

# EXPRESSION OF MIR-576-5p IN UMBILICAL CORD AS A NOVEL BIOMARKER FOR THE IDENTIFICATION OF CATCH-UP GROWTH IN SMALL-FOR-GESTATIONAL-AGE INFANTS

J. Bassols<sup>1</sup>, B. Mas-Pares<sup>1</sup>, A. Bonmati<sup>2</sup>, S. Xargay-Torrent<sup>1</sup>, G. Carreras-Badosa<sup>1</sup>, E. Lizarraga-Mollinedo<sup>1</sup>, JM. Martínez-Calcerrada<sup>1</sup>, F. de Zegher<sup>3</sup>, L. Ibáñez<sup>4</sup>, A. López-Bermejo<sup>1</sup>.

<sup>1</sup>Pediatría, Instituto de Investigación Biomédica de Girona. <sup>2</sup>Ginecología, Hospital Dr. Josep Trueta, Girona. <sup>3</sup>Development & Regeneration, University of Leuven, Belgium. <sup>4</sup>Endocrinología Pediátrica, Hospital Sant Joan de Déu, Barcelona.



## BACKGROUND

Early catch-up growth, between birth and age two years, in infants born small-for-gestational-age (SGA) is a risk factor for the development of cardiometabolic diseases in adulthood. The basis and mechanisms underpinning catch-up growth in SGA newborns are unknown.

## RESULTS

The miRNA profile showed 12 miRNAs deregulated in SGA-CU vs SGA-nonCU children, 6 of which were validated in all study children (Table 1). Among them, the miR-501-3p, miR-576-5p, miR-770-5p and miR-876-3p associated with increased weight, height, weight catch-up and height catch-up at 1 year of age (all  $p < 0.05$ ; Table 2); and the miR-374b-3p, miR-548c-5p and miR-576-5p associated with increased weight, height, waist circumference and renal fat at 6 years of age (all  $p < 0.05$ ; Table 3). Multivariate analysis showed that miR-576-5p was predictor of weight catch-up ( $\beta = 0.286$ ,  $p = 0.003$ ;  $R^2 = 63.1$ ) and height catch-up ( $\beta = 0.301$ ,  $p = 0.001$ ;  $R^2 = 64.6$ ) at 1 year of age; and waist circumference ( $\beta = 0.459$ ,  $p = 0.01$ ;  $R^2 = 65.2$ ) and renal fat ( $\beta = 0.455$ ,  $p = 0.03$ ;  $R^2 = 20.7$ ) at 6 years of age. *In silico* studies showed that miR-576-5p targets genes of the insulin, IGF-1, PDGFR-B and mTOR signaling pathways (Table 4).

**Table 2:** Pearson correlation analysis of miRNAs at 1 year follow-up

	Weight SDS		Height SDS		Weight catch-up		Height catch-up	
	r	P	r	p	r	p	r	p
miR-501-3p	0.235	0.05	0.352	0.005	0.258	0.04	0.269	0.03
miR-576-5p	0.313	0.01	0.359	0.004	0.361	0.004	0.437	<0.0001
miR-770-5p	0.279	0.03	0.297	0.02	0.211	Ns	0.197	Ns
miR-876-3p	0.391	0.004	0.226	Ns	0.241	0.05	0.173	Ns

**Table 3:** Pearson correlation analysis of miRNAs at 6 year follow-up

	Weight SDS		Height SDS		Waist		Renal fat	
	r	P	r	P	r	P	r	p
miR-374b-3p	0.313	Ns	0.230	Ns	0.469	0.02	-0.245	Ns
miR-548c-5p	0.313	Ns	0.146	Ns	0.395	0.04	-0.143	Ns
miR-576-5p	0.467	0.009	0.498	0.005	0.534	0.005	0.459	0.03

**Table 4:** Predicted signaling pathways and genes targeted by miR-576-5p

Pathways	Target genes
Insulin	EXOC5, GRB10, NCK1, PIK3CA, PTPN1, RPS6KB1
IGF-1	GRB10, IGF1, PIK3CA, PTPN1, RPS6KB1
PDGFR-B	FOS, GRB10, ITGAV, MAP2K4, NCK1, NCKAP1, PIK3CA, PTPN1
mTOR	IGF1, PIK3CA, RICTOR, RPS6KB1, VEGFA

## OBJECTIVES

We aimed to investigate the catch-up predictive ability of umbilical cord tissue miRNAs in SGA infants.

## METHODS

MicroRNA PCR Human Panels (Exiqon) were used to study the miRNA profile in umbilical cord tissue of 5 SGA infants with catch-up (SGA-CU), 5 SGA infants without catch-up (SGA-nonCU) and 5 control infants (appropriate-for-gestational-age, AGA). The miRNA with differential expression between the study groups were validated in a cohort of 64 infants (24 SGA-CU, 18 SGA-nonCU and 22 AGA) and correlated with anthropometric and metabolic parameters (weight and height, body composition and fat distribution) at 1 and 6 years of age.

**Table 1:** Clinical characteristics of the study subjects at birth and at 1 year and 6 years follow-up.

	AGA n=22	SGA-nonCU n= 18	SGA-CU n= 24
<b>Newborns</b>			
Sex (% girls)	54%	66%	42%
Gestational age (wk)	39 ± 0.2	39 ± 0.3	39 ± 0.2
Birth weight SDS	0.1 ± 0.1	-1.2 ± 0.1**	-1.5 ± 0.1**
Birth height SDS	0.1 ± 0.1	-1.1 ± 0.2**	-1.5 ± 0.1**
<b>Umbilical cord miRNA expression</b>			
miR-128-3p	6.99 ± 6.07	3.48 ± 0.28 <sup>π</sup>	9.47 ± 3.02
miR-222-5p	0.05 ± 0.01	0.03 ± 0.01	0.05 ± 0.01
miR-300	0.10 ± 0.05	0.05 ± 0.01	0.07 ± 0.02
miR-374b-3p	0.12 ± 0.04	0.07 ± 0.01	0.11 ± 0.02
miR-501-3p	0.46 ± 0.05	0.46 ± 0.04 <sup>π</sup>	0.60 ± 0.06*
miR-548c-5p	0.12 ± 0.02	0.10 ± 0.01	0.13 ± 0.03
miR-576-5p	0.12 ± 0.01	0.11 ± 0.01 <sup>π</sup>	0.19 ± 0.02*
miR-628-5p	0.06 ± 0.01	0.04 ± 0.01 <sup>π*</sup>	0.06 ± 0.01
miR-770-5p	0.27 ± 0.03	0.21 ± 0.02 <sup>π</sup>	0.35 ± 0.06
miR-873-5p	0.132 ± 0.03	0.101 ± 0.01	0.138 ± 0.04
miR-876-3p	0.16 ± 0.06	0.08 ± 0.01 <sup>π</sup>	0.20 ± 0.04
miR-940	2.70 ± 0.34	2.92 ± 0.30	3.50 ± 0.69
<b>1 year follow-up</b>			
Weight SDS	-0.9 ± 0.1	-1.7 ± 0.1** <sup>ππ</sup>	-0.2 ± 0.1*
Weight catch-up	-1.0 ± 0.1	-0.5 ± 0.1* <sup>ππ</sup>	1.3 ± 0.1**
Height SDS	-0.6 ± 0.1	-1.3 ± 0.2* <sup>ππ</sup>	0.1 ± 0.1*
Height catch-up	-0.7 ± 0.1	-0.2 ± 0.1* <sup>ππ</sup>	1.8 ± 0.1**
<b>6 years follow-up</b>			
Age (years)	6.1 ± 0.2	5.4 ± 0.3	6.3 ± 0.2
Weight-SDS	-0.5 ± 0.2	-0.8 ± 0.2 <sup>π</sup>	0.1 ± 0.3
Height-SDS	-0.3 ± 0.3	-1.3 ± 0.3* <sup>π</sup>	0.1 ± 0.3
BMI-SDS	-0.3 ± 0.2	-0.3 ± 0.2	0.1 ± 0.2
Waist (cm)	55.1 ± 2.0	51.5 ± 2.0 <sup>π</sup>	59.3 ± 3.6
Renal fat (cm)	0.12 ± 0.01	0.10 ± 0.01 <sup>π</sup>	0.13 ± 0.01

\* $p < 0.05$  and \*\* $p < 0.001$  vs AGA. <sup>π</sup> $p < 0.05$  and <sup>ππ</sup> $p < 0.001$  vs CU-SGA.

## CONCLUSION

miR-576-5p could be a novel biomarker for the early identification of catch-up growth in SGA infants. miR-576-5p may also contribute to the regulation of postnatal growth and influence the risk for cardiometabolic diseases associated with postnatal growth.