Early-onset obesity and hyperphagia associated with defects in the GNAS gene

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INTRODUCTION Childhood obesity is mainly a polygenic disease but monogenic defects are known to be responsible for 5-10% of overall cases. Obesity may form part of the clinical constellation of defined pediatric syndromes frequently associating mental retardation, dysmorphic features or neuroendocrine abnormalities. In many obese children the genetic component is poorly understood.

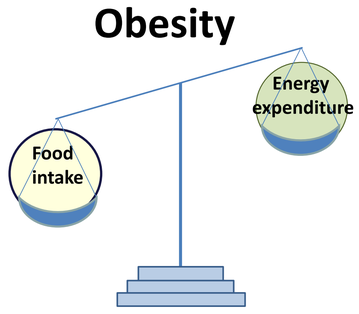
OBJETIVE

To investigate the genetic basis of severe early hyperphagic obesity in childhood with clinical suspicion of obesogenic or macrosomic syndromes.

PATIENTS AND METHODS

Clinical, hormonal and metabolic characterization of 3 pediatric patients with infantile obesity with clinical suspicion of MOMO and Prader-Willi syndromes. Chronological characterization of the phenotype, nutritional habits and energy expenditure. Investigation of the *GNAS* gene by Sanger sequencing.

Obesity



Obesity BMI +2 SD **Overweight** BMI +1-2 SD

Obesogenic environmental factors:

hypercaloric intake

sedentary lifestyle

Genetic component: 40-70% of BMI.

Appetite regulation (central).

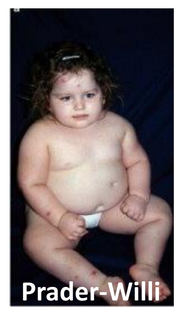
Adipose tissue (peripheral). Hypometabolism.

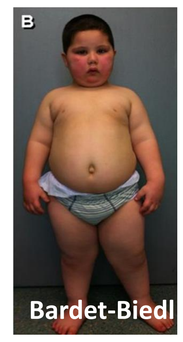
Genes associated with obesity:

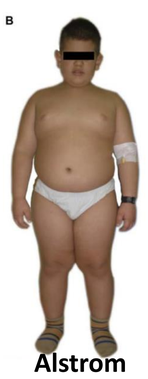
LEP, NPY, MC4R, UCPs

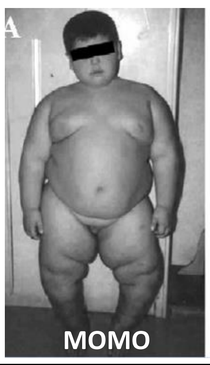
KSR2, FTO, TMEM18, IRX3

Associated with syndromes

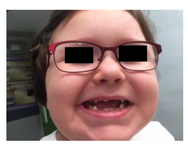
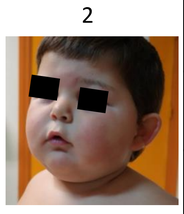
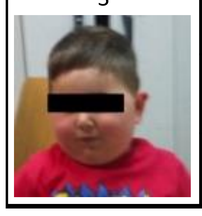




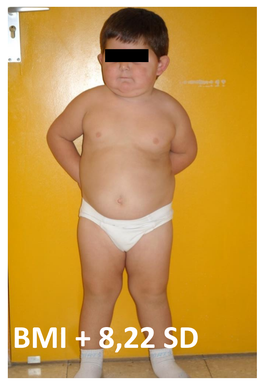




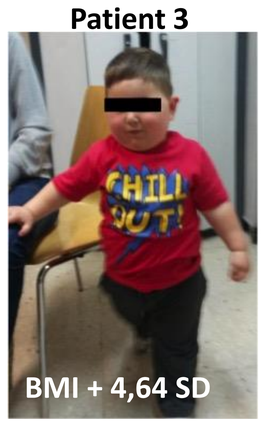
CLINICAL RESULTS

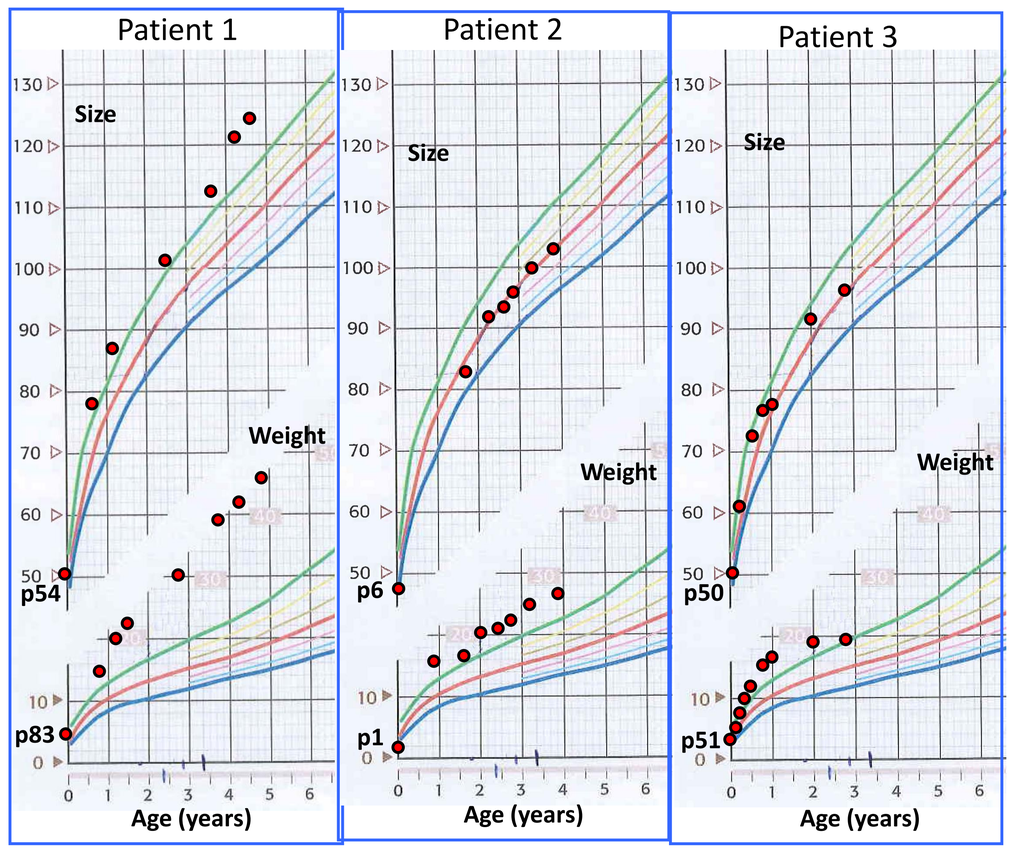
Patient	Age	Weight Kg (SD)	Size cm (SD)	BMI SD	CP cm (SD)	Clinical features	Previous studies
1 	birth	3.65 (+0.99)	50 (+0.11)	-	34 (-0.37)	Hyperphagia Obesity at **9 m** Psicomotor Retardation Nystagmus Strabismus	Normal karyotype and CGH-array **Beckwith-Wiedemann and MOMO syndromes** EXCLUDED
	9 m	**14.8 (+5.85)**	**78 (+3.95)**	**+5.48**	-		
	1 y	**16.75 (+6.43)**	**81 (+3.14)**	**+6.42**	**48 (+2.04)**		
	5 y	**47.3 (+10.4)**	**128.5 (+4.75)**	**+9.29**	-		
2 	birth	**2.02 (-2.33)**	**46 (-1.63)**	-	-	Hyperphagia Obesity at **1.5m** Psicomotor Retardation cryptorchidism	Normal karyotype Catch 22 and Williams syndromes EXCLUDED
	18 m	**16.3 (+3.92)**	83.5 (+0.42)	**+4.77**	-		
	3.6 y	**27.2 (+5.58)**	105 (+0.97)	**+8.22**	50 (-0.62)		
3 	birth	3.5 (+0.04)	50 (-0.46)		34.2 (-0.88)	Hyperphagia Obesity at **7 m** Psicomotor Retardation cryptorchidism	Normal karyotype **Prader-Willi** EXCLUDED
	11 m	**16.1 (+5.65)**	76 (+0.86)	**+7.58**	45.5 (-0.77)		
	2.6 y	**19.2 (+3.14)**	95.3 (+0.22)	**+4.64**			

Patient 2



Patient 3





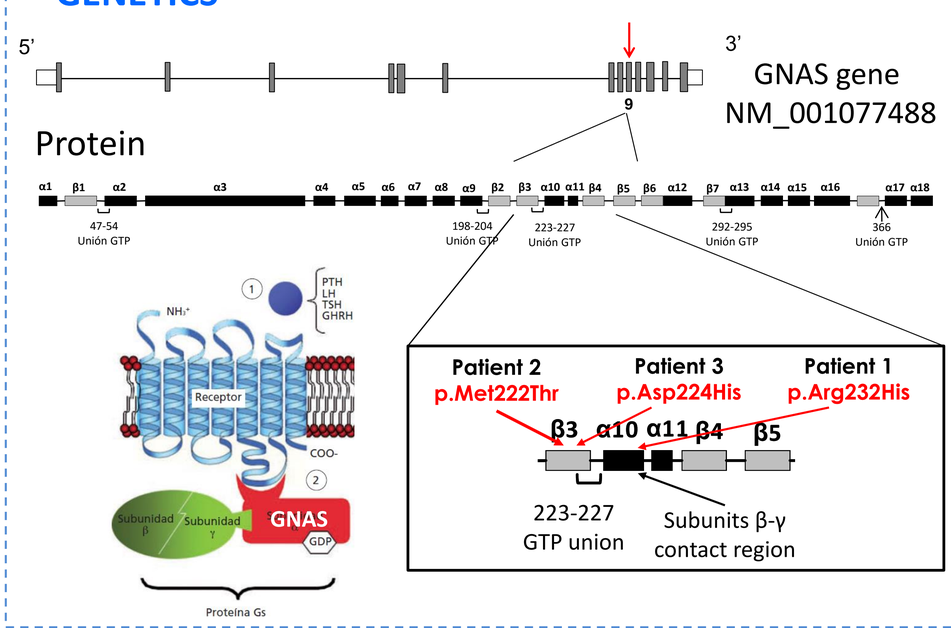
HORMONAL PROFILE

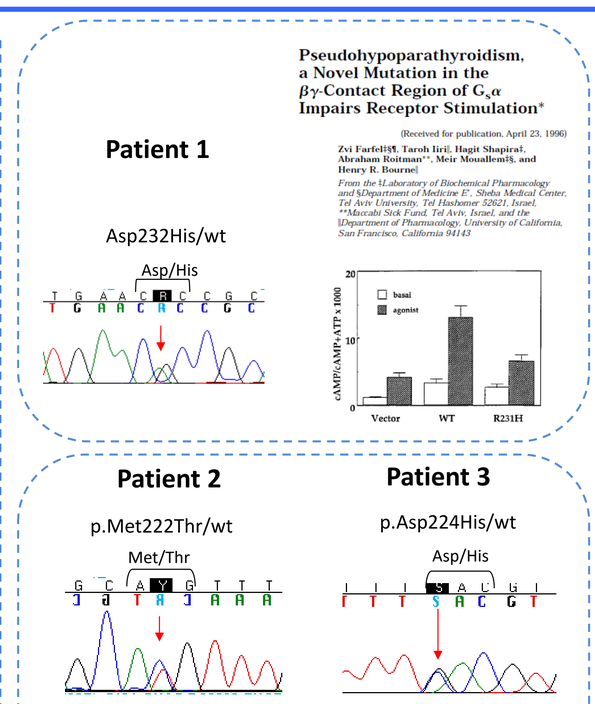
P	Age	Screening	TSH *mU/L*	FT4 *ng/dl*	PTH *pg/ml*	Ca *mg/dl*	P *mg/dl*	Vit. D *ng/ml*	ACTH *pg/ml*
1	birth	Negative	4	-	-	-	-	-	-
	9 m	-	**14.1**	**0.92**	-	-	-	-	-
	5 y	-	1.1	-	**1890**	**7.3**	**9**	26	19.5
	5.5 y	-	-	-	**756**	8.9	**6.9**	-	-
2	birth	Negative	-	-	-	-	-	-	-
	18 m	-	**12.8**	1.15	**117**	**8.2**	**6.5**	23	23
	3.3 y	-	**6.2**	1	36	9.8	**6.6**	32	-
3	birth	**Positive**	44	-	-	-	-	-	-
	9 m	-	**15**	1.36	**77**	10.3	7	-	**172**
	2 y	-	0.7	1.12	**270**	**8.6**	**6.8**	**24**	**49**

	AHO	Resistencia hormonal	AMPc orina	Ca suero	P suero
PHP-Ia	Si	PTH, TSH, Gn, GHRH	↓	↓	↑

Defects in GNAS gene? →

GENETICS





Energy Expenditure in Obese Children with Pseudohypoparathyroidism Type 1a

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Int J Obes (Lond). 2013 August ; 37(8): 1147–1153. doi:10.1038/ijo.2012.200.

CONCLUSIONS

Early-onset obesity with hyperphagia can be a prominent presenting feature of PHPIA, which should be considered in the differential diagnosis for monogenic childhood obesity. This type of obesity is postnatal and develops progressively, and its pathophysiology may include both low energy expenditure and excessive food intake through hyperphagia.

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Management of Obesity

Marta García

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