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ДИАГНОСТИКА И ЛЕЧЕНИЕ МОНОГЕННЫХ ФОРМ САХАРНОГО ДИАБЕТА: В ФОКУСЕ MODY-ДИАБЕТ

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Diagnosis and Treatment of Monogenic Forms of Diabetes Mellitus: Focus on Mody-Diabetes

Резюме

Диабет зрелого возраста у молодых (MODY) является наиболее распространенной формой моногенного диабета, возникающего в результате мутации одного гена. Он характеризуется легкой гипергликемией, аутосомно-доминантным типом наследования, ранним началом диабета (<25 лет), сохранением эндогенной секреции инсулина, а также наличием подтипов, различающихся клинически и генетически. В настоящее время идентифицировано 14 подтипов MODY, отличающихся частотой возникновения, клиническими особенностями, тяжестью диабета и связанными с ним осложнениями, а также ответом на лечение. Этот тип диабета, зачастую некорректно диагностируется как сахарный диабет типа 1 или типа 2. Причина тому — клиническое сходство с другими типами диабета, высокая стоимость и ограниченный доступ к генетическому тестированию, а также недостаточная осведомлённость клиницистов. В результате несвоевременной диагностики пациенты не получают надлежащего эффективного лечения, отличного от терапии диабета 1 и 2 типов. Цель данного обзора — повысить осведомлённость клиницистов о MODY-диабете, акцентировав внимание на обновленной информации о методах диагностики и лечения 14 подтипов.

Ключевые слова: *сахарный диабет зрелого возраста у молодых; сахарный диабет; генетическое тестирование; генные мутации; HNF1A; глюкокиназа (GCK)*

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Abstract

Maturity-Onset Diabetes of the Young (MODY) is the most common form of monogenic diabetes resulting from a single gene mutation. It is characterized by mild hyperglycemia, autosomal dominant inheritance, early onset diabetes (<25 years), persistence of endogenous insulin secretion, and clinically and genetically distinct subtypes. Currently, 14 subtypes of MODY have been identified, differing in incidence, clinical features, severity of diabetes and associated complications, and response to treatment. This type of diabetes is mostly misdiagnosed as type 1 or type 2 diabetes mellitus due to clinical similarities to other types of diabetes, high cost and limited access to genetic testing, and lack of clinician awareness. As a result, thousands of patients do not receive proper treatment. Accurate diagnosis would allow for more effective therapeutic treatments other than those used for type 1 and type 2 diabetes. The purpose of this review is to raise clinicians' awareness of MODY diabetes by focusing on updated information on methods for diagnosing and treating its 14 subtypes.

Key words: *Maturity-Onset Diabetes of the Young (MODY); diabetes; genetic testing; gene mutations; HNF1A; glucokinase (GCK)*

Conflict of interests

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DPP-4 — dipeptidyl peptidase-4, K-ATP — ATP-sensitive potassium channels, PAP — oral antidiabetic drugs, SSM — sulfonylurea derivatives, SOD — superoxide dismutase, ABCC8 — ATP binding cassette subfamily C member 8, APPL1 — Adaptor protein, phosphotyrosine, interacting with PH domain and leucine Zipper 1, ATP — Binding cassette subfamily C member 8, BLK — B-cell Lymphocyte Kinase, CEL — Carboxyl ester lipase, GCK — Glucokinase, GLP-1 — Ras — агонисты рецептора глюкагоноподобного пептида-1, GLUT2 — Glucose transporter 2, HbA1c — Glycated hemoglobin, hemoglobin A1c, HNF — Hepatic nuclear factor, HNF1A — Hepatocyte nuclear factor 1-α, INS — Insulin, KCNJ11 — K+ channel subfamily J member 11, KLF11 — Krueppel-like factor 11, MODY — Maturity-Onset Diabetes of the Young, NEUROD1 — Neurogenic differentiation factor 1 , NF-kB — Nuclear factor kappa-light-chain-enhancer of activated B cells, PAX4 — Paired box 4, PDX1 — Pancreatic and duodenal homeobox 1, PND — Permanent neonatal diabetes, RCAD — Renal cysts and diabetes, SUR1 — Sulfonylurea receptor -1

Introduction

Maturity-onset diabetes of the young (MODY) is an unusual form of diabetes mellitus resulting from mutations in a single gene [1]. MODY is characterized by β-cell dysfunction; onset at a young age (before the age of 25); autosomal dominant inheritance; mild course that requires no or very little insulin therapy; in most cases, by high sensitivity to sulfonylurea derivatives (SUDs); the presence of clinically and genetically different subtypes; as well as by the absence of insulin resistance [2]. With regard to the latest of the listed specific features of MODY, i. e., the absence of insulin resistance, the researchers have different opinions. This, according to Mohan V. et al. (1987), insulin resistance in MODY patients is not only present, but is even more pronounced than in individuals with classical non-insulin-dependent diabetes [3]. Apparently, defective genes are crucial for the development, function and regulation of β-cells and therefore can cause impaired tissue glucose tolerance and insulin secretion.

Depending on the genes involved, MODY is classified into several subtypes and clinical phenotypes. Currently, there are 14 identified and described MODY subtypes, each of which is caused by a separate gene mutation (Table) [4]. These subtypes differ in gene mutation, age of onset, treatment, and hyperglycemia pattern. Among all 14 MODY subtypes, more than 95 % of cases are caused by mutations in hepatocyte nuclear factor 1-α (HNF1A), glucokinase (GCK), HNF4A and HNF1B; other mutations are rare and uncommon in the Caucasian population [5]. All known mutations underlying MODY vary in their prevalence, clinical features, severity of diabetes and related complications, and response to treatment. Each mutation encodes proteins involved in glucose homeostasis in pancreatic β-cells [6].

Diagnosis of MODY

Advanced genetic testing based on the development of new methods (e.g., next-generation sequencing) and increased availability of genetic testing centers, allow

Table. *Aggregate data on MODY subtypes (gene names, their localization and clinical signs)*

Subtype	Gene name	Locus	Clinical signs	Source
1	*HNF4A*	20q13.12	Mild fasting and postprandial hyperglycemia, sensitivity to sulfonylurea derivatives, low levels of apolipoproteins and triglycerides, neonatal macrosomia, neonatal hypoglycemic events	[6]
2	*GCK*	7p13	Mild fasting hyperglycemia, impaired glucose tolerance, HbA1c typically 7.3-7.5 %	[6]
3	*HNF1A*	12q24.31	Decreased renal threshold for glucosuria, sensitivity to sulfonylurea derivatives, transient neonatal hyperinsulinemic hypoglycemia	[17]
4	*PDX1*	13q12.2	Pancreatic agenesis, permanent neonatal diabetes in homozygotes	[5]
5	*HNF1B*	17q12	It is characterized by kidney damage and the development of anomalies of the genitourinary system in females, dysfunction of the exocrine part of the pancreas, hyperuricemia	[53]
6	*NEUROD1*	2q31.3	Characterized by obesity and insulin resistance, neonatal diabetes, childhood or adult-onset diabetes, neurological abnormalities	[11,19]
7	*KLF11*	2p25.1	Associated with the development of malignant neoplasm in the pancreas	[11]
8	*CEL*	9q34.13	Associated with endocrine and exocrine pancreatic dysfunction, lipomatosis, and fibrosis	[11]
9	*PAX4*	7q32.1	This gene encodes a transcription factor that is essential for the development and survival of insulin-producing β-cells	[11]
10	*INS*	11p15.5	Associated with neonatal diabetes	[53]
11	*BLK*	8p23.1	Helps control beta signals	[53]
12	*ABCC8*	11p15.1	Associated with renal diabetes	[53]
13	*KCNJ11*	11p15.1	Associated with renal diabetes	[53]
14	*APPL1*	3p14.3	Associated with Wolfram syndrome	[53]

Notes: GCK: Glucokinase (glucokinase); HNF1A, HNF4A, HNF1B: Hepatic nuclear factor alpha/beta (hepatocyte nuclear factor alpha/beta); PDX1: Pancreatic and duodenal homeobox 1 (pancreatic and duodenal homeobox 1); NEUROD1: Neurogenic differentiation factor 1 (neurogenic differentiation factor 1); KLF11: Krueppel-like factor 11 (Krueppel-like factor 11); CEL: Carboxyl ester lipase; PAX4: Paired box 4 (paired box 4); INS: Insulin (insulin); BLK: B-cell Lymphocyte Kinase (tyrosine protein kinase); ABCC8: ATP binding cassette subfamily C member 8; KCNJ11: K+ channel subfamily J member 11 (K+ channel subfamily J member 11); APPL1: Adapter protein, phosphotyrosine, interacting with PH domain and leucine Zipper 1

clinicians to make correct molecular diagnoses, thereby, avoiding the misdiagnosis of type 1 diabetes mellitus (DM1) or type 2 diabetes mellitus (DM2) [7]. Furthermore, several extrapancreatic signs can be used as specific MODY subtypes markers (e.g., macrosomia and neonatal hypoglycemia in the HNF4A-MODY subtype, or renal cysts in the HNF1B-MODY subtype). It should also be known that several MODY subtypes are characterized by a stable blood glucose level throughout the patient's life, others — by a progressive deterioration in insulin secretion and glucose control, and still others are predisposed to the development of micro- and macrovascular complications.

MODY can be distinguished from other types of diabetes by the age of the disease onset. However, it should be considered that MODY subtypes with different age of onset, low penetrance, or atypical signs may not meet the diagnostic criteria of the disease [8]. Furthermore, while a family history of diabetes is highly suggestive of MODY, several mutations in MODY-associated genes may occur at high frequency in individuals with no family history of diabetes [9].

According to the MODY diagnostic guidelines, genetic testing should be performed in individuals diagnosed with diabetes at a young age (25 years), as well as in individuals with the family history of diabetes, signs of endogenous insulin secretion as determined by C-peptide levels, and negative antibody results [10]. Direct sequencing with sensitivity approximating 100 % and next-generation sequencing can be successfully used to detect mutations in the MODY gene [1]. According to the model proposed by Shields B. M. et al. (2010), the onset under the age of 30 is an important differentiating factor between MODY and type 2 DM, while diabetes in parents increases the probability of a later change in a previously diagnosed type 1 DM to MODY 23-fold [5].

Clinical relevance of MODY diagnosis

Patients with MODY are often misdiagnosed with DM1 or DM2, and it leads to incorrect treatment [11]. The reason is not only the overlapping clinical signs common in diabetes mellitus; the high price and limited availability of genetic testing, as well as the lack of clinician awareness are also relevant. Exact diagnosis of MODY and its subtypes is crucial for patients and their families allowing them to choose the optimal

therapeutic approach that differs significantly from that used in DM1 and DM2 [4]. Thus, the patients treated for DM1 can shift to oral medications (e.g., SUDs) that will improve their life quality and glycemic control [12]. Similarly, patients with HNF1A-MODY (MODY 3) and HNF4A-MODY (MODY 1) may avoid unnecessary insulin therapy, as the results of studies have demonstrated that oral sulfonylurea agents are the optimal choice [13]. The diagnosis of MODY is the key to providing accurate consultation for predictive clinical outcome and genetic screening of family members [14].

MODY subtypes and management

HNF4A-MODY (MODY 1). MODY 1 is caused by a mutation in the hepatocyte nuclear factor 4A (*HNF4A*) gene that is expressed predominantly in liver, as well as in pancreas and kidneys. *HNF4A* gene regulates the expression of genes involved in lipid metabolism and gluconeogenesis in liver [15]. The mutations in *HNF4A*, associated with autosomal dominant inheritance lead to decreased insulin production [16]. Heterozygous mutations in this gene cause dysfunction of β-cells, impaired glucose-stimulated insulin secretion, and contribute to the development of atherogenic dyslipidemia [16]. MODY 1 can be associated with fetal macrosomia, transient neonatal hyperinsulinemic hypoglycemia, progressive development of hyperglycemia, and onset of diabetes mellitus in late adolescence or by the age of 25 [17]. During the first decade of life, patients with MODY 1 show normal glucose tolerance [15]. At the time of diagnosis and at the early stages of the disease, the patients with MODY 1 can control their glycemia just with diet, despite the elevated postprandial glucose levels after eating carbohydrate-rich food [18]. However, in most patients, β-cell function deteriorates over time requiring drug treatment [19]. Individuals with HNF4A-MODY are sensitive to sulfonylurea [19]; the best treatment is this compound in low doses rather than insulin [12]. However, in the later stages of the disease or during pregnancy, insulin therapy is usually required [15].

GCK-MODY (MODY 2). Glucokinase (GCK), also known as hexokinase IV or D, belongs to hexokinase family. *GCK* gene plays an important role in glucose-stimulated insulin secretion in pancreas, facilitating glucose uptake and its conversion to glycogen in liver [20, 21]. Mutations of *GCK* gene underlie the development of MODY 2 [21] and have been shown to cause abnormal sensitivity of β-cells to glucose that contributes to the development of a higher threshold for the start of glucose-stimulated insulin secretion. Glycated hemoglobin (HbA1c) levels are usually under 7.3–7.5 %. The vast majority of patients with MODY 2 have slightly elevated fasting plasma glucose levels, with no postprandial hyperglycemia, indicating adequate insulin production in response to elevated postprandial blood glucose levels [19]. Patients with confirmed GCK-MODY do not require any treatment other than recommendations on diet as their long-term outcomes are comparable to those in healthy individuals [20]. However, insulin should be administered during pregnancy to reduce the risk of fetal macrosomia [22]. Fetal genotype is not always known, therefore, series ultrasound measurements can be used to determine the height. If there is evidence of increased abdominal circumference on series ultrasound, then it can be assumed that the fetus has no GCK mutation and maternal hyperglycemia in this case should be managed to reduce the risk of macrosomia. If no signs of accelerated growth are found, then there is reason to suggest that the fetus has inherited the GCK gene mutation, and, in this regard, no treatment for maternal hyperglycemia is provided [23].

HNF1A-MODY (MODY 3). MODY 3 is a common variant of maturity-onset diabetes of the young and is caused by mutations in *HNF1A* gene [20]. *HNF1A* gene was found in liver, kidneys, intestine, and pancreatic β-cells and has been shown to control the expression of insulin genes in mature β-cells, as well as of the GLUT2 glucose transporter genes [4]. Mutations in *HNF1A* gene can cause impaired dimerization processes that, in turn, leads to the impaired metabolism of carbohydrates and the development of diabetes mellitus. HNF1A-MODY has a glycemic pattern that includes moderate fasting hyperglycemia and extremely high glucose levels after glucose administration [15]. HNF1A-MODY is characterized by transient neonatal hyperinsulinemic hypoglycemia, progressive hyperglycemia throughout the childhood, and the onset of diabetes mellitus at the age of 25 [17]. Insulin secretion in patients with HNF1A-MODY gradually decreases, glucose control upon that deteriorates over time and requires treatment. In addition, 63 % of patients develop diabetes under the age of 25, 79 % — under the age of 35, and 96 % — under the age of 55 [15]. Treatment of patients with HNF1A-MODY is carried out depending on their age and HbA1c level [24]. HNF1A-MODY is initially managed with a low-dose diet and sulfonylurea agents, however, insulin is required at the later stages of the disease or during pregnancy [15]. Glucagon-like peptide-1 receptor agonists (GLP-1 Ras) have been shown to effectively control HNF1A-MODY [25].

PDX1-MODY (MODY 4). Pancreatic and duodenal homeobox 1 (PDXI) is a homeodomain-containing transcription factor that regulates insulin gene expression and pancreatic development [20]. PDX1-MODY is a rare type of MODY that is caused by heterozygous mutations in *PDX1* gene that is important for the regulation of genes encoding the enzymes of glucagon, insulin, glucose transporter 2 (GLUT2), and glucokinase (GCK) [26]. *PDX1* gene acts as a main switch for the hormonal and enzymatic functions of pancreas [27]. Heterozygous mutations in *PDX1* gene can lead to impaired insulin

secretion, while homozygous mutations cause permanent neonatal diabetes (PND) and exocrine pancreatic insufficiency [28]. Patients with PDX1-MODY have type 2 diabetes with early onset and no extrapancreatic involvement. Metformin [29] and dipeptidyl peptidase-4 (DPP-4) [30] inhibitors have been shown to be effective in clinical cases. Diet, oral antidiabetic drugs (OADs), and insulin are all treatment options for individuals with MODY 4 [15].

HNF1B-MODY (MODY 5). MODY 5 is a rare type of the disease caused by mutations in *hepatocyte nuclear factor 1B* (*HNF1B*) gene [20]. *HNF1B* is a transcription factor of the superfamily of homeodomain-containing transcription factors and is found in a wide range of tissues such as liver, intestine, stomach, lungs, and pancreas [15, 20]. It is involved in many processes, including the development of nephron and embryonic pancreas [31]. Patients with HNF1B-MODY often have significant histologic abnormalities such as renal cysts and diabetes (RCAD). Variable multisystem phenotypes with a wide range of pancreatic and extrapancreatic clinical signs are observed in HNF1B-MODY [15]. Severe renal disease is caused by mutations in *HNF1B* that may start before the onset of glucose intolerance [32]. MODY 5 can cause such complications as vaginal aplasia, rudimentary uterus, hyperglycemia, gout, and low birth weight (900 g) [31]. Patients with HNF1B-MODY demonstrate hepatic insulin resistance [12] and resistance to sulfonylurea therapy, thus, early insulin administration may be required [33].

NEUROD1-MODY (MODY 6). Neurogenic differentiation factor 1 (NEUROD1) is a transcription factor with a basic loop and helix structure that is expressed in neurons and pancreatic cells. NEUROD1 is essential for pancreatic and neuronal development and has an effect on pancreatic morphology and neuronal differentiation [34]. NEUROD1 plays a role in the activation of insulin transcription by binding and activating the promoters of the sulfonylurea receptor 1 (SUR1), GCK, and PAX6 (a protein related to the catalytic subunit of glucose-6-phosphatase) [15]. Mutations in *NEUROD1* gene lead to the development of MODY 6 [20], and heterozygous mutations of this gene result in the dysfunction of β-cells [35]. Although insulin therapy is a standard treatment option, it should be kept in mind that patients with MODY 6 have diabetes with incomplete penetrance. This fact explains the possibility of obtaining benefits from both OADs and diet in half of patients with MODY 6 [36].

KLF11-MODY (MODY 7). Krueppel-like factor 11 (KLF11)-MODY is a result of heterozygous mutations in *KLF11* gene. *KLF11* gene encodes a transcription factor from the KLF/Sp1 family that is found in all human tissues [20, 37]. KLF11 regulates the expression of free radical scavengers such as catalase and superoxide dismutase (SOD) that are required for pancreatic β-cell function [20, 34]. Heterozygous mutations in *KLF11* gene ultimately lead to the dysfunction of β-cells and impaired insulin secretion [37]. KLF11-MODY is a type of diabetes with the onset at an early age and is managed with either OADs or insulin [15].

CEL-MODY (MODY 8). MODY 8 is caused by mutations in *carboxyl ester lipase* gene (CEL) that regulates pancreatic exocrine and endocrine functions. This gene is usually found in mammary glands and acinar tissue of pancreas [20, 38]. CEL is important in infants as it contributes to milk digestion and hydrolysis of food esters in duodenum [39]. Heterozygous mutations in *CEL* are associated with early pancreatic atrophy and subsequent exocrine failure, pancreatic lipomatosis, and endocrine dysfunction caused by carboxyl ester lipase misfolding and cytotoxic aggregation [38]. CEL-MODY manifests as adult-onset diabetes. Insulin appears to be the most appropriate treatment option for MODY 8; however, oral antidiabetic drugs can also be used [15, 38].

PAX4-MODY (MODY 9). MODY 9 develops as a result of heterozygous mutations in paired box *4* gene (PAX4) that encodes a transcription factor required for the formation, differentiation, development, and survival of insulin-producing β-cells [15, 20]. At the early stages of embryonic development, PAX4 is expressed in endocrine promoter cells, and then in β-cells [40]. Ketosis-prone diabetes was associated with mutations in *PAX4* gene [41]. At the early stages, patients with MODY 9 are treated using dietary agents or OADs [42]. However, at later stages of the disease, patients may require insulin administration [43].

INS-MODY (MODY 10). *Insulin* gene (*INS*) encodes proinsulin, and its mutation can lead to primary defects in nuclear factor kappa-B (NF-kB, nuclear factor kappa-light-chain-enhancer of activated B cells) [20]. Heterozygous gene mutations in *INS* gene result in MODY 10 which is characterized by decreased β-cell mass, gradually decreased insulin secretion, and diabetes mellitus with variable onset. Although dominant misfolding mutations in *INS gene* are a common cause of isolated permanent neonatal diabetes, the age of disease onset varies [44]. These mutations lead to a severe folding defect, an abnormal response to unfolded proteins, and β-cell apoptosis [45]. Diet or OADs can be used to treat patients with MODY at the time of diagnosis, however, patients eventually become insulin-dependent [44].

BLK-MODY (MODY 11). MODY 11 is caused by heterozygous mutations in *tyrosine protein kinase* gene (*BLK*, *B cell lymphocyte kinase*). *BLK* gene belongs to the SRC family of proto-oncogenes and encodes a tyrosine receptor protein that stimulates β-cells to produce and secrete insulin [20]. *BLK* gene is expressed in β-cells and is required for thymopoiesis in immature T-cells [46].

BLK-MODY has incomplete penetrance, so not all carriers develop diabetes. Heterozygous mutations in this gene reduce the expression and/or activity of BLK; it leads to PDX1 and NKX 6.1 deficiency, impaired glucose-stimulated insulin secretion, and decreased β-cell mass [47]. Environmental and genetic factors are suggested to play a role in the development of BLK-MODY, with overweight being the most important cause of hyperglycemia [48]. Pregnancy can also affect hyperglycemia [49]. Although the vast majority of patients require insulin, some of them can be treated with diet or OADs [15].

ABCC8-MODY (MODY 12). MODY 12 is based on heterozygous mutations of *ATP-binding cassette subfamily C member 8* gene (*ABCC8*) that encodes the sulfonylurea receptor 1 (SUR1), a subunit of the ATP-sensitive potassium (K-ATP) channel found in β-cell membranes [20, 34]. ABCC8 is responsible for the secretion of insulin that controls blood glucose levels [50]. Mutations in *ABCC8* gene can lead to congenital hyperinsulinism which can be caused by dominantly inherited inactivating mutations. Moreover, mutations in *ABCC8* gene (activating or recessive loss-of-function mutations) can cause the development of permanent or transient neonatal diabetes [50]. Most patients with MODY 12 are misdiagnosed with diabetes of another type and mistreated with insulin; it results in poor control and episodes of hypoglycemia [15]. Rafiq M. et al. (2008) suggested that in adulthood, all carriers of the ABCC8 mutation can be switched to sulfonylurea drugs [51].

KCNJ11-MODY (MODY 13). MODY 13 is caused by heterozygous mutations in *KCNJ11* gene that encodes Kir6.2 protein, one of the subunits of ATP-dependent potassium channels that regulate the flow of potassium ions across the cell membrane in pancreatic β-cells and play an important role in the regulation of glucose-stimulated insulin secretion [4]. This gene mutation results in the development of severe conditions such as inactivation of potassium channels due to the impaired interaction of subunits. This disorder has been found to be associated with Arg301 mutations that commonly lead to hyperinsulinism and possibly — to neonatal diabetes [34]. Patients with KCNJ11-MODY are best treated with high doses of a sulfonylurea for a long period of time [15].

APPL1-MODY (MODY 14). MODY 14 is a rare subtype caused by mutations in an adapter protein *phosphotyrosine* and *leucine lightning 1* gene (*APPL1*, adaptor protein, phosphotyrosine interacting with PH domain and leucine zipper 1) that regulates cell proliferation and the interaction between adiponectin and insulin signaling pathways [52]. Heterozygous loss-of-function mutations in this gene lead to impaired insulin secretion in response to glucose stimulation and decreased survival of β-cells [52]. *APPL1* mutations can induce apoptosis in the tissues with high expression; overexpression causes dysmorphic phenotypes and developmental delay [52]. Diet, oral antidiabetic drugs, and insulin are all possible treatments options for APPL1-MODY [15].

Conclusion

MODY is a rare type of diabetes mellitus that in many cases leads to the delayed diagnosis. As a result, patients often receive ineffective treatment that can aggravate the disease course. Molecular diagnostics is crucial for finding the optimal management in most patients with MODY. Clinicians should be aware of MODY pathogenesis and biomarkers, as this information is crucial for diagnosis verification, individual case management, and family screening.

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