42 Genetic variations in the GLUT3 gene associated with myelomeningocele

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OBJECTIVE: Maternal diabetes and obesity are known risk factors for developmental embryopathy including myelomeningocele (MM). Previous studies have shown associations between known genetic variations in glucose transporter genes involved in glucose metabolism and MM. The objective of our study is to examine the diversity and extent of known sequence variations in the glucose transporter 3 (GLUT3) gene in patients with MM and to identify novel variations that may confer risk of MM.

STUDY DESIGN: We performed DNA sequencing of the 10 exons of GLUT3, including the exon-intron boundaries, on 96 patients with MM (48 Caucasian, 48 Hispanic of Mexican descent). Sequencing was carried out with the Sanger method and results were analyzed with the DNA Sequencing Analysis Software v5.1 from ABI. The frequencies of known single nucleotide polymorphisms (SNPs) were identified, and sequences that differed from the reference sequence (February 2009 GRCh37/hg19 assembly) were considered novel variants.

RESULTS: Six novel, and nine previously described, genetic variations were identified in our patient population. These findings are shown in table 1 with frequencies compared to reference populations (1000 Genome and NHLBI studies), as well as potential functional implications. The novel variations include a large, 83 base pair deletion involving the promoter region and part of Exon 1 found in 1/96 patients (0.5% allele frequency), and a two base pair deletion in the coding sequence of Exon 4 found in 1/96 patients (0.5% allele frequency).

CONCLUSION: We identified previously undescribed deletions and single nucleotide polymorphisms involving the GLUT3 gene that may be associated with increased susceptibility to MM. Of particular interest, the two deletions involve both an important promoter site, and a coding region. Additionally, one of the known variations identified (rs17847972) has the rare allele frequency significantly higher than expected. The functional significance of these findings is under investigation.

			Rare Allele (A2) Frequency						
				Caucasian			Hispanic		
Known Variations	Function	A/A2[a]	All MM	MM	REF[b]	p	MM	REF[b]	p
rs2541279	Intron	T/C	27%	30%	29%	0.8	25%	30%	0.4
rs17847967	Synonymous	T/C	20%	23%	14%	0.02	18%	20%	0.7
rs74059377	Intron	G/A	1%	1%	0%	0.1	1%	0.7%	1
rs17847972	**Splicing**	**C/T**	**47%**	**49%**	**0.1%**	**<0.001**	**46%**	**6%**	**<0.001**
rs41438344	Intron	C/G	1.5%	1%	0.2%	0.2	2%	8%	0.08
rs741361	Intron	A/G	41%	43%	37%	0.3	39%	36%	0.7
rs151144610	3'-UTR	C/T	0.5%	1%	0.6%	0.7	0%	0%	--
rs25684	Synonymous	G/A	40%	43%	48%	0.3	37.5%	44%	0.3
rs112948014	Intron	AG/--	2%	1%	ND	--	3%	ND	--
Novel Variations									
Exon1:g:8088945_8088862del83bp	**Promoter/ 5'-UTR**	**--**	**0.5%**	**0%**	**ND**	**--**	**1%**	**ND**	**--**
Intron 3: g:8085543C>G	Splicing	A/G	0.5%	1%	ND	--	0%	ND	--
Exon 4: c.467_468delCT	**Coding - Frameshift**	**CT/--**	**0.5%**	**0%**	**ND**	**--**	**1%**	**ND**	**--**
Intron 5: g:8083043T>C	Intron	T/C	0.5%	0%	ND	--	1%	ND	--
Intron 6: g:8082222C>A	Intron	C/A	0.5%	0%	ND	--	1%	ND	--
Intron 9: g:8074240C>A	Intron	C/A	0.5%	0%	ND	--	1%	ND	--

a – A1 is reference allele, A2 is the rare allele
b – REF – Reference populations – NHLBI ESP dataset and 1000 Genomes project
MM – Myelomeningocele
ND – No data reported

Table 1 depicts known and novel variations identified within the GLUT3 gene in our patient population, and includes potential functional implications and comparisons of rare allele frequencies to reference population frequencies.

43 Medical and pregnancy complications among women with congenital heart disease at delivery

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OBJECTIVE: The objective of this study was to estimate nationwide prevalence of medical and pregnancy complications at delivery among pregnant women with congenital heart disease (CHD).

STUDY DESIGN: The Nationwide Inpatient Sample for the years 2008-2010 was queried for all delivery-related discharges. Women with CHD were identified by ICD-9-CM codes and compared to women without CHD. The prevalence of selected severe medical and obstetric complications during admission for delivery were compared between the two groups while controlling for age, multiple gestation and pre-existing medical complications (hypertension, diabetes, thyroid and rheumatologic disorders, asthma, pulmonary hypertension, thrombophilia, anemia, renal failure, drug/alcohol/tobacco use).

RESULTS: From 2008-2010, there were 10,871 deliveries to women with CHD and 12,617,875 to women without (8.6 per 10,000 deliveries). Women with CHD were more likely to be Caucasian ($p = 0.0001$) while women without CHD were more likely to be African American or Hispanic ($p<0.0001$). Women with CHD were 2.5-25 times more likely to die or develop severe medical complications including stroke, myocardial infarction, cardiac arrest, and acute heart failure compared to women without CHD (Table). Women with CHD were also more likely to be delivered by cesarean (adjusted OR [aOR] 1.3, 95% CI 1.3, 1.4) or operative vaginal delivery (aOR 1.5, 95% CI 1.4, 1.6), or have fetal growth restriction (aOR 2.1, 95% CI 1.9, 2.3), oligohydramnios (aOR 1.3, 95% CI 1.2, 1.4), placental abruption (aOR 1.4, 95% CI 1.2, 1.6) or placenta previa (aOR 2.1, 95% CI 1.4, 2.9).

CONCLUSION: Pregnant women with CHD are more likely to die or experience significantly more medical and obstetric complications at time of delivery compared to women without CHD. Women with CHD should be counseled of these risks prior to becoming pregnant and once pregnant, should be managed by a multidisciplinary team at a specialized center.

Medical complications among women with CHD at delivery

Condition	Adjusted Odds Ration with 95% CI	p-value
Death	10.1 (5.8, 16.5)	<0.0001
Mechanical ventilation	6.0 (4.8, 7.5)	<0.0001
Myocardial infarction	24.7 (12.8, 43.5)	<0.0001
Cardiac arrest	13.4 (7.8, 21.8)	<0.0001
Acute heart failure	15.9 (13.2, 19.0)	<0.0001
ARDS	7.1 (5.0, 10.3)	<0.0001
Pneumonia	2.8 (2.2, 3.6)	<0.0001
Stroke/CVA	14.8 (10.5, 21.0)	<0.0001
Pulmonary embolism	4.0 (2.7, 5.7)	<0.0001
Deep vein thrombosis	2.5 (1.6, 3.8)	<0.0001
Sepsis	2.6 (1.7, 4.0)	<0.0001
Acute renal failure	3.1 (2.1, 4.5)	<0.0001

Adjusted OR given for each condition while controlling for age, multiple gestation, and pre-existing medical conditions.