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Highly penetrant alterations of a critical region including *BDNF* contribute to human psychopathology

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Abstract

CONTEXT—Brain-derived neurotrophic factor (BDNF) is suspected of being a causative factor in psychiatric disorders based on case reports or studies involving large structural anomalies.

OBJECTIVE—To determine the involvement of *BDNF* in human psychopathology

DESIGN—Case- Control study

SETTING—Microarray-based comparative genomic hybridization (aCGH) data from seven molecular diagnostic centers including 38, 550 affected subjects and 28, 705 unaffected subjects.

PATIENTS—Subjects referred to diagnostic screening centers for aCGH for physical or cognitive impairment.

MAIN OUTCOME MEASURE—Genomic copy number gains and losses

RESULTS—We report five individuals with psychopathology and genomic deletion of a critical region including *BDNF*. The defined critical region was never disrupted in control subjects or diagnostic cases without developmental abnormalities.

CONCLUSION—Hemizygosity of the *BDNF* region contributes to variable psychiatric phenotypes including anxiety, behavioral, and mood disorders.

Introduction

BDNF (brain-derived neurotrophic factor) is a nervous system growth factor that plays a critical role in synaptic modeling, neurodevelopment, and cell signaling[1]. It is a member of the nerve growth factor (NGF) family with structural similarity to NGF and neurotrophin 3/4, and structural differences distinct from the other nervous system growth factor families which include fibroblast growth factor, insulin-like growth factor, transforming growth factor-beta, and cytokine families[2]. While all nervous system growth factors support neurodevelopment, BDNF has been singularly implicated for its role in obesity, pain, and memory[3–7]. The protein is encoded by *BDNF*, located on the short arm of chromosome 14 at band p14, where a polymorphic variant at codon 66 specifies either Valine or Methionine and is thought to affect processing of proBDNF to BDNF. This locus has been considered as a risk factor for schizophrenia, major depression, ADHD, bipolar disorder and many other psychopathologies[8, 9], primarily from association-based studies evaluating the non-synonymous Val66Met variant and studies comprising cases with deletions on 11p associated with deletions in *WT1* and *PAX6*[10, 11].

BDNF sequencing studies in psychiatry and genomic copy loss studies support a link between *BDNF* with behavior and obesity. WAGR syndrome, a deletion syndrome of the short arm of chromosome 11 associated with Wilms tumor, aniridia, genitourinary anomalies and mental retardation in which deletions include *PAX6* and *WT1*, sometimes

includes larger deletions extending to *BDNF*. Two recent studies associated subjects with WAGR syndrome, with deletions extending to *BDNF*, with obesity, bipolar disorder, or ADHD[10, 11]. In support of a psychiatric phenotype due to copy loss at the *BDNF* locus, two independent case reports (three subjects in total) described obese patients who presented with complex neurobehavioral phenotypes[12, 13]. Further, a deep re-sequencing study of *BDNF* exons and flanking regions from subjects with major depression (MD) and controls, revealed several novel variants associated with MD, suggesting that genetic variation in *BDNF* may have an impact on mood[14].

Molecular studies in rodents have supported a role for *Bdnf* in behavior, in particular through the finding that defective neuronal release of BDNF by *in vivo* knock-down leads to increased anxiety-like traits in mice[15, 16], while heterozygous *Bdnf* knock-out mice do not display anxiety traits[17], they are reported to be more aggressive and hyperphagic than wild-type mice[18]. *BDNF* has also been shown to have a key role in mediating social defeat stress in rodents[19], in particular, it is required for the development of experience-dependent social aversion[15]. With respect to sensory systems, homozygous *Bdnf* knock-out mice show sensory deficits with decreased survival of sensory ganglia while sparing motor neuron development[20, 21], in line with data from human WAGR patients with a *BDNF* deletion that suggest a deficit in nociception[11]. Together, data from rodents suggests that whole-organism deletion of *BDNF* leads to behavioral, sensory, and weight alterations, while deletion of *BDNF* specifically in brain areas associated with behavior lead to anxiety and aggression.

In view of the large number of association studies with suggestive evidence for *BDNF* polymorphisms in psychopathology, case reports describing large genomic alterations involving *BDNF* in subjects with psychiatric symptoms, and extensive phenotyping in animal models, we sought to better resolve the relationship between *BDNF* and psychopathology by identifying subjects with genomic copy number changes that include *BDNF*.

Methods

Table 1 summarizes all subjects used in this study. From Signature Genomics (SG), we analyzed a total of 26,144 probands studied using oligonucleotide-based whole-genome array-Comparative Genomic Hybridization (aCGH), using either a 105K-feature platform (SignatureChipOS version 1.0, custom-designed by SG, manufactured by Agilent Technologies, Santa Clara, CA) or a 135K-feature platform (SignatureChipOS version 2.0, custom-designed by SG, manufactured by RocheNimbleGen, Madison, WI), according to previously described methods[22, 23]. From this initial cohort, we divided subjects into those referred with an indication of a neurodevelopmental disorder (n = 14,616) and those referred with an indication for study that did not involve a known neurodevelopmental abnormality (n=11,528). Unlike the microarrays used to analyze controls, these specific SG platforms are incapable of detecting intragenic *BNDF* variations and are limited to whole-gene *BDNF* deletions, at a resolution of approximately 270 kb and 120 kb, respectively. The ethnic distribution in the samples from Signature Genomics Inc. was estimated from a sampling cross section previously described[24]. This sample (n=144 subjects, self reported) was composed of 75% Caucasian, 7% African-American, and 18% other. The gender distribution was 59% male, 41% female. The only alterations spanning *BDNF* observed in the SG group were WAGR syndrome patients (N=2), so there was no contribution to these analyses from this dataset, although they are included in all statistical analyses. The ethnicity of each patient described here with a copy gain or loss of *BDNF* was Caucasian.

The clinical cytogenetics laboratory at The Hospital for Sick Children in Toronto, Canada screened patients using either Agilent 4×44K array[25] or the 4×180K ISCA v2 microarray

manufactured by Agilent and designed by Oxford Gene Technologies. Previously published CNV data from 11,509 controls genotyped with high resolution SNP microarrays were compiled from several subject groups including: 1,234 Affymetrix 6.0 controls from Ottawa[26], 1,123 Affymetrix 6.0 controls from POPGEN[26], 4,783 WTCCC Affymetrix 6.0 controls from WTCCC[27], 1,056 HapMap3 Affymetrix 6.0 controls[28], 1,287 Illumina 1M data from SAGE controls[29], and 2,026 Hap550k controls[30].

From the Developmental Genome Anatomy Project (DGAP) database (www.dgap.harvard.edu), we had access to information on 221 subjects, all of whom had a balanced chromosomal rearrangement. Identification of *BDNF* hemizygosity in one of these subjects (DGAP173) was assessed by an Agilent G3 1M array. Based on available karyotype information (t(2;11)(q11.2;p13), this deletion appears to be independent of the chromosomal rearrangement but we cannot rule out a more complex rearrangement involving both regions. Array processing for all other clinical diagnostic centers was done using commercially available Agilent 244K arrays, except for the Mayo Clinic, which used 180K Agilent arrays.

Control individuals were obtained from a variety of sources listed above as well as control data from the International Schizophrenia Consortium[31], the Database of Genomic Variants[32] (filtered for overlap with other studies), and those described and publicly available from Cooper and colleagues[24], filtering WTCCC controls to avoid redundancy with the above control set. Table 1 describes these control subjects in more detail. All genomic coordinate positions are with reference to the human genome reference 18 (hg18). Statistical analyses were performed using Fisher's exact test in the statistical package R.

Clinical diagnoses from all patients were performed by independent, qualified physicians who had seen the patient over a period of at least two years. We defined obesity as either BMI >30 kg/m^2 or if it was specifically indicated by the primary caregiver. We defined overweight as a BMI >25 kg/m^2. Psychiatric diagnoses were done using DSM-IV criteria by caregiver interviews with affected subjects. In all *BDNF* deletion cases, referring physicians were contacted and provided clinical information for all subjects, allowing for psychiatric phenotyping.

These studies were approved by the Institutional Review Boards of our institutions, and all caregivers for each subject gave informed consent.

Results

We screened microarray-based comparative genomic hybridization (aCGH) data for over 38,000 subjects from clinical diagnostic centers at Children's Hospital Boston, The Hospital for Sick Children Toronto, the Mayo Clinic, Brigham and Women's Hospital Boston, Manchester Academic Health Sciences Center, St. Justine Hospital Montreal, and Signature Genomics, Inc., for any subjects with copy number changes of the *BDNF* region (see Table 1 for complete description of all subject groups). We identified five subjects with deletions encompassing the entire *BDNF* gene and one subject with a duplication spanning *BDNF* (Figure 1 and Table 2). For all subjects, aCGH was used to initially identify *BDNF* copy changes and Figure 2 shows a visual example of aCGH data in subject 2 from this study. The deletion group displayed varied phenotypes that included neurodevelopmental, behavioral and mood disorders, in addition to being obese or overweight and insensitive to pain in some cases, as summarized in Table 2 and presented in greater detail below. The subject with a duplication also presented with developmental delay and dystonia, but no further information was available. Additional subjects identified with WAGR syndrome were excluded from this analysis (N=2 subjects from Signature Genomics) due to the very

large number of genes in WAGR deletions, the severity of the associated neurodevelopmental phenotype[33], and the inability to obtain any follow-up information on these subjects.

Subject 1 was identified with a *BDNF* deletion at chr11:22,858,513–29,066,320 and a small deletion at chr19: 61453936–61530271 intersecting the testes-specific gene *ZSCAN5A*. The 10-year-old male has been diagnosed with pervasive developmental disorder not otherwise specified, attention deficit hyperactivity disorder (ADHD), anxiety, behavioral issues (e.g., constantly hitting head against the wall), and mood dysregulation. At four years of age, his condition regressed markedly and to date he has been treated with escitalopram (Lexapro), aripiprazole (Abilify), citalopram (Celexa), guanfacine (Tenex), methylphenidate (Ritalin), atomoxetine (Strattera), and clonidine. His height and weight at age nine were 138.7cm and 43.5kg (95^{th}–97^{th} percentile), respectively, with a BMI of 22.6 (see online-only Figure S1 for a weight chart for this subject taken at different time points showing a progression towards obesity). He is extremely aggressive and parental report notes that the subject does not complain of pain when accidents occur. Array results were confirmed using clinically available Multiplex Ligation-dependent Probe Amplification probes targeting *BDNF* (MRC-Holland; SALSA MLPA P219).

Subject 2 (DGAP173) is a 21-year-old female with a karyotype of 46,XX,t(2;11)(q11.2;p13) who also has a 2.5Mb deletion (Chr11: 27, 050, 622–29, 550, 113) on chromosome 11 that includes *BDNF* (Figure 2). Array CGH results were confirmed using clinically available Multiplex Ligation-dependent Probe Amplification probes targeting *BDNF*. She has mild developmental delay (combined language and motor delay), major depression, generalized anxiety, sleep disturbance (sleep apnea), self-injurious behaviors, agitation, and tantrums. In 2009 at age 19, she weighed 167.6 kg and had a height of 180.1cm, with a body mass index of 51.7. Her head circumference was 61cm, which is outside of the normal adult range of 55–58cm. She has male pattern hirsutism (thought to be associated with a tentative diagnosis of polycystic ovarian syndrome, maternally inherited) and has had only a single period with no further menstruation even with trials of oral contraceptive pills. Impaired glucose tolerance without evidence of type 2 diabetes, poor lipid profile with elevated triglycerides and total cholesterol and low HDL, elevated testosterone, some deepening of the voice, and history of one non-febrile seizure at two years of age, were also noted. Her skin was remarkable for eczema, moles, and skin tags. She has dysmorphic features including bilateral epicanthal folds giving a saddle appearance to the nasal bridge, a small nose, complex malocclusion with upper teeth more narrow and frontal than lower. Morphologically, she has somewhat short hands, slightly hyperkeratotic and sweaty palms, fifth finger brachydactyly and clinodactyly, minor extension limitation of the right elbow, hypoplastic toenails, short feet, and copper-colored verrucous lesions in intertriginous regions (acanthosis nigricans versus epidermal nevi) present on the back, chest and neck.

Subject 3 was identified with a maternally inherited deletion at chr11:23,484,198–27,857,928. He was referred for investigation at 2 years 9 months of age for severe receptive and expressive speech delay. He has impaired social, play, and behavioral skills as well as global developmental delay and a duplex left kidney. He is a large child with weight of 29.3 kg, height of 103.5 cm and a BMI of 27.4, all of which are greater than the 97^{th} percentile. His head circumference is 52 cm, which is considered within the normal range at age 2.75 years, but is at the 94^{th} percentile. Family history is of note in that his mother has intellectual difficulties. Her height was 171 cm and weight of 114.3 kg and BMI of 39.5. No further information is available for her. *FISH* analysis confirmed she has the same deletion. Maternal grandparents are of normal intellect and growth, and *FISH* analyses were normal.

Subject 4 is a 16 year-old male whose 36-week gestation was notable for the umbilical cord being wrapped around his neck. 180K Agilent microarray screen revealed a chr11:23,002,186–27,956,720 (HG18) de novo deletion. He has hypercholesterolemia, a fatty liver, hypertension, and is prediabetic. At an assessment done at age 16, he was 151 kg, 1.73 meters, and had a BMI of 50.1. He has speech delay and pervasive developmental disorder, an IQ/DQ of 58. With respect to psychopathology, he has been diagnosed with an adjustment disorder (mixed disturbance of emotion and conduct) depressive disorder, and anxiety disorder. *FISH* confirmed the array results using RP11–1150I2.

Subject 5 is male with a disruption in *BDNF* (chr11:25,649,116–31,566,599). No other genetic anomalies were detected in this subject, initially ascertained through learning difficulties, severe speech and language delay, and obesity (BMI 28.3 at 5 years 10 months; >97th percentile). He has a statement of special educational need and at 4.5 years his overall general conceptual ability is limited (score on the British Abilities Scale BAS II was 47 (<0.4%ile) in keeping with a severe learning disability); he was reported to be able to write his name at six years of age. He has poor fine motor skills and poor problem solving skills. With respect to sensory systems he has hyperacusis and a high pain threshold. He is described as having inappropriate toddler-like tantrums triggered by not getting his own way or not being able to eat when he wishes. He has sleeping difficulties and is currently taking melatonin. A strengths and difficulties questionnaire completed by his teacher at age five years noted very high scores for overall stress, hyperactivity and attentional difficulties and high scores for difficulties getting along with other children.

Subject 6 has a *BDNF* duplication and was indicated for screening because of developmental delay and dystonia (chr11:27,179,904–28,837,666). No further information was available on this subject.

There was a notable relationship between age and BMI in subjects with a *BDNF* deletion, strongly supporting a role for a deletion in this region and obesity. Specifically, while all subjects were overweight at a young age, older subjects had even higher BMIs, suggesting a progression towards increasing obesity (BMI vs age, Pearson = 0.86, p=0.06), with a particular increase after the later teen years (Figure 3). We were able to further support the hypothesis that people with a *BDNF* deletion have increased BMIs over time by acquiring data from a single subject (subject 1) who received multiple assessments over time. Supporting on-line figure S1 shows the increase in BMI over time compared to age standards.

While each of the *BDNF*-containing deletions reported here disrupted multiple genes, the critical region of overlap included only *BBOX1, CCDC34, LGR4, BDNF* and *LIN7C* (Figure 1). We therefore attempted to narrow the critical region responsible for the mood and behavior phenotypes by examining structural variations in datasets from individuals without a comparable phenotype. We found no structural variations affecting *BDNF* in CNV data from 28, 705 control individuals with high resolution chromosomal microarrays (Figure 1 and Table 1), despite the superior resolution of these platforms relative to those used to analyze most of the cases. There was also no disruption of the BDNF locus from clinical diagnostic cases not reported to have a neurological abnormality (n=11,528) assayed through SG's Genoglyphix Chromosome Aberration Database. Collectively, though disruption of this locus was rare, we find a nominally significant burden of dosage alterations spanning *BDNF* in cases compared to all controls (Fisher's exact test p = 0.042) as well as the combination of controls and clinical diagnostic cases without a neurodevelopmental abnormality (n = 40, 233; p = 0.014). Similar results were obtained if we restricted analyses to only those cases with deletion of the locus (p = 0.076 and 0.028, respectively). There was evidence for deletion of *BBOX1*, as well as for duplication of

BBOX1, CCDC34 and *LGR4*, though there were no disruptions of *LIN7C*. *CCDC34* has previously been reported as disrupted in a case of translocation[34] without an associated neurodevelopmental phenotype. Taken together, these findings indicate that deletions encompassing *BDNF* are rare, but when they occur they are highly penetrant in producing a distinct phenotypic spectrum which includes behavioral/psychiatric traits due to alterations in *BDNF, LIN7C, LGR4* or some combination of these genes.

Comment

This study represents the largest and highest genomic resolution study to date investigating the role of *BDNF* in psychopathology. Previous reports identified single cases with large deletions encompassing *BDNF* or cases with *BDNF* deletions and WAGR syndrome, where one study identified four different WAGR syndrome subjects with behavioral disturbances[10]. The current study included over 38,000 probands collected internationally and found five subjects with *BDNF* deletions with heterogeneous, but always psychiatric, phenotypes. Despite being the most extensive study to date of the role of *BDNF* in psychopathology, this study should be considered supportive of the role of *BDNF* in psychopathology and not unequivocal, as the critical region included two other potentially causative genes affected in all *BDNF* deletion cases. Nonetheless, animal data and analysis of the function of these two genes in the critical region strongly suggest that *BDNF* hemizygosity leads to psychopatholgy.

Mouse studies of *LGR4* and *LIN7C* orthologues suggest a less central role for these genes in behavior. *Lgr4* knock-out mice show embryonic lethality, thought to be due to its fundamental role in organogenesis, particularly of the kidney and the sex organs[35, 36]. Subject 3 in our study had a duplex left kidney and subject 2 had polycystic ovary syndrome. Notably, expression of *Lgr4* is largely absent from brain except in the olfactory bulb and periventricular area; expression is highest in kidney, gall bladder, heart, bone and spinal cord[37]. Thus, *LGR4* hemizygosity is unlikely to contribute to psychopathology in humans, but could account for other observed abnormalities. *Lin7c* (aka *MALS-3*) has a role in maintaining cell polarity during development in the mouse[38] though two paralogues, *Lin7a* and *Lin7b*, are suspected of being able to compensate for *Lin7c* deficiency[39]. Distribution of *Lin7c* expression in mouse brain is low compared to *Lin7a* and *Lin7b* and is restricted to the dentate gyrus, cerebellum, and superior colliculus. In contrast, *Lin7a* and *Lin7b* are abundantly expressed in other brain regions, especially cortex and dentate gyrus[39]. While this expression pattern does not suggest a primary role for *LIN7C* hemizygosity in psychopathology, such a contribution, alone or in interaction with *BDNF*, cannot be excluded.

The presence of psychiatric manifestations in subjects with *BDNF*-associated deletion is consistent with previously reported cases, as delineated in Table 2, along with their associated neurodevelopmental and behavioral phenotypes. Taken together, this collection of subjects support the conclusion that gross disruption of *BDNF* in humans is associated with psychopathology, being obese or overweight, and, at least sometimes, pain insensitivity - phenotypes consistent with data from manipulation of *Bdnf* in rodents. No information was available for three deletion subjects with respect to pain insensitivity (one of the subjects with a *BDNF* deletion is reported to engage in self-injurious behavior, a phenotype frequently associated with pain insensitivity in individuals with intellectual disability[40]), so we cannot draw a conclusion concerning the universality of pain insensitivity, but follow-up studies are warranted. Both the overweight/obese and nociceptive phenotypes in humans are also supported by a study of WAGR patients; while those with deletions that extended to *BDNF* were more likely to be obese and insensitive to pain[11] than those without *BDNF* deletion.

The consensus phenotype for individuals with a deletion in *BDNF* suggests that young children are hyperactive, anxious, and have an intolerance to change. As subjects age, they likely develop more pronounced anxiety and mood disorders, exemplified by the 16 year-old and 21 year-old subjects with major depressive disorder and generalized anxiety disorder, and by a 25 year-old female with mood disturbances from a previous report[12]. Identification of a single locus that may be linked to major depression or anxiety highlights the heterogeneity of these psychiatric diseases - most subjects with major depression do not have deletions in *BDNF* for example - and the need to possibly re-assess how clinical categorization proceeds[41].

Chromosomal aberrations at genomic loci that associate with mental retardation are common, but hemizygosity of a locus that can affect a spectrum of phenotypes including mood is less common, and the mechanisms that could contribute to such phenotypic diversity remain to be elucidated. Deeper investigation of the regulation of *BDNF* and of the molecular actions of the transcribed product will be required to better understand how hemizygosity at this locus contributes to psychopathology.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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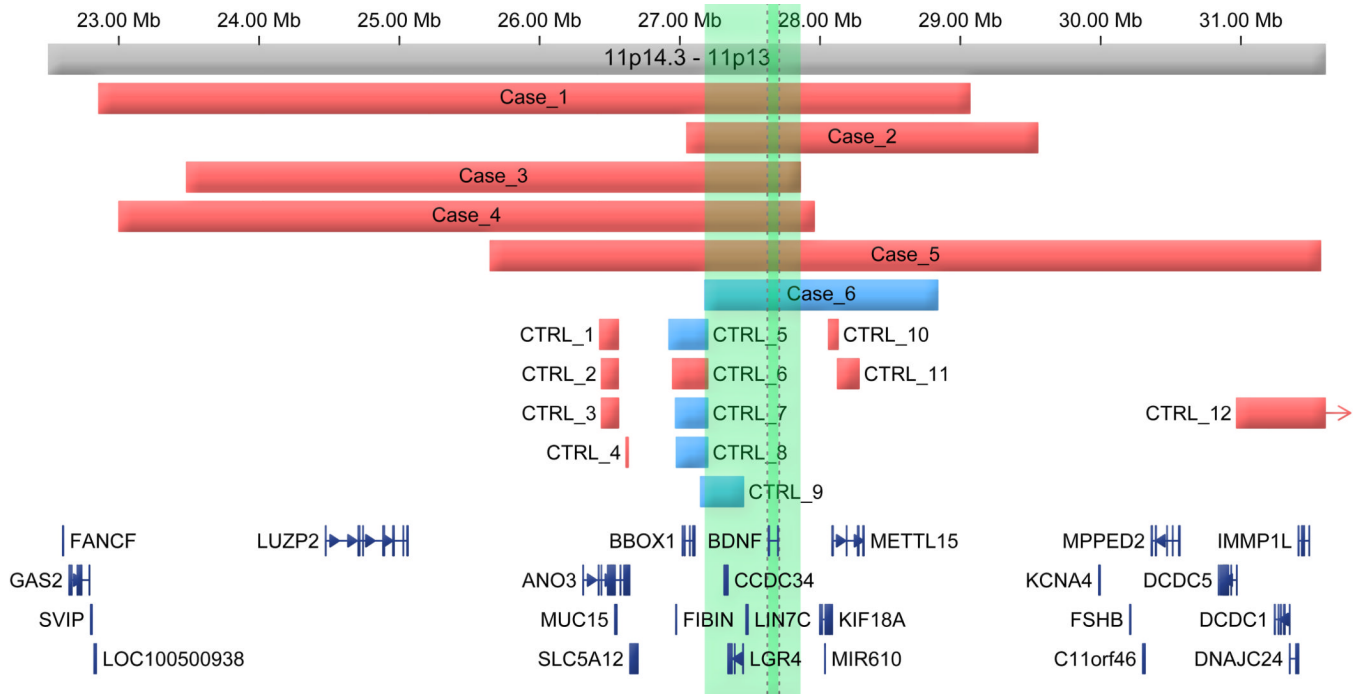

Figure 1. All cases and controls (CTRL) with copy gains (blue) or losses (red) near the *BDNF* locus

Megabase marks (Mb) represent hg18 build coordinates. Green shading represents identified critical region while darker green shading corresponds specifically to the genomic location of *BDNF*.

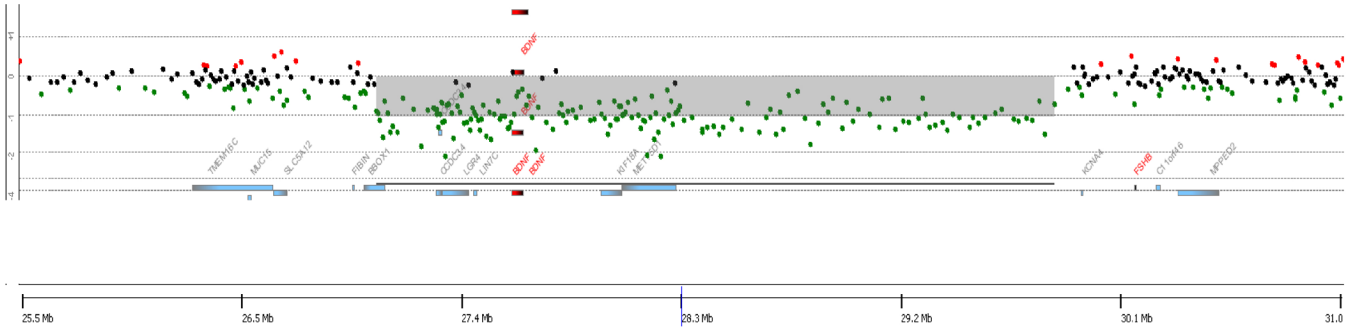

Figure 2. A ~2.5 Mb deletion in Subject 2, including *BDNF*

aCGH results demonstrating a deletion on chromosome 11. Gray shading represents the predicted size of the deletion, while individual probes from the array are represented by dots colored black, green, or red. Probes colored green represent decreased probe intensity from DNA from Subject 2, reflecting copy loss. hg18 build coordinates are shown on the X-axis.

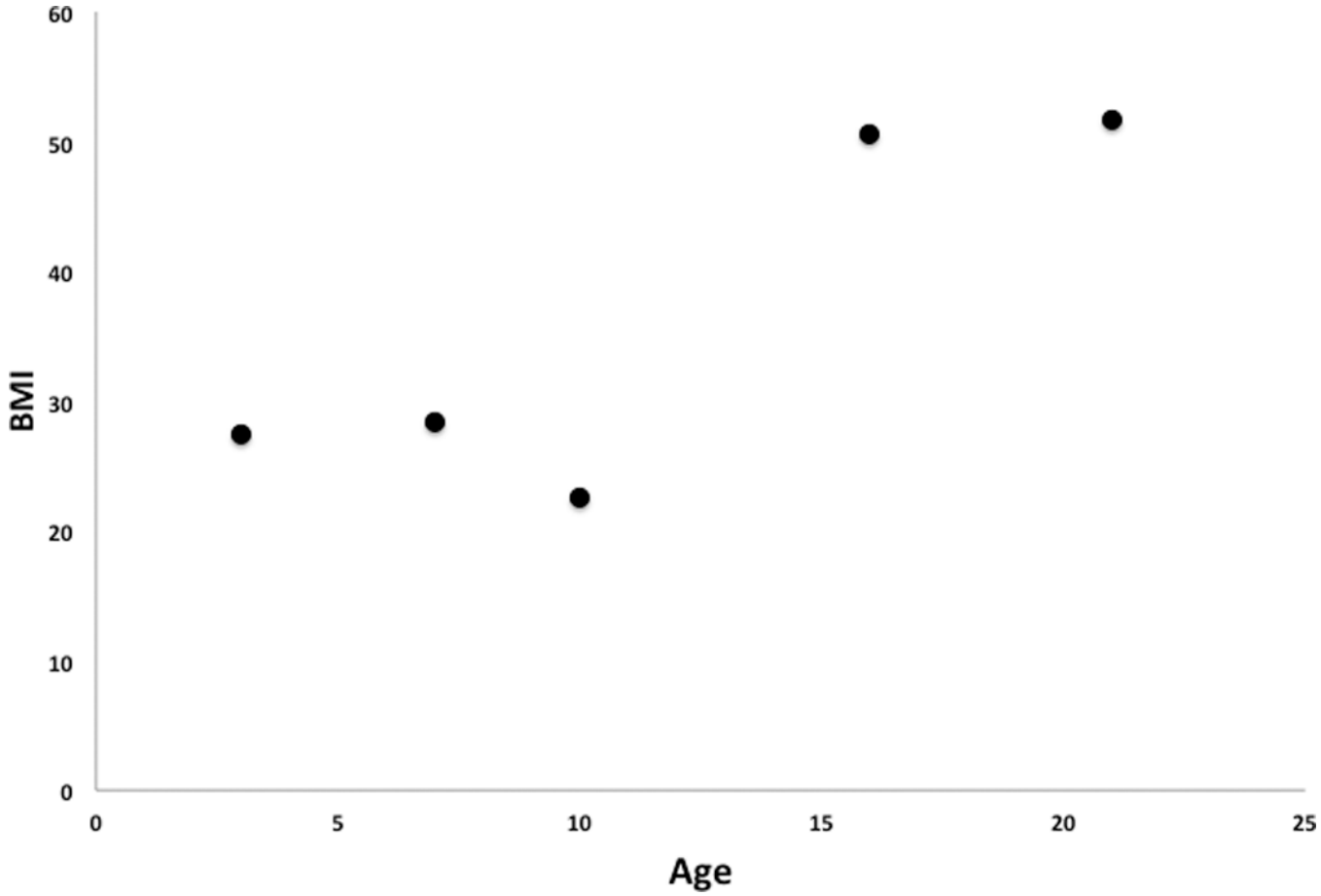

Figure 3. Subjects with deletions in *BDNF* have increasing BMI's over time

Table 1

Information on cases and controls[1]

Site	Indications for Study	N	Platform
	Cases		
SickKids	NDD, MCA only	3,258	Agilent 44K/180K
Children's Hospital	All	7,320	Agilent 244K
Signature	NDD only	14,616	Signature ChipOS 105K/135K
Mayo	All	13,135	Agilent 180K
Harvard	Balanced chromosomal rearrangement with phenotype	221	Next Generation sequencing
	Controls		
ISC	Unaffected	7,878	Affymetrix 5.0/6.0
Cooper et al.*	Unaffected	6,113	Affymetrix 6.0
OHI	Unaffected	1,234	Affymetrix 6.0
POPGEN	Unaffected	1,123	Affymetrix 6.0
HapMap3	Unaffected	1,056	Affymetrix 6.0
SAGE	Unaffected	1,287	Illumina 1M
Shaikh et al.	Unaffected	2,026	Affymetrix 6.0
DGV**	Unaffected	7,988	Multiple

NDD = any neurodevelopmental disorder, behavioral, or neuropsychiatric disorder, including autism and autism spectrum disorder.
MCA = multiple congenital anomalies.
All = all indications for study included; precise phenotypes of all individuals were not available for further delineation of NDD.

*Publicly available control data from Cooper et al. (2011) with WTCCC controls already analyzed in the ISC control set removed.

**Controls from DGV filtered for overlap with other control studies presented.

[1]See manuscript for references for each cohort

Table 2

Characteristics of current subjects as well as those previously reported to have alterations in *BDNF*.

Subject	Age/sex	Genotype	Nociception	Psychopathology	Overweight/obese	Mental Dx
1	10/M	Deletion: 22,858,513–29,066,320	Pain insensitivity	ADHD, anxiety disorder, aggressive behaviors	BMI=22.6	PDD-NOS
2	21/F	Deletion: 27, 050, 622–29, 550, 113	self—injurious behaviors	Major depression, generalized anxiety disorder	BMI=51.7	Mild MR
3	2.75/M	Deletion: 23,484,198–27,857,928	N/A	Impaired behavior	mother BMI= 39.5 proband BMI=27.4	GDD in proband; ID in mother
4	16/M	Deletion: 23,002,186–27,956,720	N/A	Adjustment disorder, Major depression, generalized anxiety disorder	BMI= 50.5	PDD
5	7/M	Deletion: 25,649,116–31,566,599	Pain insensitivity	Anxiety, ADHD, temper tantrums, intolerance to frustration	BMI=28.3	Moderate MR
6	3/F	Duplication: 27,179,904–28,837,666	N/A	Not reported	No	Moderate MR and dystonia
[42]Ref	13/M	Deletion	N/A	Not reported	Yes	MR
[12]Ref	25/F	Deletion	N/A	Mood disturbances, obsessive–compulsive behavior, temper tantrums, intolerance to frustration requiring antipsychotic medications	Yes	Mild/moderate MR
[12]Ref	14/F	Deletion	N/A	Chronic anxiety, poor acceptance of change, logorrhea, echolaly, poor social interactions, labile mood, and bouts of aggressiveness and motor agitation that required treatment with risperidone	Yes	PDD: Moderate/severe MR
[13]Ref	9/F	Position effect due to an inversion	Pain insensitivity	Complex neurobehavioral phenotype, repetitive behaviors, extreme hyperactivity, no concept of danger	Yes	Low IQ

Abbreviations: ADHD: Attention Deficit Hyperactivity Disorder; PDD-NOS: Pervasive Developmental Delay, not objectively specified; MR: Mental retardation; GDD: Global Developmental Delay; ID: intellectual disability IQ: Intelligence quotient. All genomic coordinates according to human reference hg18.