Prevalence of melanocortin 4 receptor (MC4R) mutations in Turkish obese children

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Background:

- Melanocortin-4-receptor gene (MC4R) is a key regulator of energy homeostasis, food intake and body weight which has intensively been analyzed in molecular genetic obesity research.
- MC4R dysfunction in humans causes hyperphagia, impaired satiety and obesity.

Objective and hypotheses:

- To identify MC4R mutations prevalence in familial obese Turkish children and adolescents

Method:

- Ninety three (45 female/48 male)pediatric and adolescent patients aged between 1.3–15 years old with early onset obesity (before 6 years) were enrolled.
- Obesity was defined as a body mass index (BMI) standard deviation score (SDS) of + 2.0 according to the Turkish Population.
- Children with genetic syndromes associated with obesity or mental retardation, or taking drugs that promote changes in eating behavior or weight were excluded.
- Coding region of the MC4R gene was sequenced by Illumina MiSeq Next Generation Sequencing System.

Results:

- Mean age of the patients was 7.3 ± 3.7 years and mean BMI was SDS 3.7 ± 0.7SD.
- Seventy nine patients (85%) were pre-pubertal and 14 (15 %) were pubertal.
- We identified four different mutations in eight patients, giving a mutation detection rate of 8.6 %.
- Three were previously identified missense heterozygous mutations (p.N274S, p.S136F and p.V166I).
- One was a novel homozygous mutation (p.I291Sfs*10) detected in a severely obese 2-year-old boy.
  - By in-silico analysis softwares this novel mutation predicted to be disease causing and it is expected to have a-32 amino acids shorter MC4R protein.
- Table 1 shows clinical and molecular features in MC4R mutation (+) patients.

Table 1. Clicinical and molecular features of MC4R mutation (+) patients.

Family/Patient	Sex/Age	Height SDS/ BMI SDS	Clinical features	HOMA-IR	cDNA	Protein	MT	Polyphen2 score	SIFT	ExAC*,# (Overall Allele frequency)	Novel
Family 1/ P1	M/10	1.9/3.7	IR	6.3	c.821 A>G/wt	p.N274S/wt	DC	PD	D	0.00001647	-
Family 2/P2	F/8.6	1.9/2.7	IR, HT, NASH	4.4	c.496 G>A/wt	p.V166I/wt	DC	PD	D	-	-
Family 3/P3	M/8.5	3.2/4.6	IR, depression, sosial isolation	8.1	c.496 G>A/wt	p.V166I/wt	DC	PD	D	-	-
Family 4/P4	M/14	0.8/3.6	IR, HT, NASH, Elevated TSH	7.3	c.407 C>T/wt	p.S136F/wt	DC	PD	D	-	-
Familiy 5/P5	M/2	-1.8/7.3	IR	3.2	c.870delG/ c.870delG	p.I291Sfs*10/ p.I291Sfs*10	DC	NA	D	-	yes
Family 1/P6	F/8	1.2/2.9	IR	3.4	c.821 A>G/wt	p.N274S/wt	DC	PD	D	0.00001647	-
Family 3/P7	F/14	1.0/3.1	IR, HT, NASH,	4.6	c.407 C>T/wt	p.S136F/wt	DC	PD	D	-	-
Familiy 6/P8	M/14.5	1.1/3.0	IR	6.2	c.821 A>G/wt	p.N274S/wt	DC	PD	D	0.00001647	-

D: Damaging, DC: Disease causing,F: Female, IR: Insulin resistance, NA: Not available, NASH..Non alcolicsteatohepatitis, M: male, MT: MutationTaster, P: Patient, PD: Probably Damaging, T: Tolerated,, wt: Wild Type,
*Exome Aggregation Consortium (http://exac.broadinstitude.org), # The allele frequency in the ExAC database does not contain representative controls for all ethnic groups.

Conclusion: MC4R gene mutations is quite common in childhood obesity in Turkish population. Investigating the mutations in MC4R gene in patients with severe childhood-onset obesity is necessary.

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