Letter to the Editor

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3q29 microduplication in a small family with complex metabolic phenotype from Southern Italy

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To the Editor,

Obesity is a multifactorial disorder caused by a combination of environmental, behavioral and genetic factors [1]. The most common forms of obesity are the polygenic ones (up to 95% of all cases), where each susceptibility gene marginally contributes on the weight increase [2]. By contrast, monogenic obesity is rarely observed, and causative mutations have been described in a few genes, i.e. melanocortin 4 receptor (*MC4R*), proopiomelanocortin (*POMC*), uncoupling protein 3 (UCP3), prohormone convertase 1 (*PC1*), leptin (*LEP*) and leptin receptor (*LEPR*) genes [3]. In other cases with a documented genetic cause, obesity is usually associated to other clinical features and is only one of the aspects of more complex syndromes [4].

In addition to the investigation of mutations/polymorphisms in single genes associated to obesity, comparative genomic hybridization (CGH) array technology allows the rapid identification of genomic imbalances in the entire genome supporting the possible role of genomic gains and/or losses in the etiology of a number of genetic disorders [5] and behavioral abnormalities [6]. At present, thanks to the great analytical power of CGH array to detect ever small chromosomal rearrangements, a large number of copy number variants (CNV) have been discovered both in apparently healthy control individuals and in obese patients [7]. We describe the genetic characterization of five related individuals (two males, one female and their parents) from a family with a high prevalence of obesity, living in Southern Italy for at least three generations. We screened the presence of genomic alteration by CGH array (as described in Supplemental material, References 1S, 2S). All patients gave their written informed consent to the study, which was performed according to the Declaration of Helsinki II and was approved by the Ethics Committee of our Faculty of Medicine (authorization no. 193/06, October 25, 2006; amendment no. 193/06/ESES1, October 1, 2014).

The male II.3 (Figure 1) came to our attention at 10 years for his morbid obesity (body mass index [BMI] = 49 kg/m^2), type 2 diabetes, hypertension and dyslipidemia. Clinical and biochemical characteristics of the patient are reported in Supplemental Table 1. Behavioral examination evidenced a "snacker" phenotype, whereas no mental retardation or any other intellectual disabilities were reported. CGH array analysis showed the presence of a 3q29 microduplication of 1.59 Mbp (chr3:195,747,856-197,339,329) (Figure 2A and B). Clinical follow-up highlighted that the patient underwent a first endoscopic intragastric balloon (IGB) placement in 2013, then removed 6 months later, and a second IGB placement in 2015, also removed after 6 months,

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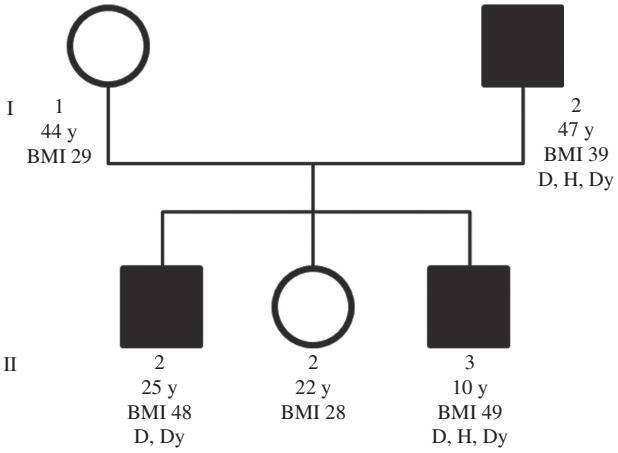

Figure 1: Pedigree of the studied family members.
The clinical features detected in each family member together to BMI are also indicated. Mother (I.1), Father (I.2), Son 1 (II.1), Son 2 (Daughter, II.2), Son 3 (II.3). D, diabetes; H, dypertension; Dy, dyslipidemia; y, age in years; BMI, body mass index (kg/m^2).

both procedures with no significant (~10 kg) weight loss, current BMI being equal to 47.7 kg/m^2. In 2016, he underwent a melanoma excision surgery on the right leg (Supplemental Table 2).

Clinical, biochemical and genetic characterization was then extended to other members of the family. The obtained results are the following:

- I.1: The mother (44 years) was overweight at admission (BMI = 29 kg/m^2), with normal blood pressure and normal glycemic and lipidemic profiles. 3q29 microduplication was observed by CGH array. Clinical follow-up showed no variation up to 2017.
- I.2: The father (47 years) presented at admission mild obesity (BMI = 39 kg/m^2), type 2 diabetes, dyslipidemia and hypertension. The clinical follow-up highlighted that the patient underwent a sleeve gastrectomy surgery in March 2015 with a subsequent weight loss of ~33 kg (current BMI = 33.9 kg/m^2).

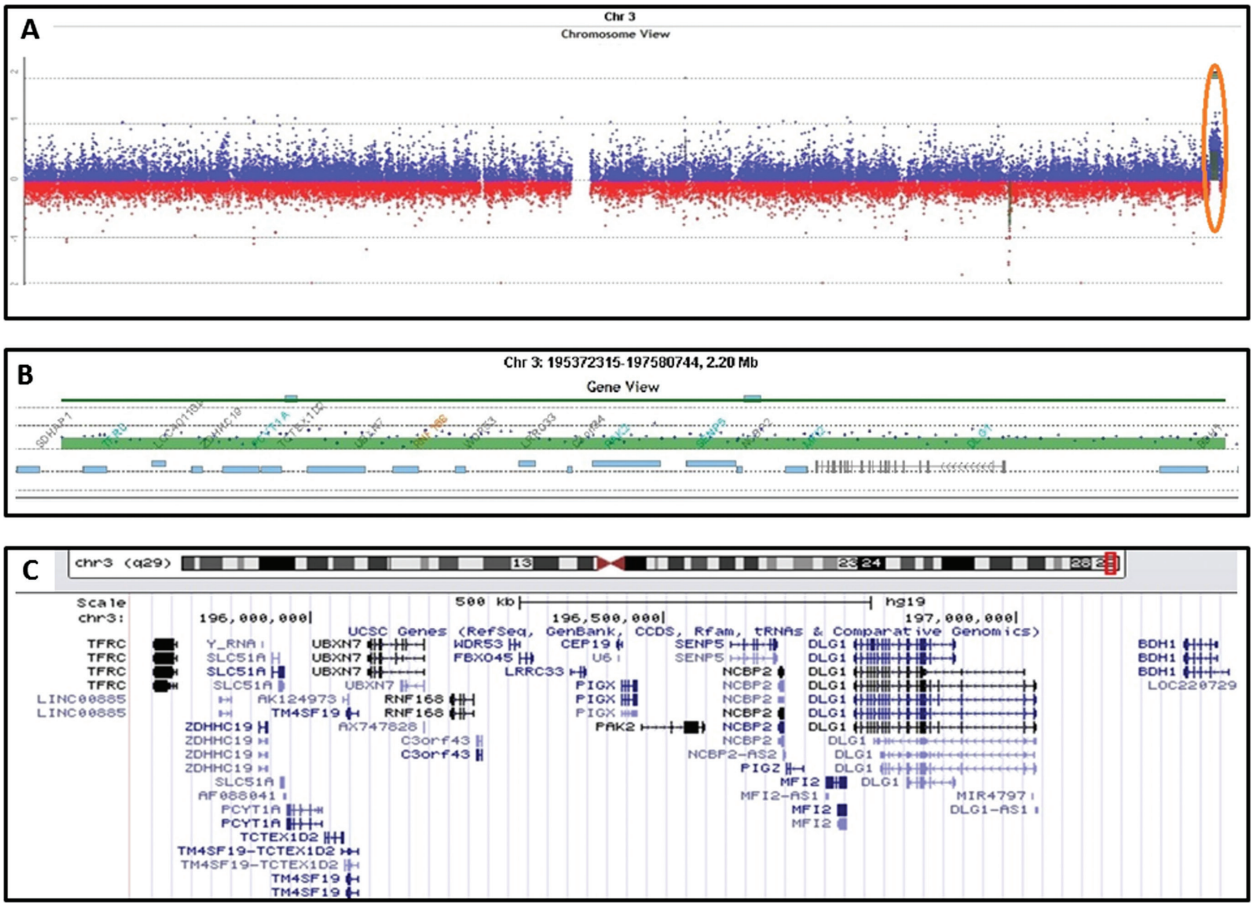

Figure 2: Molecular details of 3q29 duplication.
Array-CGH profile of chromosome 3 showing (A) a terminal microduplication of 1.59 Mb at 3q29 indicated by an elliptical red circle, and (B) an enlargement of the 3q29 microduplication. Genomic view of the terminal 1.59 Mb of chromosome 3q29 (C): UCSC genes (GRCh37/hg19) are shown.

- II.1: The first male son (25 years) showed at admission severe obesity (BMI = 48 kg/m^2), dyslipidemia and type 2 diabetes. The presence of the maternally inherited 3q29 microduplication resulted at CGH array analysis. The clinical follow-up showed that the patient lost ~30 kg after dietary intervention (current BMI = 36.2 kg/m^2).
- II.2: The daughter (22 years) at admission was overweight (BMI = 28 kg/m^2), with normal blood pressure and normal glycemic and lipidemic profiles. No variation was present at CGH array analysis. The clinical follow-up highlighted that the patient had a pregnancy during which she developed gestational diabetes. After pregnancy, she lost ~30 kg by dietary intervention (current BMI = 28 kg/m^2).

The presence of a 1.59-Mbp microduplication in the 3q29 region resulted by CGH array was observed in three family members (I.1, II.1 and II.3). The genomic view reporting the UCSC genes (GRCh37/hg19) is shown in Figure 2, panel C. The altered region includes several disease-related (OMIM) genes listed as follows: *TFRC* (OMIM*190010), *ZDHHC19*, *OSTalpha* (OMIM*612084), *PCYT1A* (OMIM*123695), *TCTEX1D2*, *TM4SF19*, *UBXN7* (OMIM*616379), *RNF168* (OMIM*612688), *C3orf43*, *WDR53* (OMIM*615110), *FBXO45* (OMIM*609112), *LRRC33* (OMIM*615322), *C3orf34* (OMIM*615586), *PIGX* (OMIM*610276), *PAK2* (OMIM*605022), *SENP5* (OMIM*612845), *NCBP2* (OMIM*605133), *LOC152217*, *PIGZ* (OMIM*611671), *MFI2* (OMIM*155750), *DLG1* (OMIM*601014) and *BDH1* (OMIM*603063). The duplication of this region was confirmed by RTqPCR analysis: the tested genes were ~1.5 times more abundant in subjects bearing the 3q29 microduplication compared to control subjects (mean RQ obtained in the three patients bearing the CNV: *TFRC* = 1.55, *PAK2* = 1.63, *BDH1* = 1.60). The 3q29 microduplication was neither observed in confirmation cohort of 100 unrelated morbid obese patients previously screened by our group for the presence of alterations in obesity-related genes (i.e. *POMC*, *MC4R*, *MC3R*, *FTO*, *UCP1*, *UCP3*) [8, 9] (mean RQs: *TFRC* = 1.03, *PAK2* = 1.00, *BDH1* = 0.97) nor in 100 normal weight control subjects analyzed by CGH array.

Twenty genes were included in this duplicated region. Among these genes, *TFRC*, *OSTalpha*, *PCYT1A*, *TCTEX1D2*, *PAK2* and *C3orf34* were previously associated to the obese phenotype, some of them contributing to the impaired insulin sensitivity and body fat accumulation (Supplemental Material, References 3S-11S).

In summary, most of the members of this family showed common features, including overweight or obesity, diabetes and hypertension. The clinical features of these patients suggested a familial form of obesity together with obesity-associated disorders. In addition, the male second-generation patients (II.1 and II.3) harbored the maternally inherited 1.59-Mbp microduplication in 3q29.

The clinical features of patients bearing such microduplication are extremely heterogeneous, including mild to moderate intellectual disability (90%–100%), obesity (60%), speech delay (50%), delayed walking (50%), autistic features (25%) and ataxic gait (25%–30%) [10].

The absence of any intellectual disability or speech delay in our index case and his relatives should be explained by the reduced penetrance of the 3q29 microduplication already reported; in fact, other patients bearing the same genomic alteration with no mental retardation have been described [11].

Finally, the 3q29 region was also found to have significant evidence of linkage to melanoma susceptibility in 42 Swedish families at-risk for melanoma [12]; in agreement, the subject II.3 in this family and his maternal aunt (reported data) were affected by cutaneous melanoma.

Based on these literature data, we could hypothesize that a duplication of the genes encompassed by the 3q29 microduplication could concur in both the altered insulin sensitivity and obese phenotype that we observed in the second-generation male patients; in this family, the absence of the phenotype related to cognitive and intellectual abilities highlights variable expressivity and reduced penetrance.

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Supplemental Material: This article contains supplementary material (https://doi.org/10.1515/cclm-2017-1090).