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RESEARCH ARTICLE

Placental *SLC38A4* gene polymorphisms 1304 G > A and 292 C > T, and their association with glucose > 95 mg/dL in normal weight full-term healthy newborns

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Abstract

Background: *The SLC38A4 gene encodes for the SNAT4 protein, which has been related to glucose metabolic alterations in human newborns. This study aimed to determine whether the 1304 G > A and 292 C > T polymorphisms of the SLC38A4 gene are associated with the presence of glucose levels > 95 mg/dL in normal weight full-term healthy newborns.* **Methods:** *We conducted a case–control study and analyzed 50 normal weight full-term healthy newborns. Groups were defined based on glucose levels: > 95 mg/dL (cases; n = 13) and < 95 mg/dL (controls; n = 37). The 1304 G > A and 292 C > T polymorphisms of the SLC38A4 gene were determined through quantitative polymerase chain reaction using placental DNA. The association between polymorphism and glucose levels > 95 mg/dL was established using multivariate logistic regression analysis.* **Results:** *No significant differences were observed either for gestational age or body weight at birth between groups. In the case group, newborns showed significantly higher homeostatic model assessment for insulin resistance than those in the control group (p < 0.0005). The odds ratio (OR) between the SLC38A4 gene 292 C > T single-nucleotide polymorphism (SNP) and glucose levels > 95 mg/dL was 7.78 (p = 0.024), whereas no significant association was found for the 1304 G > A SNP (OR 1.46; p = 0.77).* **Conclusions:** *Our results suggest that the SLC38A4 gene 292 C > T SNP is associated with glucose levels > 95 mg/dL in normal weight full-term healthy newborns.*

Key words: *SLC38A4. Polymorphisms. Glucose. Newborns.*

Polimorfismos 1304 G > A y 292 C > T del gen placentario SLC38A4 y su asociación con glucosa > 95 mg/dL en recién nacidos a término, sanos y con peso normal al nacimiento

Resumen

Introducción: *El gen SLC38A4 codifica la proteína SNAT4, que se ha relacionado con alteraciones en el metabolismo de la glucosa en los humanos. El objetivo de este estudio fue determinar si los polimorfismos 1304 G > A y 292 C > T del gen SLC38A4 se asocian con concentraciones de glucosa > 95 mg/dL en recién nacidos a término.* **Métodos:** *Se llevó a cabo*

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un estudio de casos y controles con 50 recién nacidos a término, sanos, con peso normal al nacimiento. Los grupos se definieron de acuerdo con las concentraciones de glucosa: > 95 mg/dL (casos; n = 13) y < 95 mg/dL (controles; n = 37). Los polimorfismos 1304 G > A y 292 C > T del gen SLC38A4 se genotipificaron por qPCR utilizando ADN de la placenta. La asociación entre los polimorfismos y la concentración de glucosa > 95 mg/dL se estableció mediante la estimación de la razón de momios (RM) en un análisis múltiple de regresión logística. **Resultados:** *No se observaron diferencias estadísticamente significativas para la edad gestacional y el peso al nacer entre los grupos de estudio. El modelo homeostático para evaluar la resistencia a la insulina (HOMA-IR) fue significativamente más alto en los recién nacidos del grupo de casos que en el grupo control (p < 0.0005). La RM mostró asociación significativa entre el polimorfismo de nucleótido único (SNP) 292 C > T del gen SLC38A4 y la concentración de glucosa > 95 mg/dL (RM: 7.78; p = 0.024); el SNP 1304 G > A no mostró asociación significativa (RM: 1.46; p = 0.77).* **Conclusiones:** *Los resultados de este estudio sugieren que el SNP 292 C > T del gen SLC38A4 se asocia con concentraciones de glucosa > 95 mg/dL en recién nacidos a término.*

Palabras clave: *SLC38A4. Polimorfismos. Glucosa. Recién nacidos.*

Introduction

In the early postnatal period, newborn infants maintain glucose homeostasis through glycogenolysis and gluconeogenesis, both essential processes for the central nervous system after birth. Neonatal glucose imbalance is among the most common metabolic abnormalities in preterm newborns and is inversely related to gestational age and birth weight[1]. Furthermore, conditions such as perinatal asphyxia, respiratory distress, chronic stress, and some mothers' characteristics such as a history of gestational diabetes, high blood pressure, obesity, and aging are risk factors for neonatal glucose imbalance[2,3].

Normal glucose levels vary between 60 and 80 mg/dL in newborns, while values ≥ 126 mg/dL are considered as hyperglycemia[1].

The genetic/environment interaction during pregnancy results in fetal programming, a process that may alter the structure and function of tissues, predisposing to the presence of adulthood diseases[4]. Furthermore, several genes expressed in the placenta play an essential role in resource utilization. Thus, single-nucleotide polymorphisms (SNPs) in these genes may affect the growth and development of the fetus or placental function, thereby determining the susceptibility to certain diseases[5].

Human solute carrier family 38 member 4 (*SLC38A4*) gene, located in 12q13.11, is subjected to genomic imprinting in the human placenta and highly expressed at all stages of the development[6]. The encoded protein, sodium-coupled neutral amino acid transporter 4 (SNAT4), belongs to the amino acid transport system (known as system A). Given that SNAT4 facilitates the cationic amino acid transport independently from Na^+ and pH, it has a crucial role in fetal growth and development. Alterations in the *SLC38A4* gene due to polymorphisms have been implicated in the development of impaired gluconeogenesis in the adult population[7,8].

The activity of this system is important for hepatic gluconeogenesis through the conversion of amino acids and glucose. The neutral amino acid transporter SNAT4 role in the placenta is crucial in fetal growth and development[9,10].

In this context, the objective of this study was to determine whether placental polymorphisms 1304 G > A (rs11183610) and 292 C > T (rs2429467) in the *SLC38A4* gene are associated with glucose > 95 mg/dL in normal weight full-term healthy newborns.

Methods

The study was conducted following the Code of Ethics of the Declaration of Helsinki. The Mexican Social Security Institute Ethics Committee approved the protocol. We obtained the written informed consent from the mothers of all the infants who participated in the study.

We conducted a case–control study with normal weight healthy newborns born from non-diabetic mothers with no history of gestational diabetes, high blood pressure, or malnutrition. Apgar score was > 8 in all newborns. The corresponding placentas were analyzed as reported elsewhere[8]. Newborns with umbilical cord venous blood glucose levels ≥ 95 mg/dL were considered cases and those with cord venous blood glucose levels < 95 mg/dL as controls. We used a cut point between the normal values and hyperglycemia. Some mothers' characteristics, such as age, smoking, alcohol intake, number of gestations, weight, and body mass index (BMI) before pregnancy, were matching criteria.

For identifying polymorphisms of the *SLC38A4* gene (1304 G > A and 292 C > T), DNA was obtained from

formalin-fixed, paraffin-embedded (FFPE) placental fragments. Maternal weight and height before pregnancy were obtained from medical records. BMI was calculated according to the following formula:

BMI = weight (kg)/height^2 (m^2)[11].

Definitions

Hyperinsulinemia was defined by umbilical cord venous insulin levels ≥ 5 μU/mL[12]. The homeostatic model assessment for insulin resistance (HOMA-IR) was calculated[13] as follows:

insulin levels (μU/mL) x glucose levels (mmol/dL)/22.5

Assays

We determined serum glucose levels using the glucose oxidase method. Insulin levels were measured by microparticle enzyme immunoassay (Abbott Axsym System, Alameda, CA, USA). Measurements were performed using an automated device (VITROS 250, Ortho-Clinical Diagnostics Inc., Raritan New Jersey, USA).

Umbilical cord venous blood was collected at birth for measuring serum glucose and insulin levels. The FFPE placenta blocks were processed as previously described[8]. DNA integrity was verified through 1% agarose gel electrophoresis, while purity and concentration by spectrophotometry at 260/280 nm using Nanodrop 2000c equipment (Thermo Scientific®).

Using TaqMan technology, we performed real-time PCR (quantitative polymerase chain reaction) system StepOne™ (Applied Biosystems®) for the genotyping. A total of 25 ng of genomic DNA were used under the following reaction conditions: one cycle of initial denaturation at 95°C/10 min, followed by 42 cycles of denaturation (95°C/15 s), annealing (60°C/1 min), and extension (60°C/30 s). The TaqMan probe used to recognize the SNP 1304 G > A (rs11183610) was C_25751555_10 (TaqMan® SNP Genotyping Assays, Thermo Fisher Scientific), whereas the SNP 292 C > T (rs2429467) was identified using the TaqMan probe C_15797142_10 (TaqMan® SNP Genotyping Assays, Thermo Fisher Scientific).

Statistical analysis

The data are presented as mean ± standard deviation for variables with normal distribution or median (25th and 75th percentiles) for skewed data. Differences between numerical variables were established using a Student's t-test (Mann–Whitney *U*-test for skewed data) and Fisher's exact test for categorical variables.

Genotype frequencies were obtained by direct count, and Hardy-Weinberg equilibrium (HWE) was calculated through X^2 goodness-of-fit statistics. Both analyses were carried out using the program SNPstats[14].

The MutationTaster2 software was used as a prediction tool for the functional consequences of the studied polymorphisms[15].

The association between polymorphisms 1304 G > A and 292 C > T of the *SLC38A4* gene (independent variable) and glucose ≥ 95 mg/dL (dependent variable) was determined using multivariate logistic regression analysis.

Statistical significance was established with a 95% confidence interval (95% CI) and $p < 0.05$. The statistical analysis was performed using the SPSS V.15.0 statistical package.

Results

A total of 13 (26%) newborns with glucose levels ≥ 95 mg/dL were compared with 37 (74%) newborns with glucose levels < 95 mg/dL.

Table 1 shows the anthropometric and biochemical variables of newborns and mothers in both case and control groups. In the case group, newborns showed significantly higher HOMA-IR than those in the control group. No significant differences were found neither in gestational age nor in body weight at birth between the groups.

Furthermore, no significant differences were observed regarding mothers' characteristics between the groups (Table 1).

For the SNP 292C > T, the allele C frequency was 58% and 76%, and the allele T frequency was 42% and 24% ($p = 0.08$) for cases and controls, respectively. Regarding the SNP 1304G > A, the allele G frequency was 81% and 82%, and the allele A frequency was 19% and 18% ($p = 1$) for cases and controls, respectively.

Regarding the SNP 292C > T, the genotype TT frequencies were 30.8% and 5.4% ($p = 0.56$); genotype C/C, 46.1% and 57.8% ($p = 0.003$); and genotype C/T, 23.1% and 37.8% ($p = 0.0004$) for cases and controls, respectively.

For the SNP 1304G > A, the genotype AA frequencies were 7.7% and 5.4% ($p = 1$); genotype G/A, 23.1% and 24.3% ($p = 0.04$); and genotype G/G, 69.2% and

Table 1. Demographic characteristics of newborns and mothers

n = 50	Cases	Controls	p-value
	13	37	
Newborns			
Weight at birth (g)	3485.8 ± 729.3	3312.8 ± 731.4	0.47
Gestational age (weeks)	39.4 ± 2.0	39.0 ± 1.5	0.33
Glucose levels at birth (mg/dl)[a]	109.0 (97, 141.1)	75.5 (65.7, 82.2)	<0.0005[b]
Insulin levels at birth (μU/ml)[a]	7.3 (3.3, 12.5)	5.5 (4.1, 7.5)	0.24[b]
HOMA-IR[a]	2.32 (0.85, 4.46)	0.99 (0.81, 1.51)	<0.0005[b]
Mothers			
Age (years)	26.8 ± 3.5	25.3 ± 4.5	0.27
Number of gestations[a]	3 (2, 3)	2 (1, 3)	0.25[b]
Weight before pregnancy (kg)	61.5 ± 10.6	61.9 ± 11.6	0.9
Height (cm)	158 ± 5.9	162.3 ± 4.6	0.01
Weight gain (kg)[a]	12 (11, 20)	14 (11.7, 16)	1[b]
BMI before pregnancy	24.7 ± 4.6	23.5 ± 4.1	0.4

Values are expressed as mean ± SD unless indicated otherwise.
[a]Median (25th, 75th percentile); [b]*p*-value estimated using Mann–Whitney *U*-test.
BMI: body mass index; HOMA-IR: homeostatic model assessment for insulin resistance.

70.3% (p = 0.004) for cases and controls, respectively,

The total population and the case group were in HWE (p = 0.3 and p = 0.086, respectively).

Although the MutationTaster 2 software indicated that polymorphisms 292 C > T and 1304 G > A are probably harmless, the logistic regression analysis showed that the SNP 292 C > T is significantly associated with glucose > 95 mg/dL (odds ratio [OR] 7.78; 95% CI 1.2-49.4, p = 0.02) but not the SNP 1304 G > A (OR 1.46; 95% CI 0.1-17.6, p = 0.77). Results of the SNP 292 C > T fit with a recessive model according to Akaike's criterion value (AIC)[14]. The results regarding inheritance models are shown in tables 2 and 3.

Discussion

Our results suggest that the *SLC38A4* gene SNP 292 C > T but not SNP 1304 G > A is associated with glucose > 95 mg/dL in normal weight full-term healthy newborns. This association is consistent with a recessive inheritance model.

During fetal life, the appropriate maternal amino acid supplementation is essential for the fetus's proper growth and development. The amino acid transport across the human placenta is active and mediated by specific transporters in syncytiotrophoblast plasma membranes[16].

The *SLC38A4* gene belongs to the amino acid transport system A and plays an essential role in hepatic gluconeogenesis and placental amino acid transport through the conversion of amino acids and glucose recycling[9]. Therefore, it has been hypothesized that alterations in the hepatic system A may increase glucose levels through impairing gluconeogenesis[17].

Some polymorphisms in the *SLC38A4* gene are related to glucose alterations[8]. The frequency of mutant alleles of the *SLC38A4* gene varies depending on the population. In Asian and Central American individuals, the frequency of mutant alleles for the SNP 1304 G > A is 8% and 21%, and for the SNP 292 C > T, 24% and 20%, respectively[18,19]. In this study, the frequency of allele A for the SNP 1304 G > A was 18%, and the frequency of the allele T for the SNP 292 C > T was 29%. Both frequencies are similar to those reported by the PAGE study in Mexican subjects (23% and 26%, respectively)[18,19].

According to UniProt Consortium[20], the studied polymorphisms in the *SLC38A4* gene generate amino acid changes that might alter the function of SNAT4. For example, SNP 292 C > T (G29R) is found in an extracellular topological domain, while SNP 1304 G > A (T366M) is found in a cytoplasmic topological domain. In this regard, the SNAT4 protein contains a total of six potential *N*-linked glycosylation sites, and *N*-glycosylation occurs typically at the extracellular side of the membrane proteins[21,22].

The *SLC38A4* gene is subjected to imprinting, and the placental expression of this gene is determined by a paternal allele, suggesting the critical role in promoting fetal growth[23]. Topological domains in the protein may exert different effects depending on gene expression.

Table 2. Inheritance models for SNP 292 in a biallelic locus C > T of the *SLC38A4* gene

Inheritance model	Genotype	Controls	Cases	OR	95% CI	p-value	AIC
		n (%)	n (%)				
Codominant	CC	21 (57.8)	6 (46.1)	1	—	—	
	CT	14 (37.8)	3 (23.1)	0.75	0.2-3.5	0.07	48.4
	TT	2 (5.4)	4 (30.8)	7.0	1.02-48.0	0.05	40.2
Dominant	CC	21 (56.8)	6 (46.1)	1	—	—	
	CT-TT	16 (43.2)	7 (53.9)	1.53	0.4-5.4	0.5	60.9
Recessive	CC-CT	35 (94.6)	9 (69.2)	1	—	—	
	TT	2 (5.4)	4 (30.8)	7.78	1.2-49.4	0.02	56.1
Overdominant	CC-TT	23 (62.2)	10 (79.9)	1	—	—	
	CT	14 (37.8)	3 (23.1)	0.49	0.1-2.1	0.32	60.3
Log-additive	—			2.04	0.8-5.0	0.12	58.8

AIC: Akaike's criterion value; 95% CI: 95% confidence interval; OR: odds ratio; SNP: single-nucleotide polymorphism.

Table 3. Inheritance models for SNP 1304 in a biallelic locus G > A of the *SLC38A4* gene

Inheritance model	Genotype	Controls	Cases	OR	95% CI	p-value	AIC
		n (%)	n (%)				
Codominant	GG	26 (70.3)	9 (69.2)	1	—	—	
	GA	9 (24.3)	3 (23.1)	0.96	0.2-4.4	0.96	57.4
	AA	2 (5.4)	1 (7.7)	1.44	0.1-18.0	1	47.7
Dominant	GG	26 (70.3)	9 (69.2)	1	—	—	
	AG-AA	11 (29.7)	4 (30.8)	1.05	0.3-4.1	0.94	61.3
Recessive	GG-AG	35 (94.6)	12 (92.3)	1	—	—	
	AA	2 (5.4)	1 (7.7)	1.46	0.1-17.6	0.77	61.2
Overdominant	GG-AA	28 (75.7)	10 (76.9)	1	—	—	
	AG	9 (24.3)	3 (23.1)	0.93	0.2-4.1	0.93	61.3
Log-additive	—			1.10	0.4-3.1	0.86	61.3

AIC: Akaike's criterion value; 95% CI: 95% confidence interval; OR: odds ratio; SNP: single-nucleotide polymorphism.

The monoallelic expression of both the gene and mutation 292 C > T, located in the extracellular domain, would be enough to disturb protein function, as no functional alleles would be present. Therefore, we hypothesize that the paternal transmission of only one 292 T mutant allele could be enough to disturb the gene function in the placenta, giving rise to glucose imbalance.

SLC38A4 gene expression is postnatally downregulated in the lungs and kidneys. In contrast, the expression of the *SLC38A4* gene in the liver increases as the rate of organ growth slows down. This finding suggests an essential role for this gene in gluconeogenesis[24]. Such increase could be related to the hepatic biallelic expression of the *SLC38A4* gene. For this reason, it is

possible that the double mutant genotype 292 T/T or the inheritance of heterozygous genotype 1304 G > A could increase the risk of developing hyperglycemia in adult life.

Previous findings support this idea. In a population with diabetes, the linkage disequilibrium between these two SNPs was D' > 0.82, and the presence of the A/T haplotype was associated with hyperglycemia[8].

According to Desforges et al.[6], evidence shows complex changes in placental transporters' expression and activity during pregnancy. The *SLC38A4* gene generates five *SLC38A4* isoforms (201-205), which produce lengthy proteins of 547 aa, 547 aa, 219 aa, 191 aa, and 141 aa, respectively. According to the expression score reported by Bgee (database for gene expression evolution), these proteins are expressed predominantly in the embryonic (94%) and adult liver (94%). However, lower levels can be detected at the placental level (53%) in late embryonic stages[25].

In contrast, our results differ from a previous study that showed an association of the SNP 1304 G > A but not of 292C > T with hyperglycemia in individuals with diabetes type 2[8]. These paradoxical results can relate to gestational regulation expression and monoallelic expression of *SLC38A4* mRNA at the placental level and differences in the targeted populations.

Amino acid transport system A is accurately regulated by various hormones and growth factors *in vivo* and substrate availability evidenced *in vitro*[26]. According to recent studies, the insulin-like growth factor II (*IGF-2*) gene is also imprinted in the placenta. It acts as a controller of nutrient supply by affecting placental development and as a signal of fetal demand by modulating the expression and activity of key placental supply genes such as the system A transporters Slc38a4, Slc38a2, and the glucose transporter Slc2a3 in mouse placenta[26-29]. Therefore, any alterations or interaction between these two genes could develop glucose imbalance in early life[30].

Finally, case group newborns showed a trend for higher insulin levels than those in the control group, which was expected given each group's inclusion criteria. However, no significant statistical differences were observed between the groups. According to Wilcox[31], normal pregnancy is characterized by insulin resistance that reaches its highest levels in the third trimester, which appears to be a physiological response to birth stress or an adaptive response that diverts glucose and lipids to the developing fetus. Furthermore, increased insulin resistance could also be related to increased levels of lactogen, progesterone, and cortisol, which act as counter-regulatory factors for insulin. This response is typically observed in pregnancy, and its imbalance is related to the development of gestational diabetes and hypertension[31].

Moreover, we found that newborns in the case group exhibited higher HOMA-IR than those in the control group; thus, it is possible that the lack of insulin action at peripheral tissues also contributes to the elevated glucose levels in the newborn. Further research is required in this field.

The following recommendations are mandatory to understand the role of *SLC38A4* function: (1) to measure placental *SLC38A4* gene expression for the transcripts and correlate them with the genotype, (2) to correlate IGF-2 serum concentration in pregnant women with *SLC38A4* placental expression, and (3) to evaluate the gene methylation pattern and the parental origin of the alleles.

Some limitations of this study should be mentioned. First, as no data regarding mothers' serum glucose levels was available, we could not exclude their potential role on newborns' glycemia. Second, given the small sample size, the statistical power was low (0.47). As a II error was possible in the statistical analysis, our results should be considered preliminary. Third, we could not determine the parental origin of the alleles and analyze samples from siblings. Undoubtedly, further research in this field is necessary to confirm our findings.

Our results suggest that the presence of 292 C > T of *the SLC38A4* gene is associated with glucose levels ≥ 95 mg/dL in normal weight full-term healthy newborns.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on patient data publication.

Right to privacy and informed consent. The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author has this document.

Conflicts of interest

The authors declare no conflicts of interest.

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