SUPPLEMENTARY ONLINE MATERIAL

Reciprocal extreme BMI phenotypes associated with gene dosage at the 16p11.2 locus

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Supplementary Text

Clinical phenotype

No prenatal effect was documented. The mean birth weight (n=48) was at the 50th percentile (3075 g at a mean gestational age of 38.3 weeks). Significant low height was observed in pediatric cases (mostly < 5 years of age) but not in adults. To appreciate the effect on height in children, we assessed longitudinal data available from 14 pediatric patients (data not shown). Decline in weight gain preceded the decline in height gain. In no instance was the reverse true. In several cases, both curves seemed to falter simultaneously. This is a well documented phenomenon in children with "failure to thrive" (FTT) [1], where early onset weight stagnation has a direct impact on height.

Significant neurological signs were present in 32/95 cases ascertained for DD/ID (including literature cases) (**Supplementary Table S9**, Materials and Methods for details on selection criteria), a similar frequency to that observed for DD/ID deletion carriers (37/165). Weight and BMI were similar ($p > 0.2$) in patients with or without neurological symptoms. Other co-morbidities or malformations were infrequent (**Supplementary Table S9**).

Double hits

Six of the 73 duplication carriers (8%) referred for DD/ID exhibited an additional large (> 500 kb) genomic rearrangement, similar to the frequency observed in the general population [2] (**Supplementary Table S2**). A trend for lower frequency of such second hits (3/128; 2%) was found in carriers of the highly-penetrant reciprocal 16p11.2 deletion ($p = 0.08$ Fisher's exact test). Our results, therefore, do not support a strong two-hit model expressivity for the 16p11.2 duplication [3], contrary to findings pertaining to the 16p12.1 microdeletion [4].

Gender bias

Duplication carriers ascertained through population-based cohorts show a significant excess of females (approximately 2.1F:1M), and the few carrier adult men (n=10) ascertained in this way present BMI and height in the normal range. The most likely explanation for this gender ratio is that our adult ascertainment was biased towards less severe DD/ID/ psychiatric cases.

This is in sharp contrast with the high frequency of moderately to severely underweight males observed in DD/ID children and adults. A similar bias was observed among transmitting parents.

Eating disorder cohort screening

To further assess the role of the duplication and deletion in the etiology of eating disorders (ED) we screened for 16p11.2 rearrangements in a cohort of 441 patients diagnosed with anorexia, bulimia, binge eating disorder or ED not otherwise specified and 335 controls using Multiplex Ligation-dependent Probe Amplification (**Supplementary Table S10)**. We identified an atypical duplication in one patient (AB505) with AN (incidence 1/109) (**Supplementary Figure S4A**). We used quantitative PCR [5] and a custom aCGH that specifically targets a portion of the short arm of chromosome 16 to confirm the rearrangement and pinpoint its extent (Materials and Methods). The patient presents two small independent duplications: one known copy number polymorphism [6] of 104 kb (16:30,081,217-30,185,324), and a second rearrangement, which was not found in 5,612 individuals from the general population (CoLaus cohort), of 136 kb (16:29,514,638-29,650,991) that encompasses the *SPN* and *QPRT* genes (**Supplementary Figure S4B-C**). This atypical duplication carrier patient was a 29-year old female patient with lifetime history of AN measured by SCID-I [7] (disease onset at 16 years; current height = 1.63 m and BMI=18.3; lifetime minimum BMI=17.3 at 27 years). The patient described a presence of one to two bingeing and vomiting episodes per month and regular laxative use.

Supplementary Table S1: List of genes mapping within the 16p11.2 rearranged interval and its flanks.

	unspecific QPCR assay	failed efficiency test	specific QPCR assay	expressed in brain	expressed in hypothalamus
genes within the rearranged interval					
BOLA2/BOLA2B	1	0	0	1	1
GI1D1/GI1D2	1	0	0	1	1
SULT1A4/SULT1A3	1	0	0	1	1
SPN	1	0	0	1	1
QPRT	0	0	1	1	1
C16orf54	1	0	0	1	1
MAZ	0	0	1	1	1
PRRT2	0	0	1	1	1
C16orf53	0	0	1	1	1
MVP	0	0	1	1	1
CDIPT	0	0	1	1	1
SEZ6L2	0	0	1	1	1
ASPHD1	0	1	0	1	1
KCTD13	0	0	1	1	1
TMEM219	0	0	1	1	Unknown
TAOK2	0	0	1	1	1
HIRIP3	0	0	1	1	1
INO80E	0	0	1	1	Unknown
DOC2A	0	0	1	1	1
C16orf92	0	1	0	1	Unknown
FAM57B	0	0	1	1	1
ALDOA	1	0	0	1	1
PPP4C	0	0	1	1	1
TBX6	0	1	0	1	1
YPEL3	0	0	1	1	1
GDPD3	0	0	1	1	1
MAPK3	0	0	1	1	1
CORO1A	0	0	1	1	1
sum	6	3	19		
telomeric genes					
RUNDC2C	1	0	0	Unknown	Unknown
LOC653390	1	0	0	1	1
LAT	0	0	1	1	1
SH2B1	0	0	1	1	Unknown
ATXN2L	0	0	1	1	Unknown
EIF3C	1	0	0	Unknown	Unknown
CLN3	0	0	1	1	1
KIAA0556	1	0	0	1	1
IL21R	1	0	0	1	1
IL4R	0	0	1	1	0
AQP8	0	1	0	1	1
HS3ST4	1	0	0	1	1
ZKSCAN2	1	0	0	Unknown	Unknown
sum	7	1	5		

centromeric genes					
SEPT1	0	0	1	1	1
ZNF688	0	0	1	Unknown	Unknown
BCL7C	0	0	1	Unknown	Unknown
POL3S	0	1	0	Unknown	Unknown
ITGAD	0	1	0	1	1
sum	0	2	3		

Supplementary Table S2: List of 16p11.2 duplication and deletion carriers presenting a second large (>500kb) genomic rearrangement.

ID	gender	16p11.2 rearrangement		Second hit		
		CNV	Inheritance	locus	Size	Inheritance
169	F	dup	father	dup 22q11.2(mat) + del 5q23.1(mat)	2864 kb	mother
209	M	dup	*de novo*	del 2q33.2q33.3	3640 kb	unknown
253	F	dup	father	del 15q13.2	1500 kb	father
3	M	dup	mother	del 19q13.42	622 kb	unknown
315	M	dup	mother	del 9q34.3	506 kb	*de novo*
349	F	dup	mother	del 19p13.3	1000 kb	*de novo*
324	F	dup	father	del 10q11.22q11.23	5100 kb	father
93	M	del	father	dup 15q13.2q13.3	1980 kb	mother
198	M	del	father	del 10p15	1890 kb	*de novo*
215	M	del	father	3q25.31	662 kb	mother

Supplementary Table S3: Genetic centers and anthropometric measures of 16p11.2

Ascertainment	ID	Origin	gender	Age years	Weight		Height		BMI		HC		CNV detection platform
					kg	Z-score	cm	Z-score	kg/m^2	Z-score	cm	Z-score	
Adult psychiatry	124	Rouen	F	41	91	2.4334	172	-0.3186	30.33	1.753			QMPSF and FISH
	125	Rouen	M	22	55	-2.7118	175	-0.3186	17.9	-3.1346			
	126	Rouen	F										
	267	Rouen	F	21	54	-0.75	180	2.9631	16.66	-3.2154			
Developmental Delay/Autism	369	Iceland	F	9									Illumina Human317 or Illumina Human 370 or lllumina HumanHap550 or Illumina Human610 or Illumina 1M BeadChips
Developmental Delay	32	Amiens	M	9	16.5	-4.9333	118	-3.5446	11.87	-4.225		-4	Agilent 44K
	314	Amiens	M	3	9.24	-4.5007	85.5	-2.5356	12.8	-3.6752	44	-3.8458	
	346	Angers	M	12	33	-0.75	146	-0.25	15.5	-0.93	52.5	-1	Illumina 610K
	38	Antwerp	M	30	82.9	-0.52	174.5	-1.25	27.22	0.321	56	-0.3186	Illumina Human 370 CNV Quad Chip
	21	Bordeaux	M	5.42	25.5	1.8048	122	2.1819	17.23	1.514	52	-0.3186	Agilent 105K
	373	Bordeaux	M	21	64	-1.0533	193	2.8112	17.2	-3.8047	55		Agilent 244K
	173	Boston	M	2									Agilent 244K
	174	Boston	F	10.5	22.3	-2.7313	126.7	-2.0712	14.11	-1.709	52	-0.3186	
	175	Boston	F	10.3	30.5	-0.67	135	-0.9346	16.7	-0.14	52	-0.3186	
	176	Boston	F	1	5.85	-4.9	71.8	-0.9346	11.5	-4.5	45.5	0.3186	
	177	Boston	F	5							50	-0.6745	
	178	Boston	M	8.8	27	-0.15	130.3	-0.2793	15.9	-0.09	52.5	-0.3186	
	179	Boston	M	10.3	29.5	-0.67	133.1	-0.9346	16.7	-0.06			
	180	Boston	M	5.7	20.1	0	110.7	-0.6745	16.4	0.729	51	-0.3186	
	181	Boston	M	1.5	11.8	-1.28	81.5	0	18.1	0.675	49.5	1.2816	
	182	Boston	M	6.1	21.8	-0.32	116.2	-0.3186	16.1	0.53	52.4	0.6745	
	184	Boston	F	5.9	18.5	-0.32	112.3	-0.3186	14.7	-0.4			

185	Boston	F	1	9.7	0.319	74.1	0	17.6	0.75	42	-2.1313	
186	Boston	F	16.8	92	2.059	174.1	1.5141	30.4	1.7			
187	Boston	M	1	11.3	0.935	76	0.3186	19.8	2	47.75	0.9346	
188	Boston	M	11	32.1	-0.84	136.5	-1.2816	17.2	0.01	53.5	-0.3186	
31	Caen	F	15	36.3	-3.8022	149	-2.5376	16.35	-1.64	51	-1.5141	Agilent 44K
292	Canada	M	11.9	48	0.935	150	0.3186	21.3	1.1	52	-1.2816	Agilent 44K/Affymetrix 6.0
259	Erlangen	M	9	27.5	-0.25	135.6	1	15.2	-0.67	49	-2.5758	Affymetrix Genechip 6.0 Mapping SNP-array
262	Erlangen	F	5.2	27	2.1466	126	3.2787	17	1.514	51	0	Affymetrix Genechip 6.0 Mapping SNP-array
359	Graz	M	17.5	73	1.5	153	-3.5	31.2	2			Agilent 60K
360	Graz	M	23	55	-3.2649	160	-3.5142	21.48	-0.8	51	-2.3263	Agilent 44K
362	Graz	M	13	55	1.75	165	1.25	20.22	0.6	55	0	Agilent 60K
319	Grenoble	M	12.8			150	-0.25					Agilent 180K
367	Helsinki	M	13.6	44.2	-0.25	157.2	-0.25	16.25	-1.25	51.5	-3	Agilent 244K
123	Le Havre	F	3	14.5	0.319	94.5	0.75	16.3	0.41	49.7	0.3186	QMPSF and FISH
14	Lille	F	8.5	27.1	0.5	131	0.75	15.8	0	54.5	2.0537	
33	Lille	M	12.6	38	-0.25	162	1.5	14.5	-1.88			
37	Lille	M	0									
137	Lille	F	5	15.2	-1	102	-1	14.5	-0.67	49.5	-0.9346	
190	Lille	M	17	28	-4			16	-3.7568		-1.2816	Agilent 44K
193	Lille	M	1.6	7.18	-3.5	77.5	-1	11.9	-5.63	43	-3.4552	
313	Lille	F	7.5	16.2	-3.7444	106	-3.25	14.46	-0.67	45.5	-3	
315	Lille	M										
385	Lille	F	2.75	13.5	0.25	94	1	15.34	0			
170	Lyon	M	4	14.9	-1	96.1	-1.25	16.19	0.319	50.5	-0.6745	Agilent 180K
17	Nancy	M	2.83	11	-2.409	94.5	1	12.32	-4.4635	49	-0.9346	QPCR and Agilent 105K
19	Nancy	F	3.08	12.096	-1	88.5	-1	15.4	-0.32	43	-3.9285	Agilent 105K
253	Nantes	F	1.75	10.3	-0.5	78	-0.75	17.16	0.319	45	-1.2515	Agilent 180K

	135	Nijmegen	F	3.2	17.5	1.5627	100.5	-0.25	17.33	1.282	49	-0.6745	Affymetrix 250K SNP array
	206	Nijmegen	M	0.6	7.24	-1	67	-1	16.09	-0.25	43	-1.7411	
	219	Nijmegen	M	52	75	-0.5175	183	1.5	22.39	-1.147	52	-2	
	220	Nijmegen	F	14	56.5	1.25	158	-1	22.7	1.1	55.1	1.2816	
	357	Nijmegen	F	12.8	32.5	-1.5	151.5	-1.25	14.25	-2.0494	55	1.5141	
	164	Paris	M	9	21	-1.75	122	-1.25	14.1	-1.51	48	-2.5758	Illumina HumanCytoSNP-12 v2
	322	Paris	M	5.5	22	1.5	107	-1	19.1	2.0194	48	-3	
	349	Paris	F	6.4	13	-3	99	-3.5	13.2	-1.51	45.5	-2.5	Agilent 180K
	286	Reims	M	3	9	-4.8104	82	-3.5267	13.4	-2.9182			Agilent 105K
	287	Reims	M										
	209	Rennes	M	0									Agilent 44K
	133	Rouen	F	5.8	23	1.5	116	1	17.1	1.514	52.4	0.9346	QMPSF and FISH
	213	Siena	M	13	65	2.2073	170	1.1514	22.5	1.7369	55.5	0.9346	Agilent 44K
	143	ST-Etienne	M	2	9.5	-3.3773	83	-1	13.8	-2.5217	43	-3.8581	Agilent 105K
	324	Strasbourg	F	10	25.6	-1	132	-0.5	14.7	-0.93	50	-2	Agilent 105K
	3	Tessin	M	5.5	23	1.282	120.2	1.282	16	0.319	51.5	-0.3186	Agilent 244K
	168	Utrecht	F	16				-1.25				1.5	Agilent 105K
	169	Utrecht	F	16	64	1.098	183	3.6605	19.1	-0.32	55	0	
General population	79	Estonia	F	24	52	-1.82	165	0.1375	19.1	-1.63			Illumina CNV370-Duo
	80	Estonia	F	20	49	-0.96	167	0.8535	17.6	-1.61			
	350	Germany	F	69	61.9	-1.04611143	156	-1.37067533	25.44	-0.38678363			Affymetrix 6.0
	398	Germany	M	60	83.1	-0.1590729	172.9	-0.2830262	27.8	0.0840356			
	399	Germany	M	72	85.6	0.1576615	162.8	-1.29606	32.3	0.8730889			
	297	Iceland	F	23									Illumina Human317 or Illumina Human 370 or lllumina HumanHap550 or Illumina Human610 or Illumina 1M BeadChips
	298	Iceland	F	69	69	-0.176815	162	-0.502784	26.3	0.079308			
	299	Iceland	F	28	70	0.297591	174	0.835626	23.2	-0.051204			
	300	Iceland	F	38	88.3	1.181066	175	1.195358	28.8	0.818679			
	301	Iceland	F	55	51	-2.10249	165	-0.246	18.7	-2.121784			
	302	Iceland	F	90	58.2	-0.677843	161	-0.195263	22.45	-0.837061			
	303	Iceland	F	47	65	-0.423469	176	1.457103	20.98	-1.061948			

	304	Iceland	F	105								
	305	Iceland	F	49	63	-0.751296	165	-0.170372	23.14	-0.648291		
	306	Iceland	F	25								
	307	Iceland	M	46	90	0.150439	174	-1.110929	29.73	0.698929		
	308	Iceland	F	34	62	-0.477831	171	0.397718	21.2	-0.709787		
	309	Iceland	F	57	85.5	0.916853	166	-0.093395	31.03	0.995875		
	310	Iceland	M	52								
	311	Iceland	F	54	62	-0.824953	170	0.61074	21.45	-1.121701		
	312	Iceland	F	9								
	365	Iceland	F	48	74	0.236966	175	1.379613	26.78	0.346145		
	351	Lausanne	M	50.7	70.3	-1.28	173	-0.5982	23.5	-0.5934		Affymetrix Mapping 500K array
	352	Lausanne	F	56.6	52.4	-1.48	150	-3.1262	23.3	-0.1831		
	353	Lausanne	M	56.7	92	0.97	183	1.7837	27.5	0.616		
	354	Lausanne	M	53.8	78.4	0	176	0.1982	25.3	-0.0212		
	355	Lausanne	F	69.3	70.5	0.682	164	0.6584	26.2	0.4416		
	127	North Finland	F	31	59.4	-0.39	160.1	-0.7488	23.17	0.005		Illumina CNV370-Duo
	128	North Finland	M	31	88.2	0.762	181.4	0.5015	26.8	0.589		
	129	North Finland	M	31	80.5	0.148	179.8	0.2533	24.9	0		
	130	North Finland	M	31	79.3	0.048	177.5	-0.1181	25.17	0.095		
Relative of Proband with Developmental Delay	183	Boston	M	3.2	15.2	0.319	94.5	-0.6745	17	0.882	50	0	Agilent 244K
	191	Caen	F	51	50	-1.15	165	0.25	18.3	-1.9526			Agilent 44K
	291	Canada	F	44	67.5	0.522	159.5	-0.6745	26.5	0.879			Affymetrix 500K Array
	260	Erlangen	F	36	59.5	-1.3677	158	-0.9346	23.83	-0.5104	52	-1.5141	Affymetrix Genechip 6.0 Mapping SNP-array
	361	Graz	M	50	62	-1.9089	173.5	-0.25	20.6	-1.8717	55	-0.9346	Agilent 44K
	18	Nancy	F	1.25	7.9	-4.7857	72.5	-1.2816	15.1	-1.51	43.2	-1.7889	QPCR
	254	Nantes	M	40	48	-4.8345	165	-1.75	17.6	-3.8203			FISH
	356	Nijmegen	M	42	72	-1.68	187	0.25	20.63	-1.7768			Affymetrix 250K SNP array

323	Paris	F	28	61	0.306	160.7	-0.5	23.6	-0.11			Illumina HumanCytoSNP-12 v2
134	Rouen	F	36	51	-1.35	160	-0.9346	19.9	-1.09			QMPSF and FISH
142	ST-Etienne	M	36	71.5	-0.72	170	-0.9346	24.7	-0.16		-4	QMPSF and FISH
4	Tessin	F	34	61	0.132	164.7	0	22.5	-0.24	53	-0.9346	FISH

Data were not available for all cases shown in table 1.

Supplementary Table S4: Literature cases, anthropometric measures of carriers of the 16p11.2 duplication (29.5-30.1 Mb)

Reference	ID	ID Literature	Gender	Age years	Weight		Height		BMI		Head Circumference	
					kg	Z-score	cm	Z-score	kg/m^2	Z-score	cm	Z-score
	66	Proband 4	M	15.5	38.1	-2.8597	155	-1.6449	15.86	-2.3231	54.5	0
	67	Proband 5	F	13	29.3	-2.7914	145.5	-1.6449	13.84	-2.57289	52	0
Fernandez et al [64]	68	Proband 6	F	2.17	11.3	-0.67	82	-1.2816	16.81	0.319	46.5	-1.2816
	87	CHBDup1	M	1.17	11	0.675						
	88	CHBDup2	F	3.25	14.7	0.319	97.2	0.3186	15.56	0	46.5	-1.2816
Weiss et al [16]	90	CHBDup4	F	9.75	33.5	0.319					51	-0.9346
	100	03C15581	M	62	99.79	1.184	185.42	0.9346	28.9	0.58		
	101	03C15896	M	44	58.06	-2.0091	182.88	0.6745	17.3	-2.7623		
	102	AU002903	M	15.46	69.4	0.935	179.07	0.9542	21.7	0.583	54.8	-0.6745
	103	AU002904	F	13.36	49.44	0.319	156.21	1.562	20.2	0.413	53.3	-0.3186
	104	AU002905	F	11.94	39.46	0	153.67	0.3186	16.8	-0.54	53.4	0.3186
	105	AU011004	M	11.04							53.5	0
	111	Rap-2011	F	15	48.1	-0.32	152.4	-1.47	20.9	0.253	54	0
McCarthy et al [65]	112	Rap-676	F	13	34.5	-1.64	157.5	0	14	-2.5927	52.5	-0.6745
	113*	Shinawi et al 1	M	9	30.0628	0.3	1.2803	-0.9	18.3398	0.9509		0
	114*	Shinawi et al 2	M	5	14.6089	-2	1.0424	-1	13.4438	-2.1775		-1.9
	115*	Shinawi et al 3-Mother	F	31	78.2642	1	1.7269	2	26.2429	0.6212		-1.9
	116*	Shinawi et al 4	F	13	45.8207	0	1.6472	1.1	16.8875	-0.7533		-1.2
	117*	Shinawi et al 5	M	7	18.9768	-1.5	1.1107	-2	15.3816	-0.088		-2.6
	118*	Shinawi et al 6-Mother	F	27	44.6218	-1.88	1.6089	-0.84	17.2375	-1.8242		-2.6
	119*	Shinawi et al 7	F	4	15.7932	0	0.9647	-1	16.9706	1.1276		-3.6
	120*	Shinawi et al 8	M	13	47.4479	0.2	1.5061	-0.7	20.9182	0.8137		1.1
	121*	Shinawi et al 9	M	11	46.5158	1.2	1.4705	0.5	21.5113	1.3472		2.9
Shinawi et al [66]	122*	Shinawi et al 10	M	5.5	1.2	1.2	1.1505	0.6	17.5938	1.4053		-2.5

*Weight, height, BMI and BMI z-scores were imputed from literature z-scores for weight and height

Supplementary Table S5: Effect of the duplication on BMI, weight and height stratified by gender, condition and age.

		Combined			DD/ID or psychiatric[2]			Non medically ascertained[3]		
Strata		**Mean Z-score**	***p*-value**	**N[1]**	**Mean Z-score**	***p*-value**	**N[1]**	**Mean Z-score**	***p*-value**	**N[1]**
BMI	All	-0.47	**2.0e-03**	102	-0.56	**4.1e-03**	76	-0.45	**6.0e-03**	40
	Male	-0.54	**2.1e-02**	52	-0.71	**1.3e-02**	43	-0.31	2.0e-01	14
	Female	-0.4	**1.8e-02**	50	-0.37	8.3e-02	33	-0.52	**4.2e-03**	26
	Adult	-0.63	**1.0e-03**	47	-1.36	3.7e-02	9	-0.45	**6.2e-03**	38
	Male	-0.8	**1.6e-02**	20	-1.54	2.8e-02	7	-0.41	1.5e-01	13
	Female	-0.49	**1.5e-02**	27	-0.73	4.1e-01	2	-0.48	**7.8e-03**	25
	Pediatric <18				-0.45	**1.9e-02**	67	-0.31	4.2e-01	2
	Male				-0.55	5.8e-02	36	0.88		1
	Female				-0.34	9.0e-02	31	-1.51		1
Weight	All	-0.56	**4.4e-04**	104	-0.65	**1.3e-03**	78	-0.61	**3.0e-03**	40
	Male	-0.64	**5.8e-03**	53	-0.79	**4.4e-03**	44	-0.57	8.8e-02	14
	Female	-0.47	**1.7e-02**	51	-0.47	6.5e-02	34	-0.63	**8.6e-03**	26
	Adult	-0.58	**1.8e-03**	47	-0.8	1.1e-01	9	-0.53	**4.3e-03**	38
	Male	-0.86	**1.0e-02**	20	-1.27	3.4e-02	7	-0.64	7.9e-02	13
	Female	-0.37	4.3e-02	27	0.84	6.5e-01	2	-0.46	**1.1e-02**	25
	Pediatric <18				-0.63	**3.1e-03**	69	-2.23	2.7e-01	2
	Male				-0.7	**1.9e-02**	37	0.32		1
	Female				-0.55	4.1e-02	32	-4.79		1
Height	All	-0.24	4.8e-02	103	-0.33	3.6e-02	77	-0.15	1.8e-01	40
	Male	-0.34	4.5e-02	52	-0.4	4.6e-02	43	-0.29	1.2e-01	14
	Female	-0.14	2.6e-01	51	-0.24	2.1e-01	34	-0.07	3.7e-01	26
	Adult	-0.01	4.8e-01	47	0.39	7.1e-01	9	-0.1	2.7e-01	38
	Male	-0.13	3.4e-01	20	0.12	5.6e-01	7	-0.26	1.7e-01	13
	Female	0.08	6.3e-01	27	1.32	7.2e-01	2	-0.02	4.6e-01	25
	Pediatric <18				-0.42	**1.1e-02**	68	-0.98	9.6e-02	2
	Male				-0.5	**2.0e-02**	36	-0.67		1
	Female				-0.33	1.2e-01	32	-1.28		1

For the *p*-values, the following cutoffs control the false discovery rate (FDR) at 5%: BMI: 0.022, weight: 0.032 and height: 0.025 (all indicated in bold). Data were not available for all cases.

[1] Relatives were excluded if more than one member of the same family was present in the analysis to avoid relatedness

[2] These include 24 cases from the literature (**Supplementary Table S3**).

[3] Population based cases and first-degree relatives of probands

Supplementary Table S6: Clinical data available for carriers of the 16p11.2 duplication.

ID	Med [1]	IQ/DQ [2]	Motor delay	Speech delay	EEG	Feeding/eating problems	Behavioural problems/ psychiatric disorder	Malformations	Others	Significant neurological signs [3]
3		70						Inguinal hernia		-
4							Psychiatric hospitalization (unknown diagnosis)			-
14			+	+						+
17			+	+				Pyelo-calyceal dilatation	Constipation	+
18			+	+						+
19			+	+						+
21			+	-			ADHD		Recurrent upper airways infections	-
31		50-60	+	+		Selective and ritualistic eating behaviour			Constipation.	+
32			+	+		Enteral nutrition		Diaphragmatic hernia		+
33					N	Unspecified eating disorder	Aggressivity, Stereotypies	Bilateral ectopic testes, testicular dysgenesis	Hypogonadism	+
37								Cleft lip/palate		-
38		70					Autism, OCD, Anxiety			+
123										-
133			+							-
134							Anxiety			-
135		71								-

137						**Feeding/eating disorder, gastrostomy**	**ASD, Hyperactivity, SD**		**GERD**	**+**
142									**Constipation**	**-**
143			**+**	**+**					**Severe constipation, Hypermetropia**	**-**
164			**+**					**Hypospadias**		**+**
168			**+**	**+**			**ADD**		**Astigmatism. Constipation**	**-**
169		**72**							**Severe constipation**	**-**
170				**+**			**Intolerance to frustration**		**Strabismus**	**+**
173						**Severe oroesophageal dysphagia in the neonatal period**				**+**
174			**+**	**+**				**Costal malformation, Capillary malformation (neck)**	**Asthma, night blindness, strabismus**	**-**
175		**71**	**-**	**+**			**ADHD**		**Recurrent otitis**	**-**
176			**+**		**N**				**G6PD deficiency, recurrent upper airways infections.**	**+**
177		**71**	**-**	**+**						**-**
178		**104**	**-**	**+**			**ASD**			**-**
179			**-**	**+**			**ASD, Anxiety, ADD**			**-**
180		**81**	**+**	**+**			**ASD, SD**			**-**
181								**Left branchial cleft**		**-**
182			**+**							**-**

183			+	+			**ASD, SD**			-
184			+	+					**Asthma. Constipation**	+
185			-							+
186		**60-70**	-	+	**AN**					+
187			+	+			**ASD, sleeping disorder, anxiety**		**GERD, Strabismus**	+
188			-	-	**N**		**ADHD, SD, possible OCD**			-
190			+	+				**Dorso-lumbar scoliosis**	**Constipation. Strabismus**	+
191										-
193			+							-
206					**AN**			**Pulmonary stenosis and atrial septum defect. Small penis. Ectopic testes.**		+
209								**Unique umbilical artery**		-
213		**65**					**Vocal stereotypes. Anxiety.**			+
219	+						**ASD, compulsive behaviour, OCD, recurrent psychotic episodes**		**Hypertension**	+
220	+	**60**			**N**		**ADHD, ASD, OCD, Anxiety**			-
253			+	+						-
254										-

259		**70-80**					**ADHD**	**Unilateral auricular appendix. Inguinal hernia. Short frenulum**	**Hypermetropia. Strabismus**	**-**
260									**Strabismus**	**-**
262		**57**	**+**	**+**			**Hyperactivity**			**-**
286	**+**		**+**	**+**		**Gastrostomy**	**ASD**	**Atrial septal defect, micropenis, bilateral ectopic testes**	**Constipation, deafness**	**+**
287								**Metopic craniosynostos, ectopic testes. Inguinal hernia.**		**-**
291										**-**
292			**-**	**+**			**ADHD**			**-**
313						**Unspecified eating disorder**	**ADHD, aggressivity, SD**		**Refraction disorder**	**-**
314			**+**	**+**		**Very selective and restrictive eating behaviour**				**-**
315										**-**
319			**+**	**+**			**Aggressivity, impulsivity**			**-**
322	**+**		**+**	**+**			**ASD, aggressivity**		**Constipation, hypothyroidm, strabismus**	**+**
323				**+**						**-**
324			**+**	**+**			**Tantrum**			**-**
346	**+**		**+**	**-**		**Feeding disorder in the neonatal period**	**Aggressivity**		**Myopia**	**+**
349			**+**	**+**		**Severe eating disorder**				**-**
356								**Unilateral ectopic testis**		**-**

357		**74**					**ADHD**		**Myopia**	**-**
359										**-**
360								**Ectopic testis, pectus excavatum**		**-**
361									**Delayed puberty**	**-**
362	**+**		**-**	**+**			**Aggressivity**			**-**
367		**50**		**+**	**N**			**Cleft lip and palate. Ventricular septal defect. Mild scoliosis. Ectopic testes operated.**	**Strabismus**	**-**
373							**Anxiety**			**-**
385	**+**			**+**					**Joint hypermobility, pes planus**	**+**

[1] Medication inducing potential weight gain (psychotropic treatment & depakote)
[2] Intellectual quotient, developmental quotient (mild, moderate, severe)
[3] See online methods
GERD: gastroesophageal reflux disease
ADHD, ADD: attention-deficit hyperactivity disorder, Attention deficit disorder.
OCD: obsessive-compulsive disorder, SD: sleeping disorder

Supplementary Table S7: Proportion of duplication carriers below 2 SD for height (HT), weight (WT), BMI and head circumference (HC) stratified by gender and age.

	men 0-5	men (5-10)	men (10-18)	men (>18)
HT	0.18	0.08	0.07	0.05
WT	0.42	0.08	0.14	0.2
BMI	0.55	0.08	0.14	0.2
HC	0.3	0.5	0.08	0.4
	women (0-5)	women (5-10)	women (10-18)	women (>18)
HT	0	0.29	0.14	0.04
WT	0.17	0.25	0.23	0.04
BMI	0.08	0	0.23	0.07
HC	0.25	0.29	0	0.25

Supplementary Table S8: Effect of the duplication (A) and deletion (B) on head circumference (HC).

A		**HC in duplication carriers**			**B**	**HC in deletion carriers**		
		Mean Z-score	*p*-value	N[1]		Mean Z-score	*p*-value	N
all		-0.89	**7.8e-06**	67		0.57	**1.79e-05**	115
	male	-1.09	**1.7e-04**	36		0.68	**9.2e-05**	77
	female	-0.65	**8.5e-03**	31		0.33	**4.03e-02**	38
adult		-1.84	**5.0e-04**	9		1.06	**1.29e-02**	12
	male	-1.92	**2.0e-02**	5		1.19	**2.13e-02**	9
	female	-1.74	**7.8e-03**	4		0.67	2.53e-01	3
< 18 years		-0.85	**2.6e-05**	65		0.51	**1.91e-04**	103
	male	-1.02	**6.1e-04**	34		0.61	**7.18e-04**	68
	female	-0.65	**8.5e-03**	31		0.30	6.1e-02	35

For the *p*-values, the following cutoff control the false discovery rate (FDR) at 5%: HC: 0.0472 (all indicated in bold).

[1] Relatives were excluded if more than one member of the same family was present in the analysis to avoid relatedness

Supplementary Table S9: Malformations (A) and associated symptoms (B) present in duplication carriers ascertained for DD/ID

CNS	Visceral	Cardiac	Uro-genital	Cranio-facial	Osteo-articular
Cerebellar cysts (n=2), cerebellar hypoplasia (n=2), abnormal cerebellar striations (n=2)	Inguinal hernia (n=3)	Ventricular septal defect (n=1)	Hypospadias (n=2)	Metopic craniostenosis (n=1)	Scoliosis (n=4)
Corpus callosum agenesia (n=2), hypoplasia (n=1)	Diaphragmatic hernia (n=2)	Atrial septal defect (n=2)	Ectopic testis (n=7)	Cleft lip/palate (n=4)	Costal malformations (n=1)
Cortical dysplasia (n=2)		Pulmonary stenosis (n=1)			Pectum excavatum (n=2) and carinatum(n=1)
Myelinisation delay (n=2)					

(A) Malformations in 29/101 patients (ascertained for ID/DD, relatives and literature cases included).

Neurological signs	Ophtalmologic	Visceral	Others
Hypotonia (19)	Refraction abnormalities (7)	Constipation (10)	Joint hypermobility (4)
Pyramidal signs (6)	Pigmentary retinitis (1)	Meconial ileus (1)	Asthma (5)
Cerebellar signs (2)	Strabismus (8)	Gastro-esophageal reflux (2)	Delayed puberty (1)
Extra-pyramidal signs (2)			
Epilepsy - Unspecified (12) - Febrile convulsions (4) - West syndrome (3)			
Total: 48	**Total: 16**	**Total: 13**	**Total: 10**

(B) Symptoms in 58/101 patients (ascertained for ID/DD, relatives and literature cases included).

Supplementary Table S10: MLPA assays

Probe Name	Status	Gene	Chr.	Start	End	Band	Size (bp)
chr1_c1orf159	Control	*C1orf159*	1	1009320	1009370	1P36.33	138
chr1_193_M	Control	*MRTO4*	1	19457558	19457612	1p36.13	99
XPO6	Test	*XPO6*	16	28017393	28017455	16p11.2	126
APOB48R	Test	*APOB48R*	16	28414594	28414648	16p11.2	132
ATXN2L	Test	*ATXN2L*	16	28745049	28745104	16p11.2	102
SH2B1	Test	*SH2B1*	16	28791397	28791453	16p11.2	105
SPNS1	Test	*LAT/SPNS1*	16	28898026	28898079	16p11.2	93
RUNDC2C	Test	*RUNDC2D2*	16	29221888	29221941	16p11.2	96
QPRT	Test	*QPRT*	16	29616204	29616262	16p11.2	111
HIRIP3	Test	*HIRIP3*	16	29912953	29913010	16p11.2	114
MAPK3	Test	*MAPK3*	16	30036029	30036089	16p11.2	117
CD2BP2	Control	*CD2BP2*	16	30271431	30271491	16p11.2	123
chr19_575_Z2	Control	*ZNF528*	19	57609990	57610037	19q13.41	90
ZWINT	Control	*ZWINT*	10	57789521	57789580	10q21.1	120
chr11_CNTCN5	Control	*CNTCN5*	11	99378017	99378076	11q22.1	129
chr6_161_1P	Control	*PARK2*	6	161766507	161766563	6q26	108
chr1_238_P	Control	*PLD5*	1	240622416	240622475	1q43	135

Supplementary Table S11: Primers used for quantitative PCR assays

Gene	RefSeq Number	Chromosome co-ordinates*	Oligonucleotide Sequence 5′-3′	
Genes mapping telomeric to the rearranged interval				
IL4R	NM_001008699	chr16:27232752-27274031	F	TTTTCTGCTCTCCGAAGCCC
			R	GCGCCTCCGTTGTTCTCAG
CLN3	NM_000086	chr16:28396102-28410717	F	AGTCACGCTCAGCAATACCGC
			R	GACGCCAGCCTGGTACAGC
ATXN2L	NM_148416	chr16:28741915-28756057	F	ATTTCCAGGAGGAGCCGATGA
			R	CGCGGCCAGGACAATCTTC
SH2B	NM_015503	chr16:28782815-28793027	F	TCCTGCACCCTCATGCCC
			R	GAGGTGGTCGGTTACACAGTCACT
LAT	NM_014387	chr16:28903888-28909597	F	AAGACTGAGCCTGCCGCC
			R	CCTCTTCCTCCACTTCCTCTGC
Genes mapping within the rearranged interval				
QPRT	NM_014298	chr16:29597942-29616813	F	CTCCAGTGCCCAAAATCCAC
			R	GCCGGTGTCATCCTCTTCC
MAZ	NM_002383	chr16:29725514-29729986	F	GGATCAGAGCTGTCCCAAAGAG
			R	CTGCCCCTCCTCAAACCTC
PPRT2	NM_145239	chr16:29730910-29734703	F	CTCCCGTCACCGTTTACTCTG
			R	CCAAGCCTCGTCTAAGTGCTGT
C16orf53	NM_024516	chr16:29735333-29738935	F	GGCTCTCTCCCGGAAACTTAG
			R	TTTGCAGGCCTCACTTCTGAC
MVP	NM_017458	chr16:29739289-29766843	F	GCCTTGGCCATTGAAACG
			R	TCGGACCTTCTGGACCCTCT
CDIPT	NM_006319	chr16:29777180-29782012	F	TTTCTCTGAGGGACCTTTAGTTGG
			R	AGGCCCATCCGGAACAGT
SEZ6L	NM_201575	chr16:29790332-29818074	F	GTGGAGTCGGACTTCAGCAAC
			R	CTCCCGCGTATCCCCAG
KCTD13	NM_178863	chr16:29825161-29845046	F	GGCCTGATTGAGGACTGCC
			R	CAGCGTCTCCCTTTTTTGCT
TMEM219	NM_194280	chr16:29880852-29891874	F	GTCTCACGTCGTGGGCTTG
			R	TCTGGACCGTCTCCGAAGTT
TAOK2	NM_004783	chr16:29892723-29911082	F	CCTTCGGACCTCTAGACAGGC
			R	TGACTGCTGGACTCCACAGCT
HIRIP3	NM_003609	chr16:29911818-29914888	F	ATCATCAGTGGCTCGGGC
			R	TCCTAAAGGGTTCCAGGCTGT
DOC2A	NM_003586	chr16:29924336-29929902	F	TGGACGTCAACGGTTACTCG
			R	CGGGCCTCAGGTACGTCTT
FAM57B	NM_031478	chr16:29943250-29949405	F	CCTGCCATGTCCCTGGTG
			R	CCCAGATTGGAGGAAGCCTT
PPP4C	NM_002720	chr16:29994885-30004196	F	GTGTGCGGCGACATCCA
			R	GACGTCGCCACCTACTCTGAAC
INO80E	NM_173618	chr16:30007531-30017112	F	ACTCTTCGGACTCAGATGCCAC
			R	CCTCCGTCTCGCTGTTATCTGAT
YPEL3	NM_031477	chr16:30011136-30015022	F	TGCGAGAACTGCAAGACCAC
			R	TGCTCTCAAAGGCCTGTTCATAT
GDPD3	NM_024307	chr16:30023633-30032359	F	TTTACTTCTCTCCAGGCCACTTTG
			R	GAACCATGCGCCGGTCT
MAPK3	NM_002746	chr16:30032928-30042039	F	AGATCATGCTGAACTCCAAGGG
			R	CACAGACCAGATGTCGATGGAC
CORO1A	NM_007074	chr16:30102449-30107898	F	GGAGGTGTGAGCCCATTGC

			R	TGGAACAGGTCCGACTTTCG
Genes mapping centromeric to the rearranged interval				
SEPT1	NM_052838	chr16:30296958-30301672	F	CGTGGAGGTGGAGAACCCAC
			R	CATCCGTCGCAGGTTCAGG
ZNF688	NM_145271	chr16:30488526-30490508	F	AAAGACTGGGAGGAGCTCGG
			R	CCTCTTCCTTCCTGTTTGGGAC
BCL7C	NM_004765	chr16:30806619-30812900	F	GAGAAGGTCCGGAGATGGGAGA
			R	GGAAGTGTCGCCCACAGTCAC
Normalizing genes				
Hs *EEF1A1*	NM_001402	chr6:74283962-74287475	F	CTGAACCATCCAGGCCAAAT
			R	GCCGTGTGGCAATCCAAT
Hs *RPL13*	NM_033251	chr16:88154632-88157349	F	AGGTATGCTGCCCCACAAAA
			R	TGCCGTCAAACACCTTGAGA
Hs *GUSB*	NM_000181	chr7:64869825-64891346	F	CCACCAGGGACCATCCAAT
			R	AGTCAAAATATGTGTTCTGGACAA AGTAA
Hs *TBP*	NM_003194	chr6:170781103-170799578	F	GCCCGAAACGCCGAATATA
			R	CGTGGCTCTCTTATCCTCATGA

- From UCSC Genome Browser, Human May 2004 (NCBI35/hg17) Assembly

Supplementary Table S12: Cell lines used for gene expression analysis

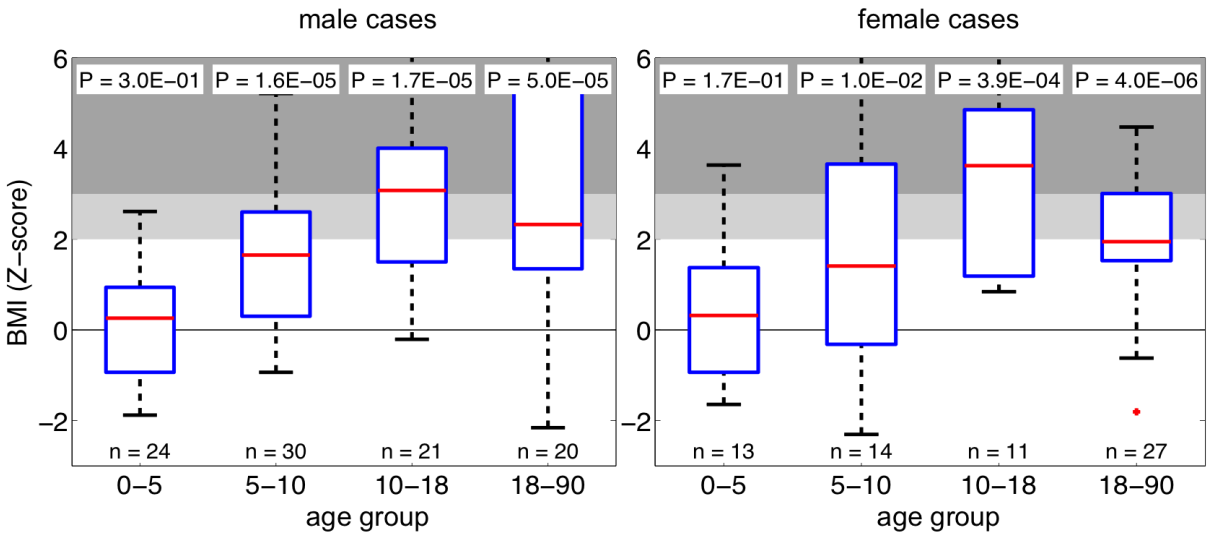
Cell Line Name	Sex	Age
Deletions:		
BOCOL	F	12
DEDAV	M	35
DEFRA	F	31
LESAN	F	38
VUCAT	F	43
VULOI	M	19
Duplications:		
BONAD	F	8
DAANA	F	17
DASYL	F	50
FRANG	F	9
FRPAT	F	44
Controls*:		
GM12042	F	10
GM12148	M	34
GM11983	F	29
GM10847	F	38
GM10859	F	41
GM13072	F	4
GM07694	F	17
TILSHA	F	57
GM07010	F	8
GM07348	F	45

*Cell lines with a GM prefix were obtained from Coriell Institute for Medical Research (http://www.coriell.org/)

Supplementary Table S13: mRNA levels of genes at the 16p11.2 locus

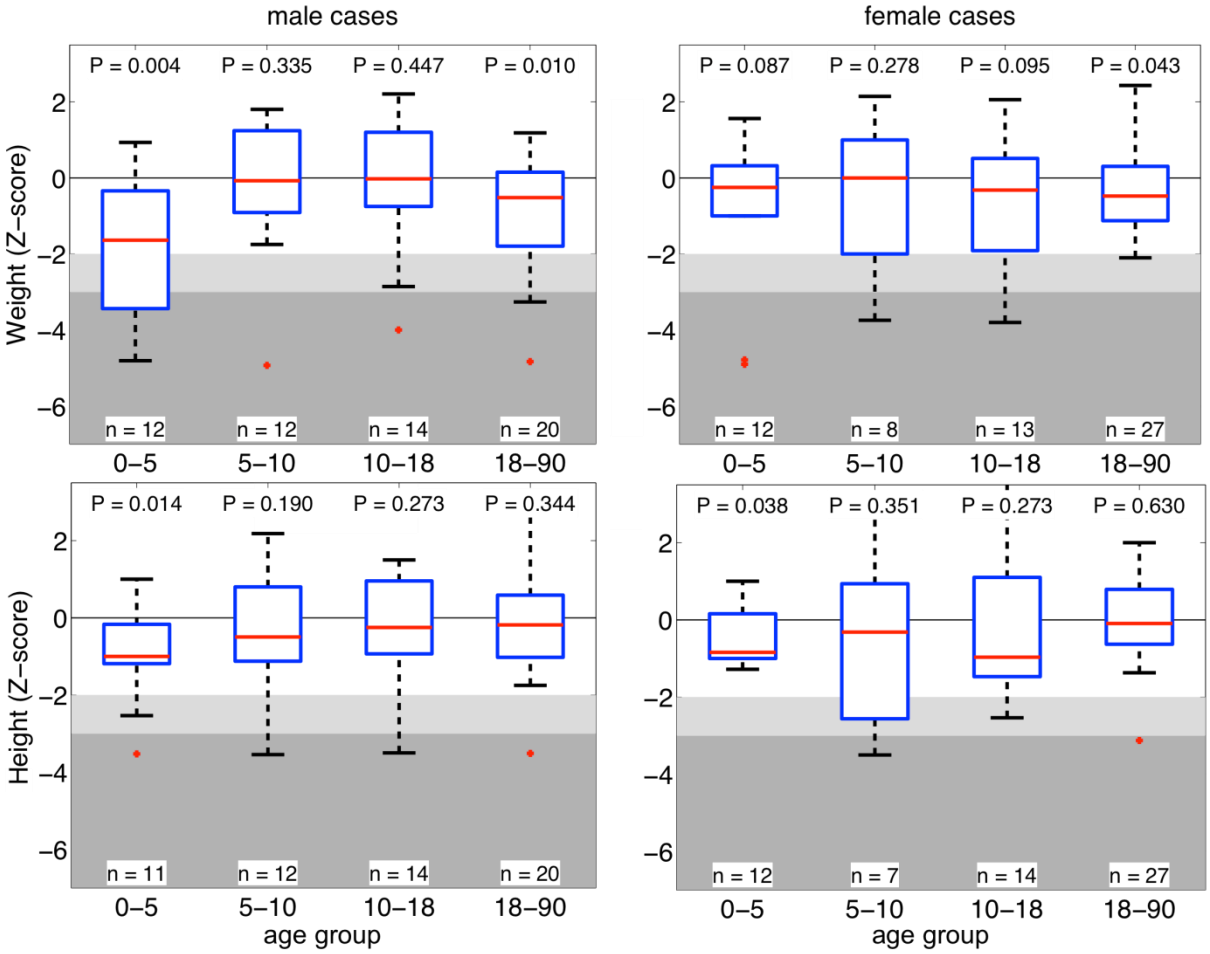
	Mean Relative Gene Expression (Standard Error)		
	Telomeric genes	Genes within CNV	Centromeric genes
Controls	0.83 (0.06)	1.02 (0.03)	0.95 (0.02)
Deletions	1.35 (0.12)	0.68 (0.02)	1.07 (0.07)
Duplications	2.49 (1.12)	2.18 (0.09)	1.24 (0.01)
	Excluding *LAT* outlier: 1.48 (0.11)		

Supplementary Figure S1: Effect of the 16p11.2 deletion on BMI.



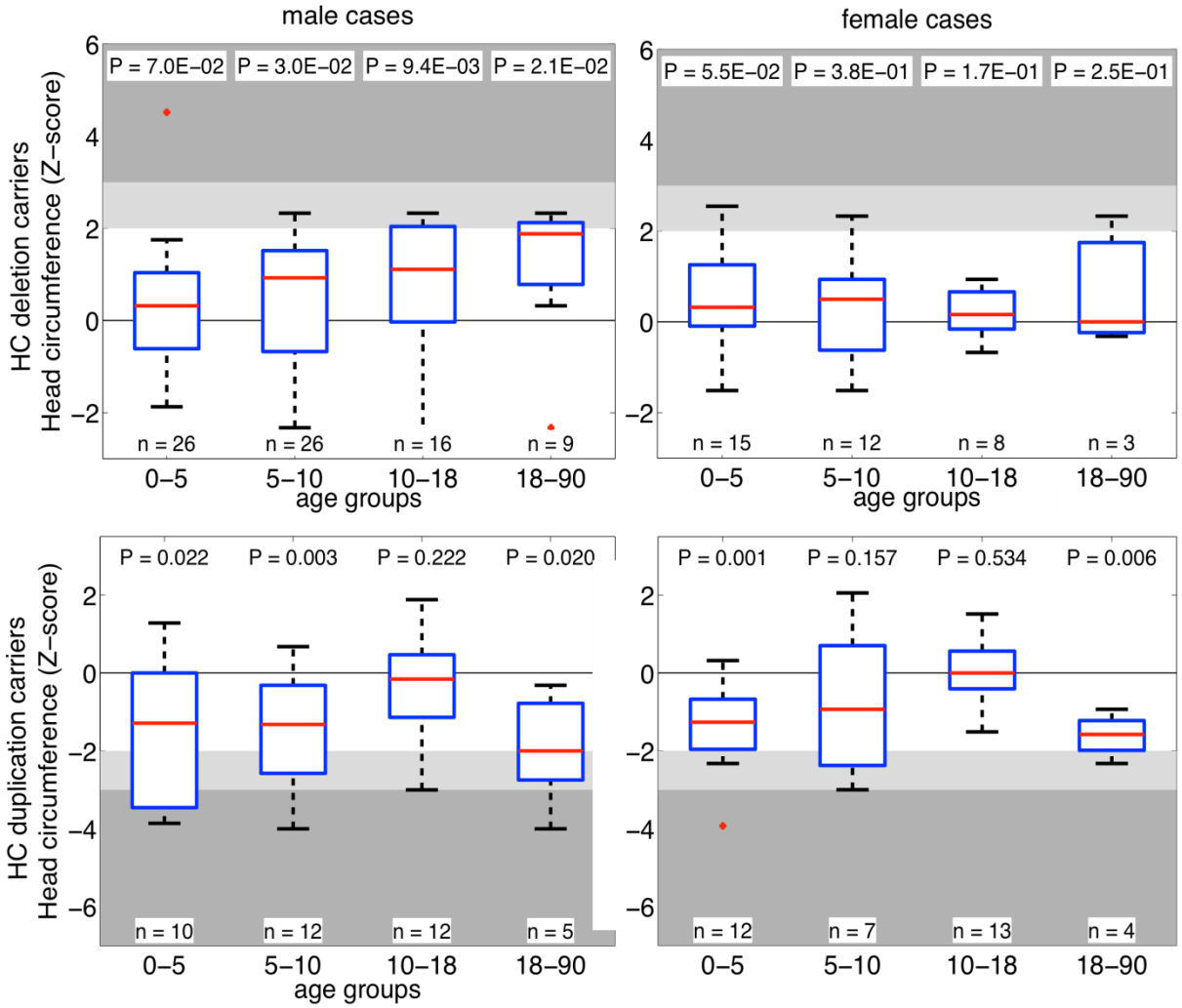
Legend: Z-score values of 16p11.2 deletion carriers' BMI stratified by age group. Abscise: age groups in years. Boxplots represent the 5th, 25th, median, 75th and 95th percentile for each age group. Light and dark grey represent +2 and +3 SD respectively.

Supplementary Figure S2: Effect of the 16p11.2 duplication on weight and height.

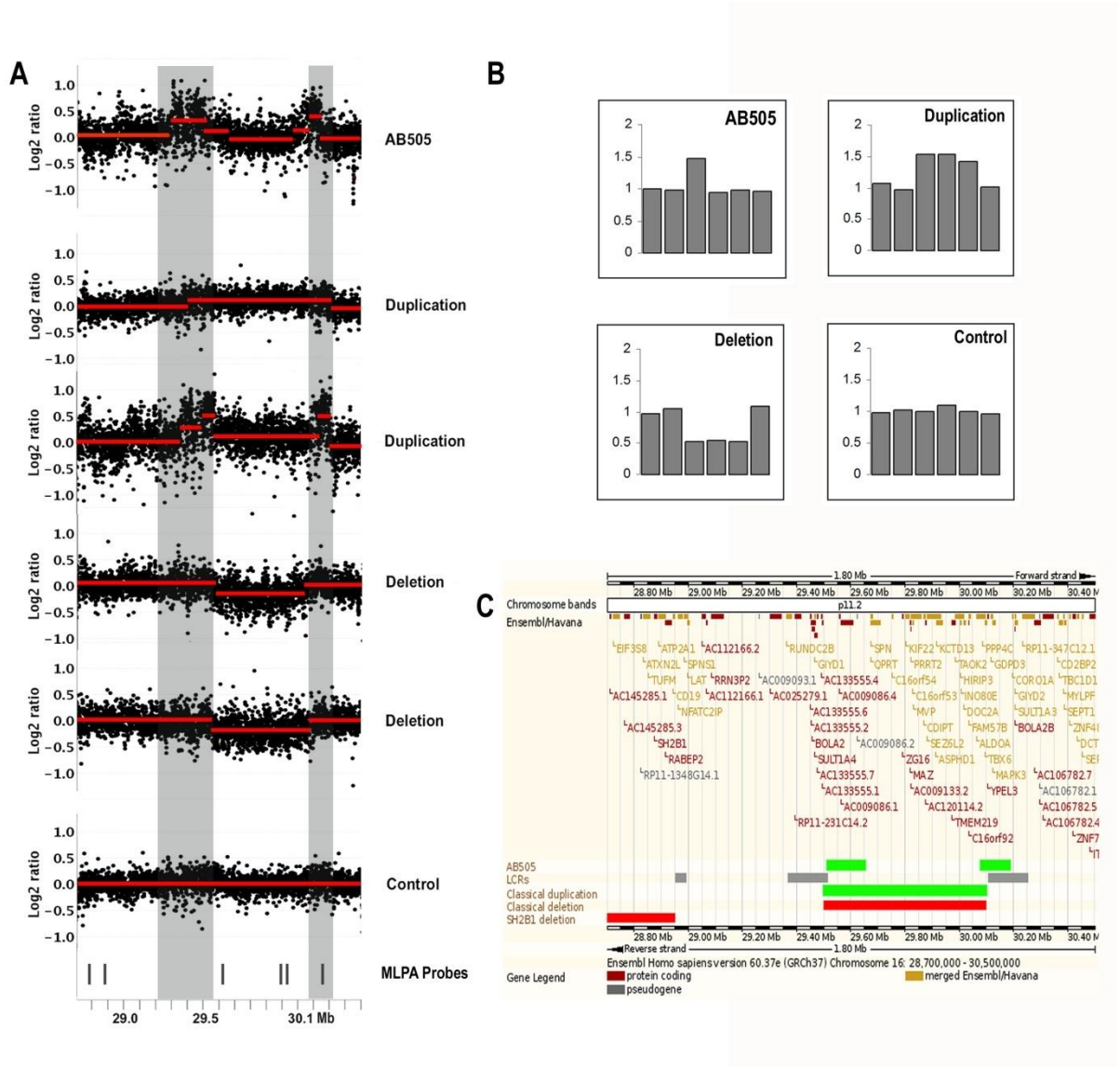


Legend: Z-score values of weight (top row panels) and height (bottom row panels) of 16p11.2 duplication carriers stratified by age group. Abscise: age groups in years. Boxplots represent the 5th, 25th, median, 75th and 95th percentile for each age group. Light grey and dark grey represent -2 and -3 SD respectively.

Supplementary Figure S3: Effect of the 16p11.2 CNV on head circumference (HC) in carriers of the both rearrangements.



Legend: Z-score values of head circumference (HC) of 16p11.2 deletion (top row panels) and duplication (bottom row panels) carriers stratified by age group. Abscise: age groups in years. Boxplots represent the 5th, 25th, median, 75th and 95th percentile for each age group. Light and dark grey background represent the 2nd and 3rd SD. Macrocephaly and microcephaly are clearly present in deletion and duplication carriers respectively.



Supplementary Figure S4: aCGH and MLPA of the 16p11.2 region

(A) Examples of custom-array CGH results for the 16p11.2 region from 28.7 to 30.5 Mb. Anorexic case AB505, two duplication cases, two deletion cases and a control case are shown from top to bottom. Grey bars indicate the location of the low copy repeats (LCRs) situated either side of the rearranged interval. **(B)** Gene dosage for 6 MLPA probes. Probe location is shown by grey bars at the bottom of **A**. **(C)** Ensembl screenshot of the genes mapping within the 16p11.2 area. The tracks at the bottom specify the extent of the duplications in anorexic case AB505 (green) (16:29,514,638-29,650,991), the LCRs (grey), the extent of the classical deletion (green) and duplication (red) and the smaller 200 kb deletion situated around the *SH2B1* gene [18] (red).

References

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