A novel highly-penetrant form of obesity due to microdeletions on chromosome 16p11.2

Supplementary online material

Supplementary Figure S1

Validation of 16p11.2 deletions by MLPA and determination of their modes of inheritance. MLPA was carried out using 9 probe pairs within and 2 lying outside the deletion (one to each side), as shown in Figure 1, together with 9 control (nominally copy number invariant) probe pairs. Panels show the relative magnitude of the normalised, integrated signal at each probe location in order of chromosomal location. Where DNA was available, samples were analysed if they were identified from GWAS data as carrying a deletion at 16p11.2 (top) or if they were a first degree relative of a proband (bottom). Labels correspond to the case ID of the proband as shown in Table S2; f = father; m = mother; a-c = siblings.
Supplementary Figure S2

Dependence of BMI on age in subjects having a deletion at 16p11.2. Data are shown for all probands identified in this study as having a deletion at 16p11.2, for whom phenotypic information is available. Lines denote the age- and gender-corrected thresholds (solid/broken – male/female) for obesity (adults – BMI ≥ 30 kg.m\(^{-2}\), children ≥ 97\(^{th}\) percentile) and morbid obesity (adults – BMI ≥ 40 kg.m\(^{-2}\), children Z-BMI ≥ 4). Symbols are as follows: Square/circle – male/female; black/grey – ascertained/not ascertained for developmental delay; filled/open – ascertained/not ascertained for obesity. Thus, individuals from general population are shown as open grey circles or squares.
Supplementary Figure S3

**Dependence of BMI on age in probands having a deletion at 16p11.2.** Data are shown for all individuals identified in this study as having a deletion at 16p11.2, for whom phenotypic information is available. Lines denote the age- and gender-corrected thresholds (solid/broken – male/female) for obesity (adults – BMI ≥ 30 kg.m⁻², children ≥ 97th percentile) and morbid obesity (adults – BMI ≥ 40 kg.m⁻², children Z-BMI ≥ 4). Symbols are as follows: Square/circle – male/female; black/grey – ascertained/not ascertained for developmental delay; filled/open – ascertained/not ascertained for obesity; grey diamond – first-degree relative of a proband. Thus, individuals from general population are shown as open grey circles or squares.
Supplementary Figure S4

Transcript levels for genes within and nearby 16p11.2 deletions. Expression data for adipose tissue from the SOS Sib Pair cohort were analysed for probes detecting transcripts for genes lying within the interval chr16:28.4–31.0Mb (see Supplementary Table S4 for details). Transcript levels in the two individuals carrying a deletion of 16p11.2 (black symbols) are plotted alongside those for their non-obese siblings (white). Also shown are box plots summarising the data for the other 157 obese subjects from this study, indicating the 10th, 25th, 50th, 75th and 90th percentiles for each transcript. The positions of the the 16p11.2 deletion and the flanking segmental duplications relative to the transcripts are indicated by a solid line and grey bars at the left axis.

Within the deleted region, there is a consistent reduction in expression in the subjects carrying a deletion, relative to both their siblings and to other obese subjects. In contrast, although CNVs have been shown to have the potential to affect expression of neighbouring genes up to 0.5Mb distant\(^{12,43}\), no such clear and consistent differences in transcript levels are observed for the genes lying nearby, outside the region of the 16p11.2 deletion.
Supplementary Figure S5

**Graphical representation of the output of CNV discovery algorithms.** Copy number calls at SNPs within and surrounding the deleted region (black bar) and its flanking segmental duplications (grey bars) are shown as follows: blue – 1 copy; cyan – 2 copies (i.e. no aberration); yellow – 3 copies; red – 4 copies. (a) cnvHap output for the NFBC cohort, showing all individuals with at least 10 aberrant probes within the deletion; (b) Gaussian Mixture Model output for the CoLaus cohort, showing all individuals with at least 1 aberrant probeset. The different patterns for the two methods reflect the locations interrogated by the respective platforms, and also the respective sensitivities of the platforms and algorithms to copy number variation.
Supplementary Figure S6

Validation of deletion calls from Illumina genotyping data. LogR ratio (LRR) data exported from Illumina BeadStudio was normalised with respect to the median and variance for each probe, and smoothed by averaging over a 9-point moving window. Example data are shown for samples from the NFBC cohort that had normal copy number (green) and which carried a deletion (blue) or duplication (purple).
## Supplementary Table S1

Cognitive/behavioral symptoms observed in carriers of 16p11.2 deletions. Data are shown for patients ascertained for developmental delay, and for affected relatives if available. ‘No data’ indicates that this phenotype was not assessed. NA – not applicable due to age of the patient.

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<th>ASD</th>
<th>Other Behavioral symptoms</th>
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Supplementary Table S2

**Obesity characteristics of carriers of 16p11.2 deletions.** The basis for ascertainment and all available data for gender, age and BMI are shown for each subject identified as carrying a deletion at 16p11.2. Also shown are the methods used to identify the deletion and for its validation, and the inheritance of the deletion as inferred from the results of analysis of parental DNAs where these were available. n.d. – not determined

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**Obesity & Developmental Delay**

**General Population**

**Adult Obesity**

**Childhood Obesity**

**Obesity Bariatric Surgery**
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\%^*The proband’s brother has the deletion, but both parents are deceased so inheritance cannot be confirmed. One instance has been reported\(^\#\) of presumed germ-line mosaicism in which a deletion was found in two siblings but neither parent.
## Supplementary Table S3

Obesity phenotype of carriers of 16p11.2 deletions from other publications, as included in Figure 2.

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Supplementary Table S4

Expression analysis transcript proseset details. The details of probes analysed in the course of expression analysis (Supplementary Figure S4), listing the Affymetrix proseset identification code, the gene whose transcript is listed as being detected by the probe, and the chromosomal coordinate (build hg18) for the start of that gene.

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**Supplementary Table S5**

**Details of genes lying within the deleted region at 16p11.2.** Gene name, coordinates and strand of protein coding region are according to genome build hg18. Protein function descriptions are based on GeneCards entries (http://www.genecards.org/) or from the indicated references. Change in expression is given as the mean transcript level (all probes) in the 2 deletion carriers relative to obese (normal/lean) subjects (data as in Supplementary Figure S4). Possible functional relevance to obesity (bold type) or developmental delay/cognitive deficit (italics) is as indicated. The first three pairs of genes lie within the segmental duplications.

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<th>Gene name</th>
<th>CDS start</th>
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<th>Protein function</th>
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<td>GIYD1</td>
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<td>1.0 (1.5)</td>
<td>Induced in response to fasting or as a result of a defect in leptin signalling</td>
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<td>SULT1A3</td>
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<td>MAZ</td>
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Supplementary references


