Highly Penetrant Alterations of a Critical Region Including BDNF in Human Psychopathology and Obesity

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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 data from 7 molecular diagnostic centers including 38,550 affected subjects and 28,705 unaffected subjects.

Patients: Subjects referred to diagnostic screening centers for microarray-based comparative genomic hybridization for physical or cognitive impairment.

Main Outcome Measures: Genomic copy number gains and losses.

Results: We report 5 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.


BRAIN-DEVELOPED NEUROTROPHIC factor (BDNF) 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 family with structural similarity to nerve growth factor and neurotrophin 3 and neurotrophin 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 β and cytokine families. While all nervous system growth factors support neurodevelopment, BDNF has been singularly implicated for its role in obesity, pain, and memory.2-7 The protein is encoded by BDNF, located on the short arm of chromosome 11 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, attention-deficit/hyperactivity disorder, 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 extend-
Table 1. Information on Cases and Controls

<table>
<thead>
<tr>
<th>Site</th>
<th>Indications for Study</th>
<th>Sample Size</th>
<th>Platform</th>
</tr>
</thead>
<tbody>
<tr>
<td>SickKids</td>
<td>NDD, MCA only</td>
<td>3258</td>
<td>Agilent 4K/180K</td>
</tr>
<tr>
<td>Boston Children’s Hospital</td>
<td>All</td>
<td>7320</td>
<td>Agilent 244K</td>
</tr>
<tr>
<td>SG</td>
<td>NDD only</td>
<td>14616</td>
<td>Signature ChipOS 105K/135K (SG)</td>
</tr>
<tr>
<td>Mayo</td>
<td>All</td>
<td>13135</td>
<td>Agilent 180K</td>
</tr>
<tr>
<td>Harvard</td>
<td>Balanced chromosomal rearrangement with phenotype</td>
<td>221</td>
<td>Next Generation sequencing</td>
</tr>
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</table>

Controls

<table>
<thead>
<tr>
<th>Site</th>
<th>Indications for Study</th>
<th>Sample Size</th>
<th>Platform</th>
</tr>
</thead>
<tbody>
<tr>
<td>ISC</td>
<td>Unaffected</td>
<td>7878</td>
<td>Affymetrix 5.0/6.0</td>
</tr>
<tr>
<td>Cooper et al&lt;sup&gt;a,b&lt;/sup&gt;</td>
<td>Unaffected</td>
<td>6113</td>
<td>Affymetrix 6.0</td>
</tr>
<tr>
<td>OHI</td>
<td>Unaffected</td>
<td>1234</td>
<td>Affymetrix 6.0</td>
</tr>
<tr>
<td>PopGen</td>
<td>Unaffected</td>
<td>1123</td>
<td>Affymetrix 6.0</td>
</tr>
<tr>
<td>HapMap 3</td>
<td>Unaffected</td>
<td>1056</td>
<td>Affymetrix 6.0</td>
</tr>
<tr>
<td>SAGE</td>
<td>Unaffected</td>
<td>1287</td>
<td>Illumina 1M</td>
</tr>
<tr>
<td>Shaikh et al&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Unaffected</td>
<td>2026</td>
<td>Affymetrix 6.0</td>
</tr>
<tr>
<td>DGV&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Unaffected</td>
<td>7988</td>
<td>Multiple</td>
</tr>
</tbody>
</table>

Abbreviations: All, all indications for study included; precise phenotypes of all individuals were not available for further delineation of NDD; DGV, Database of Genomic Variants; HapMap 3, International HapMap 3 Consortium; ISC, International Schizophrenia Consortium; Mayo, Mayo Clinic; MCA, multiple congenital anomalies; NDD, any neurodevelopmental disorder, behavioral, or neuropsychiatric disorder, including autism and autism spectrum disorder; OHI, Ottawa Hospital Institute; SAGE, Study of Addiction: Genetics and Environment; SG, Signature Genomics; SickKids, The Hospital for Sick Children.

<sup>a</sup>See text for references for each cohort.

<sup>b</sup>Publicly available control data from Cooper et al with Wellcome Trust Case-Control Consortium controls already analyzed in the ISC control set removed.

<sup>c</sup>Controls from DGV filtered for overlap with other control studies presented.

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, using either a 105K-feature platform (SignatureChip OS version 1.0; custom-designed by SG, manufactured by Agilent Technologies) or a 135K-feature platform (SignatureChip OS version 2.0; custom-designed by SG, manufactured by Roche NimbleGen), according to previously described methods. 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 BDNF 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 SG was estimated from a sampling across-section previously described. This sample (n=144 subjects, self-reported) was composed of 75% white individuals, 7% African American individuals, and 18% individuals of other race/ethnicity. The sex distribution was 59% male and 41% female. The only alterations spanning BDNF observed in the SG group were patients with WAGR syndrome (n=2), so there was no contribution to these analyses from this data set, although they are included in all statistical analyses. The ethnicity of each patient described herein with a copy gain or loss of BDNF was white.

The clinical cytogenetics laboratory at The Hospital for Sick Children in Toronto, Ontario, Canada, screened patients using either Agilent 4x4K array or the 4x180K ISCA v2 microar-
We screened microarray-based comparative genomic hybridization data for more than 38,000 subjects from clinical diagnostic centers at Boston Children’s Hospital; The Hospital for Sick Children, Toronto; Mayo Clinic, Rochester, Minnesota; Brigham and Women’s Hospital, Boston, Massachusetts; Manchester Academic Health Science Centre, St Justine Hospital, Montreal, Quebec, Canada; and SG for any subjects with copy number changes of the BDNF region (see Table 1 for complete description of all subject groups). We identified 5 subjects with deletions encompassing the entire BDNF gene and 1 subject with a duplication spanning BDNF (Figure 1 and Table 2). For all subjects, microarray-based comparative genomic hybridization was used to initially identify BDNF copy changes and Figure 2 shows a visual example of microarray-based comparative genomic hybridization 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.
Table 2. Characteristics of Current Subjects as Well as Those Previously Reported to Have Alterations in BDNF

<table>
<thead>
<tr>
<th>Patient No./Sex/Age, y</th>
<th>Genotype</th>
<th>Nociception</th>
<th>Psychopathology</th>
<th>Overweight/Obese</th>
<th>Mental Dx</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/M/10</td>
<td>Deletion: 22,858,513-29,066,320</td>
<td>Pain insensitivity</td>
<td>ADHD, anxiety disorder, aggressive behaviors</td>
<td>BMI = 22.6</td>
<td>PDD-NOS</td>
</tr>
<tr>
<td>2/F/21</td>
<td>Deletion: 27,050,622-29,550,113</td>
<td>Self-injurious behaviors</td>
<td>Major depression, generalized anxiety disorder</td>
<td>BMI = 51.7</td>
<td>Mild MR</td>
</tr>
<tr>
<td>3/M/2.75</td>
<td>Deletion: 23,484,198-27,857,928</td>
<td>Unknown</td>
<td>Impaired behavior</td>
<td>Mother BMI = 39.5; proband BMI = 27.4</td>
<td>GDD in proband; ID in mother</td>
</tr>
<tr>
<td>4/M/16</td>
<td>Deletion: 25,002,186-27,956,720</td>
<td>Unknown</td>
<td>Adjustment disorder, major depression, generalized anxiety disorder</td>
<td>BMI = 50.5</td>
<td>PDD</td>
</tr>
<tr>
<td>5/M/7</td>
<td>Deletion: 25,649,116-31,566,599</td>
<td>Pain insensitivity</td>
<td>Anxiety, ADHD, temper tantrums, intolerance to frustration</td>
<td>BMI = 28.3</td>
<td>Moderate MR</td>
</tr>
<tr>
<td>6/F/3</td>
<td>Duplication: 27,179,904-28,837,866</td>
<td>Unknown</td>
<td>Not reported</td>
<td>No</td>
<td>Moderate MR and dystonia</td>
</tr>
<tr>
<td>Gül et al13/M/13</td>
<td>Deletion</td>
<td>Unknown</td>
<td>Not reported</td>
<td>Yes</td>
<td>MR</td>
</tr>
<tr>
<td>Brémont-Gignac et al12/F/25</td>
<td>Deletion</td>
<td>Unknown</td>
<td>Mood disturbances, obsessive-compulsive behavior, temper tantrums, intolerance to frustration requiring antipsychotic medications</td>
<td>Yes</td>
<td>Mild/moderate MR</td>
</tr>
<tr>
<td>Brémont-Gignac et al13/F/14</td>
<td>Deletion</td>
<td>Unknown</td>
<td>Chronic anxiety, poor acceptance of change, logorrhea, echolalic, poor social interactions, labile mood, and bouts of aggressiveness and motor agitation that required treatment with risperidone</td>
<td>Yes</td>
<td>PDD: moderate/severe MR</td>
</tr>
<tr>
<td>Gray et al13/F/9</td>
<td>Position effect due to an inversion</td>
<td>Pain insensitivity</td>
<td>Complex neurobehavioral phenotype, repetitive behaviors, extreme hyperactivity, no concept of danger</td>
<td>Yes</td>
<td>Low IQ</td>
</tr>
</tbody>
</table>

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); Dx, diagnosis; GDD, global developmental delay; ID, intellectual disability; MR, mental retardation; PDD-NOS, pervasive developmental delay, not objectively specified.

aAll genomic coordinates according to human genome reference 18.

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 SG) because of the very large number of genes in WAGR deletions, the severity of the associated neurodevelopmental phenotype, 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 chr19:61,453,936-61,530,271 intersecting the testes-specific gene ZSCAN5A. The 10-year-old boy had been diagnosed with pervasive developmental disorder not otherwise specified, attention-deficit/hyperactivity disorder, anxiety, behavioral issues (eg, constantly hitting head against the wall), and mood dysregulation. At 4 years of age, his condition regressed markedly, and to date, he has been treated with escitalopram oxalate (Lexapro), aripiprazole (Abilify), citalopram hydrobromide (Celexa), guanfacine hydrochloride (Tenex), methylphenidate hydrochloride (Ritalin), atomoxetine hydrochloride (Strattera), and clonidine hydrochloride. His height and weight at age 9 years were 138.7 cm and 43.5 kg (95th-97th percentile), respectively, with a BMI of 22.6 (see the eFigure [http://www.archgenpsychiatry.com] for a weight chart for this subject taken at different points showing a progression toward obesity). He was extremely aggressive and parental report noted 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 (SALSA MLPA P219; MRC-Holland).

Subject 2 (DGAP173) was a 21-year-old woman with a karyotype of 46,XX,t(2;11)(q11.2;p13) who also had a 2.5-megabase deletion (chr11:27,050,622-29,550,113) on chromosome 11 that included BDNF (Figure 2). Array comparative genomic hybridization results were confirmed using clinically available multiplex ligation-dependent probe amplification probes targeting BDNF. She had 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 years, she weighed 167.6 kg and had a height of 180.1 cm, with a BMI of 51.7. Her head circumference was 61 cm, which is outside of the normal adult range of 55 to 58 cm. She had male-pattern hirsutism (thought to be associated with a tentative diagnosis of polycystic ovary syndrome, maternally inherited) and had had only a single period with no further menstruation even with trials of oral con-
trceptive pills. Impaired glucose tolerance without evidence of type 2 diabetes mellitus, poor lipid profile with elevated triglyceride and total cholesterol levels, and high-density lipoprotein cholesterol levels, elevated testosterone level, some deepening of the voice, and history of 1 non-febrile seizure at 2 years of age were also noted. Her skin was remarkable for eczema, moles, and skin tags. She had dysmorphic features including bilateral epicanthal folds giving a saddle appearance to the nasal bridge, a small nose, and complex malocclusion with upper teeth more narrow and frontal than lower. Morphologically, she had 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 vs 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 had impaired social, play, and behavioral skills as well as global developmental delay and a duplex left kidney. He was a large child with weight of 29.3 kg, height of 103.5 cm, and BMI of 27.4, all of which are greater than the 97th percentile. His head circumference was 52 cm, which is considered within the normal range at age 2.75 years but is at the 94th percentile. Family history is of note in that his mother had intellectual difficulties. His height was 171 cm; weight, 114.3 kg; and BMI, 39.5. No further information was available for her. Fluorescence in situ hybridization analysis confirmed she had the same deletion and attentional difficulties and high scores for difficulties in intertriginous regions (acanthosis nigricans vs epidermal nevi) present on the back, chest, and neck.

Subject 4 was a 16-year-old boy whose 36-week gestation was notable for the umbilical cord being wrapped around his neck. A 180K Agilent microarray screen revealed a chr11:23,002,186-27,956,720 (human genome reference 18) de novo deletion. He had hypercholesterolemia, a fatty liver, and hypertension and was prediabetic. At an assessment done at age 16 years, he was 151 kg and 1.73 m and had a BMI of 50.5. He had speech delay, pervasive developmental disorder, and an IQ/DQ of 58. With respect to psychopathology, he had been diagnosed with an adjustment disorder (mixed disturbance of emotion and conduct), depressive disorder, and anxiety disorder. Fluorescence in situ hybridization confirmed the array results using RP11-115012.

Subject 5 was a boy 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 age 5 years 10 months; >97th percentile). He had a statement of special educational need, and at age 4.5 years, his overall general conceptual ability was limited (score on the British Ability Scales II was 47 [<0.4 percentile] in keeping with a severe learning disability); he was reported to be able to write his name at 6 years of age. He had poor fine motor skills and poor problem-solving skills. With respect to sensory systems, he had hyperacusis and a high pain threshold. He was described as having inappropriate toddlerlike tantrums triggered by not getting his own way or not being able to eat when he wishes. He had sleeping difficulties and was taking melatonin. A strengths-and-difficulties questionnaire completed by his teacher at age 5 years noted very high scores for overall stress, hyperactivity, and attentional difficulties and high scores for difficulties getting along with other children.

Subject 6 had 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 toward increasing obesity (BMI vs age, Pearson = 0.86; P = .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. The supporting eFigure shows the increase in BMI over time compared with age standards.

While each of the BDNF-containing deletions reported herein 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 data sets from individuals without a comparable phenotype. We found no structural variations affecting BDNF in copy number variant 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 the SG Genoglyphix Chromosome Aberration Database. Collectively, though disruption of this locus was rare, we found a nominally significant burden of dosage alterations spanning BDNF in cases compared with all controls (Fisher exact test, P = .04) as well as the combination of controls and clinical diagnostic cases without a neurodevelopmental abnormality (n = 40 233; P = .01). Similar results were obtained if we restricted analyses to only those cases with deletion of the locus (P = .08 and .03, 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 translocation36 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 that includes behavioral/psychiatric traits due to alterations in BDNF, LIN7C, LGR4, or some combination of these genes.

**COMMENT**

To our knowledge, 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 1 study identified 4 different subjects with WAGR syndrome with behavioral disturbances.30 The current study included more than 38 000 probands collected internationally and found 5 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, because the critical region included 2 other potentially causative genes affected in all BDNF deletion cases. Nonetheless, animal data and analysis of the function of these 2 genes in the critical region strongly suggest that BDNF hemizygosity leads to psychopathology.

Mouse studies of LGR4 and LIN7C orthologs suggest a less central role for these genes in behavior. Lgr4 knockout mice show embryonic lethality, thought to be due to its fundamental role in organogenesis, particularly of the kidney and the sex organs.37,38 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 the brain except in the olfactory bulb and periventricular area; expression is highest in the kidney, gallbladder, heart, bone, and spinal cord.39 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,40 though 2 paralogs, Lin7a and Lin7b, are suspected of being able to compensate for Lin7c deficiency.41 Distribution of Lin7c expression in the mouse brain is low compared with 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 the cortex and dentate gyrus.41 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 supports 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 avail-
able for 3 deletion subjects with respect to pain insensitivity (1 of the subjects with a BDNF deletion was reported to engage in self-injurious behavior, a phenotype frequently associated with pain insensitivity in individuals with intellectual disability), 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 patients with WAGR syndrome, while those with deletions that extended to BDNF were more likely to be obese and insensitive to pain than those without a BDNF deletion.

The consensus phenotype for individuals with a deletion in BDNF suggests that young children are hyperactive and 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 woman with mood disturbances from a previous report. 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 reassess how clinical categorization proceeds.

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.

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REFERENCES


