OBESITY IN PEDIATRIC AGE: THE ANALYSIS OF GENOMIC REARRANGEMENTS

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Background

Childhood obesity became a global plague: 9% of Italian children (17% of USA children) is obese and 21% is overweight. Nowadays only a small number of obese children undergoes genetic analysis, usually when obesity is associated with dysmorphic features. Our purpose was to identify genomic rearrangement causing obesity: we analyzed the DNA of 52 children by array-CGH (platform CytoScan-HD, Affymetrix).

Materials and Methods

- We included obese children with dysmorphic features and/or mental retardation, hyperphagia and no benefit by the improvement of the nutritional approach.
- DNA has been extracted from 200 µl of blood using the automatic system QIAsymphony SP platform (QIASymphony, Qiagen Inc., Valencia, CA) and kit QIAsymphony DSP DNA.
- Analysis of DNA samples has been performed with microarray Cytoscan-HD (platform, Affymetrix Santa Clara, CA, USA). Software Chromosome Analysis Suite (ChAS) version 3.1 (Affymetrix) has been used to anlyse data. “Raw data” (CEL files) has been processed in “summarized data” (CYCHP files) and visualized as chromosomal aberrations in table and graphic format.

Results 29 males (55,8%) and 23 females (44,2%) entered the study (BMI 28.42 kg/m ^{2} ±2.64)

Del/Dup	CNV lenght	Array-CGH result	Gene/regions probably related to obesity	Clinical features associated to obesity
Del	813Kb	arr[hg19] 16p11.2(29,427,215-30,240,227)x1	Del 16p11.2	Psychomotor retardation
Comments: Proximal 16q11.2 microdeletion syndrome (MIM#611913): delay language development, mild cognitive impairment, autism spectrum disorder, mild dysmorphic features, predisposition to obesity				
Del	232Kb	arr[hg19] 16p11.2(28,819,028-29,051,191)x1	Del 16p11.2	-
Comments: This deletion in described in database of patients with early onset sever obesity (Bochukova et al., 2010)				
Del	55Kb	arr[hg19] 7q21.3(97,937,346-97,992,574)x1	BAIAP2L1	Psychomotor retardation
Comments: partial microdeletion of gene BAIAP2L1. In animal models the gene seems to be part of insulin signaling and glucose homeostasis. In obese and diabetic patients the gene is under-expressed in hepatic adipose tissues.				
Del	109Kb	arr[hg19] 20q13.13(47,777,832-47,886,899)x1	STAU1	Psychomotor retardation and dysmorphic features
Comments: In vitro , over-expression of STAU1 is linked to increased adipogenesis. Our patient, on the opposite, has a deletion.				
Dup/Del	460Kb 33Kb	arr[hg19] 3q25.32(158,225,217-158,685,925)x3, 6q21(112,416,532-112,450,351)x1	LAMA4	PWS-like
Comments: Dup3q, 460Kb, includes 5 genes (RSRC1, MLF1, GFM1, LXN, RARRES1). A shorter rearrangement has been described in a patient with obesity and cognitive impairment (DECIPHER ID 285007). Del 6q21, 33Kb, includes introns and exons of gene LAMA4 (MIM *600133), part of laminin family, glycoproteins of extracellular matrix. Rearrangements in man are associated to cardiomyopathy, in animal models the gene seems to be involved in adipose tissue development (Vaicik et al. 2014)				
Dup	393Kb	arr[hg19] 18q21.31(55,040,854-55,434,227)x3	ONECUT2	Psychomotor retardation and dysmorphic features
Comments: Microduplication including 4 genes OMIM (ONECUT2, FECH, NARS, ATP881). ONECUT2 is involved in development of hepatic steatosis and insulin release				
Dup	180Kb	arr[hg19] 3q24q25.1(148,899,788-149,080,366) x3	CP	Mild dysmorphic features
Comments: CP gene encodes for ceruloplasmin. High serum level of this protein have been described in association with obesity and metabolic syndrome. This role is to known yet				
Dup	1.6Kb	arr[hg19] Xp22.31(6,455,149-8,135,644)x2	PNPLA4	Macrosomia
Comments: Dup Xp includes 4 genes (HDHD1, STS, VCX, PNPLA4). Xp22.31 duplication has been described in patients with cognitive impairments, autism spectrum disorders, hypotonia (Esplin et al., 2014), 7 patients over 9 were overweight or obese, 2 had alimentary difficulties. Over-expression of PNPLA4 has been described in obese patients (Steinberg et al., 2007)				

Conclusions:

- 24 patients (46,15%) resulted positive on array-CGH analysis (33,4% females, 66,6% males)
- 41,2% of array-CGH positive patients presented dysmorphic features and 50% were affected by mental retardation.
- In 8 patients , genetic rearrangement was related to obesity and in 1 patient the link was suspected but not proved.
- Genetic rearrangements causative of obesity are 4 deletions and 4 duplications