Received: 29 April 2019 | Revised: 1 August 2019 | Accepted: 18 August 2019

DOI: 10.1002/mgg3.989

ORIGINAL ARTICLE

Molecular Genetics & Genomic Medicine Open Access WILEY

The first case of NEUROD1-MODY reported in Latin America

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Funding information
National Council for Scientific and Technological Development; Coordination for the Improvement of Higher Education Personnel; Oswaldo Cruz Institute

Abstract

Background: MODY-NEUROD1 is a rare form of monogenic diabetes caused by mutations in *Neuronal differentiation 1* (*NEUROD1*). Until now, only a few cases of MODY-NEUROD1 have been reported worldwide and the real contribution of mutations in *NEUROD1* in monogenic diabetes and its clinical impact remain unclear.

Methods: Genomic DNA was isolated from peripheral blood lymphocytes of 25 unrelated Brazilians patients with clinical characteristics suggestive of monogenic diabetes and the screening of the entire coding region of *NEUROD1* was performed by Sanger sequencing.

Results: We identified one novel frameshift deletion (p.Phe256Leufs*2) in *NEUROD1* segregating in an autosomal dominant inheritance fashion. Almost 20 years after the first report of NEUROD1-MODY, only a few families in Europe and Asia had shown mutations in *NEUROD1* as the cause of monogenic diabetes.

Conclusion: To our knowledge, we described the first case of NEUROD1-MODY in a Latin American family.

KEYWORDS
diabetes mellitus, MODY, MODY6, monogenic diabetes, NEUROD1

1 | INTRODUCTION

Neuronal differentiation 1 (*NEUROD1* – Gene ID: 4760 – OMIM *601724), also known as *BETA2*, encodes a basic helix-loop-helix (bHLH) transcription factor that heterodimerizes with the ubiquitous bHLH protein E47 and regulates insulin gene (*INS*) expression through binding to its E-box motif promoter (Naya, Stellrecht, & Tsai, 1995). In 1999, mutations in *NEUROD1* were associated to early onset type 2 diabetes mellitus (DM) in two European descendent families inherited in an autosomal dominant fashion for the first time (Malecki et al., 1999), being further classified as maturity-onset diabetes of the young type 6 (MODY6; OMIM #606394) (Fajans, Bell, & Polonsky, 2001). Almost 20 years after the first report, only a few families in Europe (Ağladıoğlu et al., 2016; Gonsorčíková et al., 2008; Kristinsson et al., 2001; Szopa et al., 2016) and Asia (Ang et al., 2016; Chapla et al., 2015; Doddabelavangala Mruthyunjaya et al., 2017; Horikawa et al., 2018; Liu et al., 2007) had shown mutations in *NEUROD1* as the cause of diabetes.

Epidemiological studies of monogenic diabetes are scarce in multiethnic populations, such as Brazilian. This population is very diverse and comprises individuals of multiple ethnic backgrounds and racial admixture, especially Caucasians and Afro-descendants. Studies aiming the rare forms of monogenic diabetes are needed in a mixed population and, to the best of our

knowledge, this is the first case to report a *NEUROD1* mutation in a Latin American family.

2 | MATERIALS AND METHODS

2.1 | Ethical compliance

The Ethics and Research Committee of the Clementino Fraga Filho University Hospital approved this study protocol (No. 70238). All participants were informed about the aim of this study and provided verbal and written consent according to Helsinki Declaration.

2.2 | Patients

In this cross-sectional observational study, we selected 25 unrelated Brazilian probands negative for *GCK* or *HNF1A*, *HNF4A,* and *HNF1B* mutations. The inclusion criteria were age at onset ≤35 years, BMI (body mass index) <30 kg/m^2 or 95th percentile at the diagnosis; a positive family history of diabetes in at least two generations; negative β-cells anti-glutamic acid descarboxylase (anti-GAD) and anti-IA-2 autoantibodies. We excluded patients with type 1 diabetes, history of diabetic ketoacidosis, clinical signs of insulin resistance, and presence of secondary causes of diabetes.

2.3 | Molecular screening

Genomic DNA was isolated from peripheral blood leukocytes using QIAamp DNA Blood Mini Kit (Qiagen) and from the family members who accepted to participate in this study, we extracted genomic DNA from buccal epithelial cells (Aidar & Line, 2007). The screening of the entire coding region of *NEUROD1* was carried out by amplification of two overlapping fragments using two pairs of primers (primers available upon request; RefSeq NG_011820.2, NM_002500.4 and NP_002491.2). Polymerase chain reaction (PCR) products were purified by Clean Sweep PCR Purification Reagent (Applied Biosystems) and bidirectional Sanger sequencing was performed using the Big Dye Terminator Kit v3.1 (Applied Biosystems), conducted on an ABI 3130 Automatic Genetic Analyzer (Applied Biosystems).

3 | RESULTS

The entire coding region of *NEUROD1* was screened in a cohort of 25 unrelated Brazilian patients with clinical suspicious of monogenic diabetes (10 males and 15 females; average age at diagnosis: 22.68 ± 8.9 years; BMI average: 24.8 ± 4.54 kg/m^2), previously tested and negative for mutation in *GCK*, *HNF1A*, *HNF4A,* and *HNF1B* (data not published).

We detected one novel frameshift deletion of two thymine resulting in a change from phenylalanine to leucine in the position 256 of the protein, followed by a premature stop codon (p.Phe256Leufs*2). This deletion was not seen in the remaining 24 patients and in ClinVar, dbSNP, HGMD®, ExAC Browser, GnomAD, 1000 Genomes project databases, and in the literature. Mutation Taster predicted p.Phe256Leufs*2 to be the disease-causing mutation (score 1). The mutation is located in the transactivation domain, a highly conserved domain across several species (Figure 1).

The p.Phe256Leufs*2 mutation was found in a Brazilian family segregating in an autosomal dominant pattern from the maternal side (Figure 2). The index case is a 33 years old man who was diagnosed with diabetes at 25 years of age after some months of polyuria, polydipsia, and weight loss of approximately 10 kg (BMI at diagnostic: 28.9 kg/m^2). He was included in this study at 30 years with mean fasting glucose of 137 mg/dl and glycated hemoglobin (HbA1c-HPLC) of 7.5% (HbA1c at diagnosis: 6.5%). He presented no diabetic microvascular complications such as retinopathy (normal fundoscopy), diabetic renal disease (normal renal ultrasound and negative microalbuminuria), and neuropathy after 8 years of manifestation of disease.

At diagnosis, the index case was treated with metformin 2 g/day. One month later, since he presented poor glycemic control, he started being treated with NPH insulin (0.2 UI/kg). After 4 years with the same low dose of NPH insulin, a detectable basal C-peptide and a good glycemic control with insulin (HbA1c: 6%), his treatment was changed to glimepiride and metformin, since he presented some hypoglycemic episodes during these years. Nowadays he presents good glycemic control using glimepiride 6 mg/day and metformin 2 g/day (HbA1c: 6.6%), and fewer episodes of hypoglycemia. The only comorbidity is hypertension and it is well controlled with nitrendipine 20 mg/day, losartan 100 mg/day, and atenolol 25 mg/day and the major causes of secondary hypertension were excluded (Cushing's syndrome, pheochromocytoma, primary hyperaldosteronism, and renal-artery stenosis). He never had diabetic ketoacidosis and was negative for anti-GAD and anti-IA-2 autoantibodies.

The patient's mother (BMI: 19.9 kg/m^2) was diagnosed with diabetes at the age of 23 years with a mean fasting glucose of 330 mg/dl and since then, she had been on basal insulin therapy (mean fasting glucose: 113 mg/dl; HbA1c: 9.4%). She developed diabetic retinopathy and nephropathy. The index case's sister (BMI 18.9 kg/m^2) was diagnosed with accidental hyperglycemia at the age of 26 years, with mean fasting glucose of 250 mg/dl; During the first 2 years she was initiated with NPH insulin, then

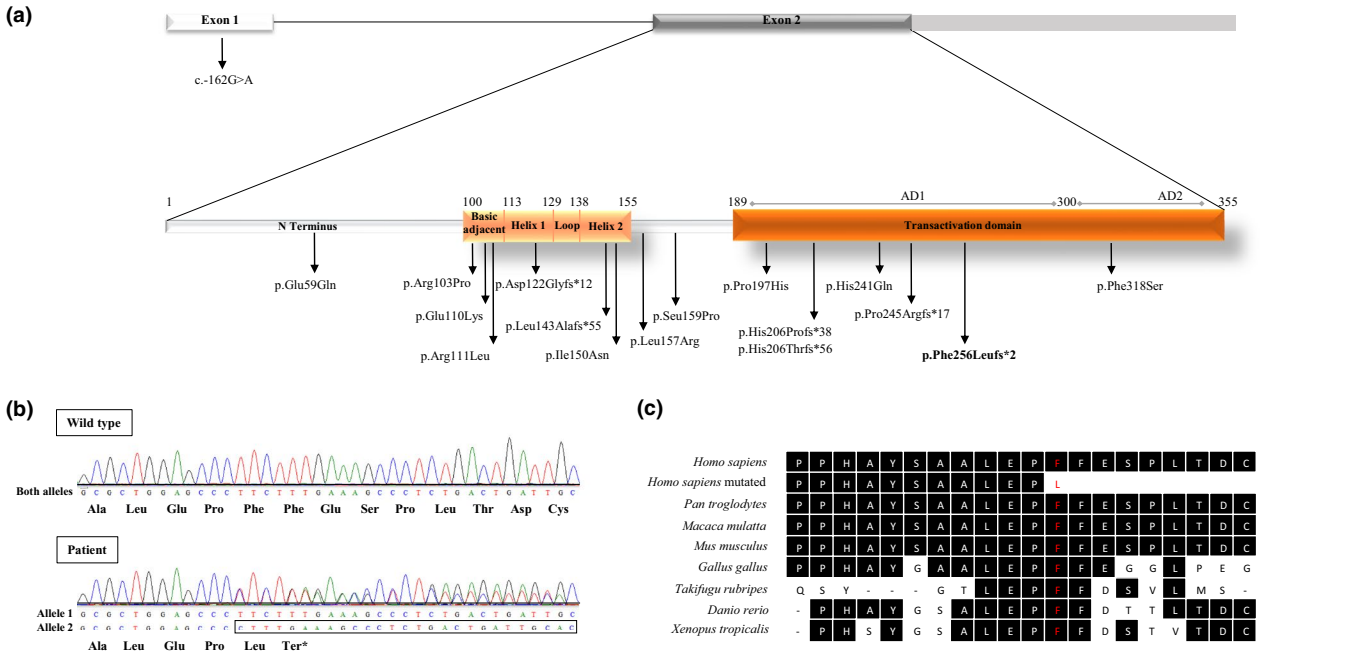
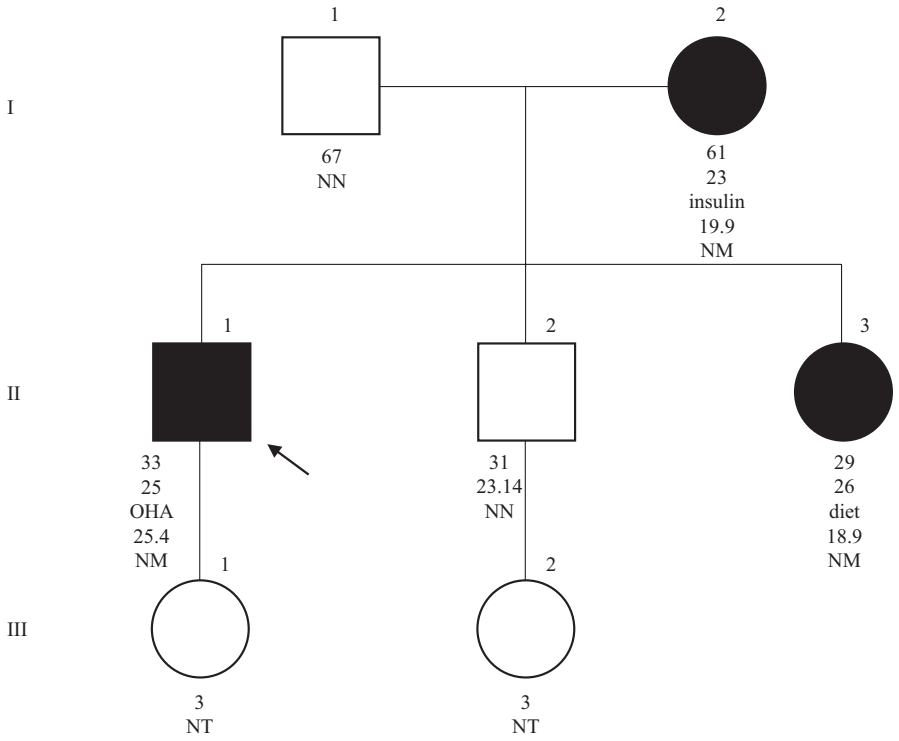


FIGURE 1 NEUROD1 mutations previously identified in diabetic patients and the novel p.Phe256Leufs*2 mutation. (a) Diagrammatic representation of *NEUROD1* and NEUROD1 protein structure. *NEUROD1* presents two exons, being exon 1 noncoding. NEUROD1 protein contains two domains: basic helix-loop-helix domain, which is divided in basic adjacent, helix 1, loop and helix 2; and transactivation domain, which has two activating domains (AD1 and AD2). Arrows indicate the position of mutations described in the literature and in this study (bold). (b) Electropherograms of *NEUROD1* exon 2 wild type (above) and p.Phe256Leufs*2 identified in the patient DM24 (below). (c) Alignment of NEUROD1 across species shows amino acid 256 (in red) evolutionary conserved across species

FIGURE 2 Pedigree, clinical characteristics, and genotype of family 24. Filled symbols and empty symbols represent diabetic patients and healthy individuals, respectively. The present age of the individuals is shown below the symbols, followed by the age at diagnosis, the most recent treatment, body mass index (kg/m^2) and genotype interpretation. OHA, oral hypoglycemic agents; Genotypes are expressed by normal allele (N) and mutated allele (M); NT, not tested. An arrow indicates the index case



with gliclazide 30 mg/day and lastly, with 29 years, her glucose levels were managed only with low-carbohydrate diet and exercise (mean fasting glucose: 97 mg/dl; HbA1c: 6.2%; C-peptide: 2.3 ng/ml). To this moment, the index case and his family members did not present neurological abnormalities.

TABLE 1 Clinical characteristics of known and novel *NEUROD1* mutations associated to monogenic diabetes

Protein level	c.DNA level	Accession number	Mutation type	Domain	Origin	Sample (%)	Sample type	Met.	Age (years)	AOD (years)	DT	Ref.
p.Arg111Leu	c.332G>T	rs104893649	Missense	Basic adjacent	European descendent	2/94 (2.12)	Type 2 DM	Sanger sequencing	65	40	Insulin	(Malecki et al., 1999)
p.His206Profs*38	c.616_617ins	rs387906384	Frameshift	AD1					74	33	Insulin	
p.Glu110Lys	c.328C>A	rs763092306	Missense	Basic adjacent	Iceland	1/3	MODY Families	Sanger sequencing	N/A	N/A	N/A	(Kristinsson et al., 2001)
p.Ser159Pro	c.475T>C	N/A	Missense	N/A	China	1/85 (1.17)	Type 2 DM	Sanger sequencing	27	27	OHA	(Liu et al., 2007)
p.His241Gln	c.723C>G	rs561017686	Missense	AD1	Czech Republic	2/30 (6.66)	MODY	Sanger sequencing	44[a]	20	Insulin	(Gonsorčíková et al., 2008)
									39	30	OHA + insulin	
p.Asp122Glyfs*12	c.364_365ins	N/A	Frameshift	Helix 1	Pakistan	2/44 (4.54)	PNDM	Sanger sequencing	N/A	8[b]	N/A	(Rubio-Cabezas et al., 2010)
p.Leu143Alafs*55	c.427_428del	rs1485945978	Frameshift	Helix 2	Hungary				N/A	4[b]	N/A	
p.Pro197His	c.590C>A	rs8192556	Missense	AD1	Turkish	2/43 (4.65)	MODY	NGS panel	15	14	Diet	(Ağladıoğlu et al., 2016)
									13	12	Diet	
p.His241Gln	c.723C>G	rs561017686	Missense	AD1	India	4/56 (7.14)	MODY	NGS panel	47	28	OHA	(Chapla et al., 2015)
									35	24	OHA + insulin	
p.Glu59Gln	c.175G>C	rs553756272	Missense	N terminus					30	30	OHA	
NA	c.−162G>A	rs537184640	NA	5′UTR					30	28	OHA	
p.Arg103Pro	c.308G>C	N/A	Missense	Basic adjacent	Poland	1/156 (0.64)	MODY	NGS panel	66	23	Insulin	(Szopa et al., 2016)
p.Pro197His	c.590C>A	rs8192556	Missense	AD1	Asian	1/84 (1.19)	MODY	NGS panel	N/A	N/A	N/A	(Ang et al., 2016)
p.Glu59Gln	c.175G>C	rs553756272	Missense	N terminus	India	2/50 (4)	GDM	NGS panel	36	36	OHA	(Doddabelavangala Mruthyunjaya et al., 2017)
p.Phe318Ser	c.953T>C	N/A	Missense	AD2					29	27	OHA	
p.His206Profs*38	c.616_617ins	rs387906384	Frameshift	AD1	Japan	4/275 (1.45)	MODY	Sanger sequencing	17	14	Insulin	(Horikawa et al., 2018)
p.Pro245Argfs*17	c.734_734del	N/A	Frameshift	AD1					25	11	Insulin	
p.Leu157Arg	c.470T>G	N/A	Missense	N/A					24	10	OHA + insulin	
p.His206Thrfs*56	c.616_616del	N/A	Frameshift	AD1					15	12	OHA + insulin	
p.Ile150Asn	c.449T>A	N/A	Missense	Helix 2	Turkish	1	PNDM family	NGS panel	13.4	9[b]	Insulin	(Demirbilek et al., 2018)
p.Phe256Leufs*2	c.766_767del	N/A	Frameshift	AD1	Brazil	1/25 (4)	MODY	Sanger sequencing	30	25	OHA	[c]

Abbreviations: AD, activating domain, AOD, age of diagnosis; DM, diabetes mellitus; DT, diabetes treatment; GDM, gestational diabetes mellitus; Met, methodology; N/A, not available/not applicable; OHA, oral hypoglycemic agents; PNDM, permanent neonatal diabetes mellitus; Ref., references; UTR, untranslated.

[a]Age at death.

[b]Weeks.

[c]Novel mutation identified in this study.

The mutation p.Phe256Leufs*2 was not present in the proband's brother, a normal weight (BMI: 23.14 kg/m^2) man of 31 years. Levels of glucose and HbA1c were 113 mg/dl and 5.6%, respectively.

4 | DISCUSSION

The genetic diagnosis of MODY in Brazil has been mostly limited to *GCK* and *HNF1A*, after a selection for testing guided by clinical criteria (Giuffrida et al., 2017). For this reason, rare forms are poorly studied. In this work, we screened all coding region of *NEUROD1* in patients with clinical phenotype of monogenic diabetes, negative for mutations in *GCK*, *HNF1A*, *HNF4A* and *HNF1B*.

After almost two decades past from the initial report of NEUROD1-MODY (Malecki et al., 1999), only a small numbers of Asian and European families were identified (Ağladıoğlu et al., 2016; Ang et al., 2016; Chapla et al., 2015; Doddabelavangala Mruthyunjaya et al., 2017; Gonsorčíková et al., 2008; Horikawa et al., 2018; Kristinsson et al., 2001; Liu et al., 2007; Szopa et al., 2016). In these populations, *NEUROD1* mutations range from low frequencies as in Poland (0.64%; Szopa et al., 2016) to high frequencies as in India (7.14%; Chapla et al., 2015). In our study, we found a frequency of 4%, similar to that observed in Turkish (4.65%; Ağladıoğlu et al., 2016; Table 1).

So far, 20 index cases with monogenic diabetes were previously reported with heterozygous mutations in *NEUROD1* and the data collection shows an average age of diagnosis (AOD) of 23.37 ± 9 years (ranging 10–40 years), similar to our patient's AOD (25 years). The treatment varied among patients, the use of oral hypoglycemic agents (OHA) was the most frequent (36.8%), followed by insulin (31.6%), OHA + insulin (21.1%) and diet (10.5%). Interestingly, all probands with frameshift mutations were treated with insulin (Table 1).

NEUROD1 is a transcription factor expressed in pancreatic cells (Naya et al., 1997), and mutations that cause a disturbance in this protein lead to the hyperglycemia that was observed in all index cases. It is also expressed in neuronal cells (Naya et al., 1997), which could explain the neuronal manifestations observed in two patients with p.Pro197His mutation in heterozygosity described with pituitary hypoplasia, growth hormone deficiency and epilepsy (Ağladıoğlu et al., 2016). Mental retardation was observed in a female patient and her mother, both carrying p.Pro245Argfs*17 (Horikawa et al., 2018). Besides, Rubio-Cabezas et al. (2010) identified two probands with p.Asp122Glyfs*12 and p.Leu143Alafs*55 frameshift mutations in homozygosity leading to the syndrome of permanent neonatal DM (PNDM) and neurological abnormalities including developmental delay, sensorineural deafness, and visual impairment (Rubio-Cabezas et al., 2010). Demirbilek et al. (2018) recently described a novel case of PNDM in a 13-year-old girl with a homozygous missense mutation (p.Ile150Asn) showing a similar clinical presentation from the previously reported PNDM cases (Demirbilek et al., 2018; Rubio-Cabezas et al., 2010).

Additionally, Horikawa and Enya (2019) observed that there are two times more affected female patients than affected male patients among the cases described and that the majority of the cases inherited the mutation from their mother, which was also observed in this study. Further analysis on the pathophysiology of *NEUROD1* will help to clarify the reason of this discrepancy in an autosomal disease (Horikawa & Enya, 2019).

To the best of our knowledge, this is the first case reported to have a NEUROD1-MODY mutation in a Latin American cohort. The novel p.Phe256Leufs*2 mutation in the activating domain 1 has similar structural effects in the protein as those caused by the first reported p.His206Profs*38 mutation (Malecki et al., 1999). It leads to the loss of 60% of the transactivation domain, and likely that p.His206Profs*38, probably has a compromised biological activity since the transactivation domain is required for the ligation of NEUROD1 with the coactivator p300 (Qiu, Sharma, & Stein, 1998). The majority of mutations found in *NEUROD1* associated with monogenic diabetes (13 cases [54.2%]) is located in the transactivation domain, comprising four frameshift mutations (Horikawa et al., 2018; Malecki et al., 1999) and three missense mutations (Ağladıoğlu et al., 2016; Ang et al., 2016; Chapla et al., 2015; Doddabelavangala Mruthyunjaya et al., 2017; Gonsorčíková et al., 2008; Figure 1).

This study has some limitations. First, our sample size was small and may not show the real frequency of *NEUROD1* mutations as cause of monogenic diabetes in our population. In addition, we did not analyze the possible presence of copy number variations that could also be compromising NEUROD1 function and would not be observed in our sequencing method.

5 | CONCLUSION

In conclusion, we described a Brazilian family with a novel mutation in *NEUROD1* segregating with diabetes in an autosomal dominant pattern of inheritance.

ACKNOWLEDGMENTS

The authors are grateful to the patients and their families. This work was supported by National Council for Scientific and Technological Development (CNPq), Coordination for the Improvement of Higher Education Personnel (CAPES), and Oswaldo Cruz Institute (IOC).

CONFLICT OF INTEREST

None declared.

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How to cite this article: Abreu GDM, Tarantino RM, Cabello PH, et al. The first case of NEUROD1-MODY reported in Latin America. *Mol Genet Genomic Med*. 2019;7:e989. https://doi.org/10.1002/mgg3.989