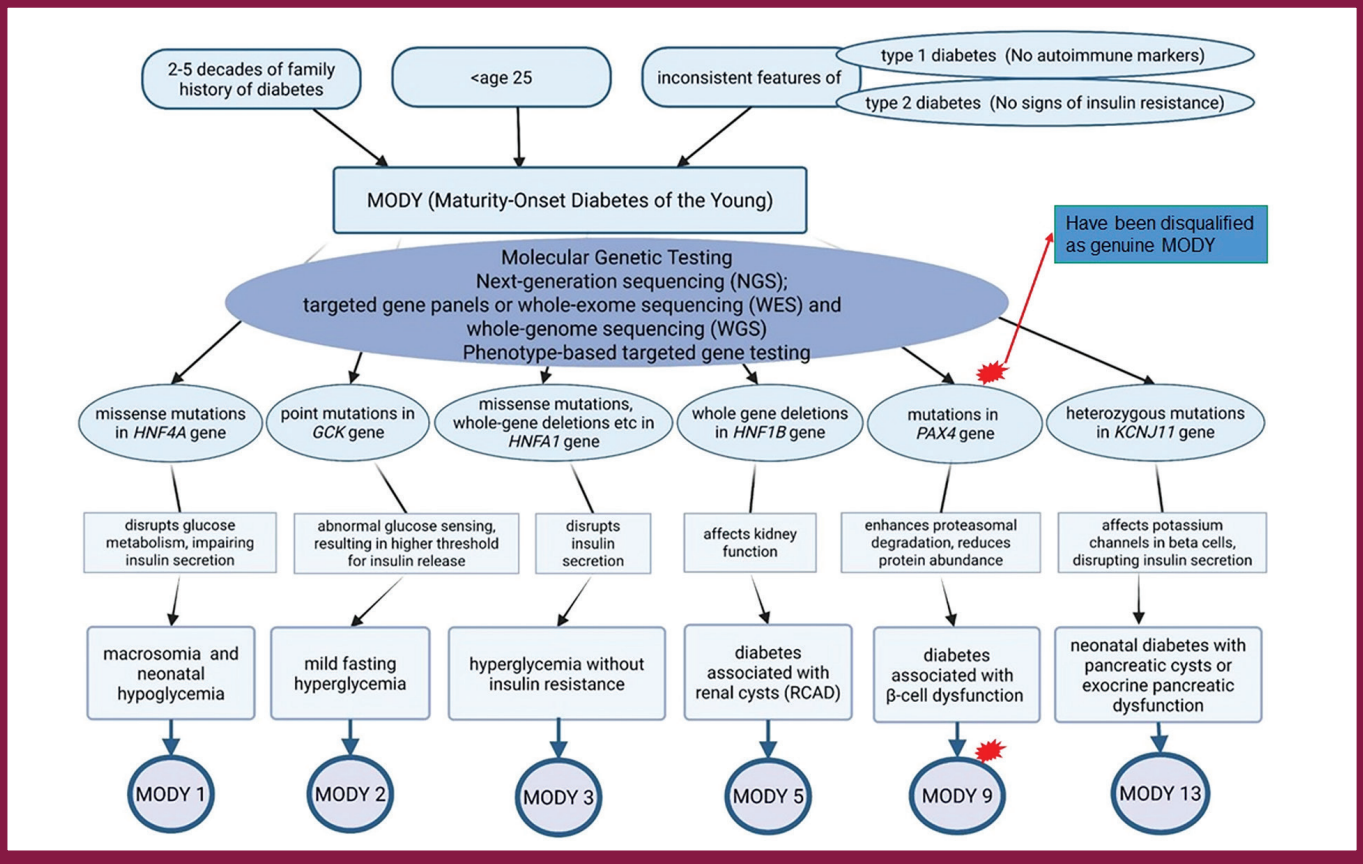

Figure 1. Overview of MODY subtypes, genetic tests, and genotype–phenotype data.
MODY, maturity-onset diabetes of the young; RCAD, renal cysts and diabetes.

are recommended instead of insulin when diet appears to be failing, because they provide better glycemic control. Regarding sulphonylurea derivatives, their safety and long-term efficacy, associated improvements in quality of life, and improved patient compliance are well established. Heterozygous variants in the *PDX1* gene, encodes the transcription factor *PDX1* essential for the formation and function of the pancreas and its β-cells, result in *PDX1*–MODY, a rare, mild form of monogenic diabetes. Diabetes appears to result from dominant-negative suppression of transcription caused by mutations in the insulin gene. Individuals with *PDX1*-MODY develop early-onset type 2 diabetes and have no extra-pancreatic manifestations. *PDX1* indirectly disrupts the incretin pathway and is crucial for glucose-stimulated insulin release, especially in postprandial hyperglycemia. Orally administered antihyperglycemic medications have been proposed as a treatment. Case reports have documented the efficacy of DPP-4 inhibitors in combination with metformin. Due to a degree of hepatic insulin resistance, patients with *HNF1B*-MODY respond poorly to sulfonylureas, and early insulin therapy may be necessary.

Future Directions in MODY Diagnosis

Considerable progress in technologies and informatics for generating and evaluating large biologicaldatasets has promoted a paradigm shift in how biomedical problems are addressed. Investigation of human health and disease at the omics level provides new opportunities. Omics data should be analyzed and integrated as a whole to achieve optimal results. Different levels of data, such as genomics, transcriptomics, proteomics, and metabolomics, can be evaluated jointly. The complexity of the human genome and its regulation at multiple levels requires consideration of data across those levels. A multi-omics approach enables characterization of patients' molecular and cellular profiles. In this way, the underlying causes of pathologies and cell-level errors that have not yet had an impact can be analyzed. A multi-omics approach can also be used to classify variants of MODY. NGS techniques, such as WES and WGS, together with CNV analysis, can be used to specify the MODY variant in question. Translation of variant gene sequences into protein sequences allows researchers to gather focused information on specific variant genes and proteins and facilitates their studies by integrating genomics and proteomics. The integration of omics data with this new method holds great potential, as it paves the way for precision medicine.

Development of targeted therapies requires confirmation of suspected MODY variants with genetic testing. Targeted therapies provide a basis for further pre-symptomatic screening of genetically related individuals of the patient. Early molecular genetic diagnosis enables necessary modifications to therapy. Diagnosing monogenic diabetes may be challenging because symptoms are similar. Genetic testing enables a genetic diagnosis and identifies the definitive cause of the symptoms. Targeted therapies are needed for the appropriate management of MODY.

Although NGS has made diagnosis easier by reducing the cost of genetic testing, our knowledge of DNA and pathogenic genes is far from sufficient. The vast amount of data produced by NGS must be analyzed using computational tools to enable effective research and to reduce time and costs. Nevertheless, artifical intelligence and machine learning may be effective tools for evaluating DNA sequencing data, as well as overall patient data and broader factors that may influence the disease. Ten algorithms used in precision medicine employ machine learning (35). Support Vector Machine (classifies and analyzes symptoms to improve diagnostic accuracy), Deep Learning (used in medical image analysis such as computed tomography scan, magnetic resonance imaging, colonoscopy, mammograpy etc), Logistic Regression (evaluates the potential risks and patient survival rates), Discriminant analysis (classifies patients for operation process, symptom-relief satisfaction data), Decision Tree (used in real-time healthcare monitoring, detection of aberrant data and helps in therapeutic decision), Random Forest (widely used in healthcare system for predicting metabolic pathways of individuals, mortality rates, healthcare cost and diagnosis), Lineer Regression (computational analyses and predictions), Naive Bayes, KNN (preserving patient information, pattern classification), HMM (drug side effect extraction from online forums, examining patient data), and Genetic Algorithm (36).

Conclusion

Genetic testing is essential for accurately diagnosing MODY, a monogenic form of diabetes. It enables precise identification of the causative gene mutation, guides personalized treatment decisions, and differentiates MODY from type 1 or type 2 diabetes, reducing misdiagnosis and ensuring appropriate management and family screening.

Footnotes

Authorship Contributions

Concept: Ş.S.Ş., E.E.D., A.C.K., E.İ., M.E., G.H., Design: M.E., G.H., Data Collection or Processing: Ş.S.Ş., E.E.D., A.C.K., E.İ., Analysis or Interpretation: Ş.S.Ş., E.E.D., A.C.K., E.İ., M.E., G.H., Literature Search: Ş.S.Ş., E.E.D., A.C.K., E.İ., M.E., G.H., Writing: Ş.S.Ş., E.E.D., A.C.K., E.İ., M.E., G.H.

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