A NOVEL MELANOCORTIN 4 RECEPTOR (MC4R) GENE MUTATION ASSOCIATED WITH EARLY ONSET SEVERE OBESITY

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INTRODUCTION

Monogenic obesity accounts for 2-4% of obesity. Mutations on the *MC4R* are the most frequent monogenetic cause of human obesity. MC4R plays a critical role in body weight regulation through the leptin-melanocortin axis. Homozygous and heterozygous mutations on the *MC4R* gene may lead to hyperphagic and severe early onset obesity phenotypes. It is speculated that associations between *MC4R* and *FTO-rs9939609* variants are relevant to changes in eating behavior and enhance severe obesity phenotypes.

PATIENT & METHODS

Patient

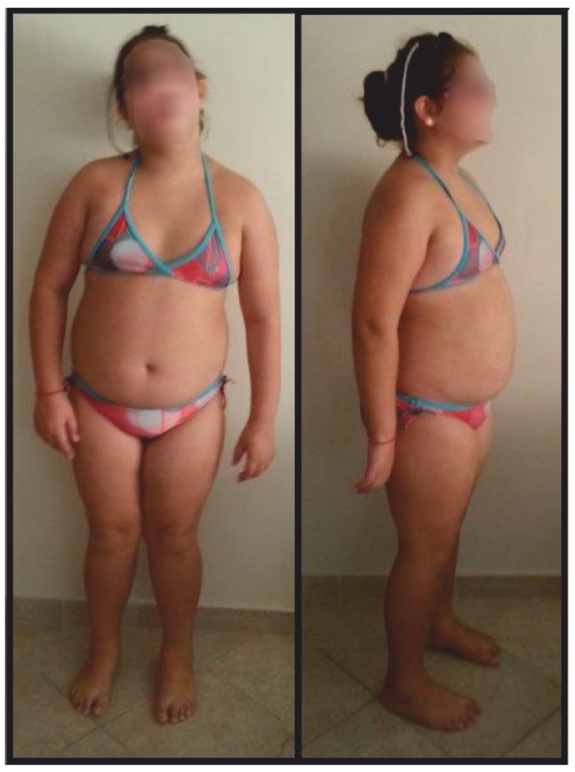
This is a 6 year old girl, firstly presented at the age of 3 years with early onset and severe obesity. She is the first child of non consanguineous parents. She was full term and appropriate for gestational age in size. There were no postnatal complications. The patient's psychomotor development was normal and she had no signs of puberty or adrenarche. She had no syndromic features and no muscle weakness but her red-brown hair was characteristic. Father was also obese with body mass index (BMI) 33 kg/m2. Mother's BMI was normal. She was advised to follow special diet under the observation of a clinical dietician. The family's attempt on a healthy lifestyle by reducing caloric intake and increasing daily physical activity had no success. At the age of 5.2 years she developed hyperinsulinemia and she was commenced on treatment with metformin 500mg per day. Six months after treatment she showed a slight improvement on her BMI (growth curves).

Methods

Growth charts in Growth analyzer 3.5 Application Ed Dutch Growth Foundation, PO Box 23068, 3001 KB, Rotterdam, The Netherlands, were used. Blood samples were collected after an overnight fast. Routine biochemistry and hormones were measured by using the usual assays. Both parents gave their consent for this presentation.
Genetic analysis was performed by direct sequencing for mutation in the *MC4R* and *FTO* genes.

RESULTS

1. Phenotype



Patient at the age of 6 years.

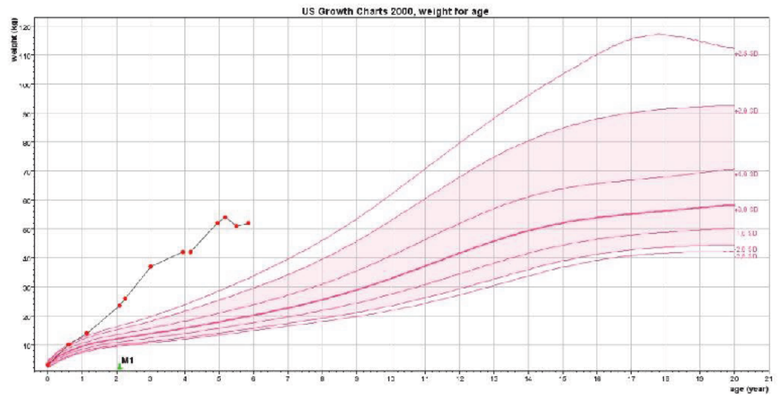


Table 1: Auxological and Metabolic parameters

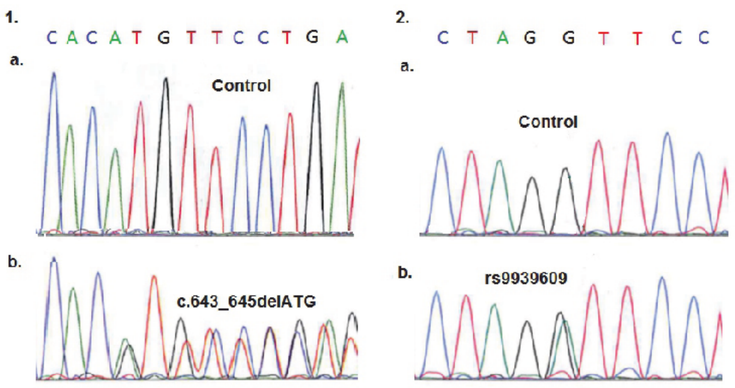
Age(y)	Weight SDS	Height SDS	BMI SDS	Waist SDS	Bone Age (y)	BP (mmHg)	Kcal/day	TCho/HDL/LDL/TRG) (mg/dl)	HOMA	Other hormonal (TFTs, cortisol, ACTH, PRL, IGFs)	Treatment
0.6	+3.3	+2.5	+1.8					153/46/89/101		NS	
3	+5.3	+3.6	+4.5	+5.7	5	75/45 (75th)	2500	183/54/99/148	1.8	NS	
5.2	+4.1	+4.6	+3.1	+4.6		100/55 (75th)	3100	200/58/123/150	2.5	VitaminD3:12ng/ml IGF1: +2SDS	Metformin 500mg/day Vitamin D3 supl
6	+3.6	+4.3	+2.8	+4.7	6.5	90/50 (50th)	2500	180/60/110/130	2.1	NS	

Table 2: Oral Glucose Tolerance test (75 gr/m2)

Time (min)	Basal	30	60	90	120
Glucose (mg/dl)	85	110	122	95	89
Insulin (μiu/ml)	12	170	154	123	110

2. Genotype

A novel heterozygous mutation *MC4R* p.M215del (c.643_645delATG) deletion was found on the patient and her father. 3D structural dynamic simulation studies have been used to investigate the conformational changes induced by this novel amino acid deletion and have shown distinct conformational changes in the protein structure. Additionally, the *in silico* software package 'Mutation Taster' was used to predict the pathogenicity of p.M215del deletion and identified it as a disease causing mutation. The patient was also found with the *FTO* mutation rs9939609 that was inherited from the mother.



CONCLUSIONS

- The deletion of methionine at position 215 causes global conformational and functional changes as it is localized at the alpha-helical transmembrane regions and the membrane spanning regions of the beta-barrel.
- This novel mutation produces overgrowth phenotype with severe early onset obesity and height acceleration with age even in heterozygote patients.
- Additionally, negative effect of environmental factors and unhealthy lifestyle habits, aggravates obesity phenotype.
- The phenotype of severe obesity exacerbates with the additional effect of other variants as the known high risk obesity related *FTO-rs9939609* polymorphism.

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