11p14.1 Microdeletions Associated With ADHD, Autism, Developmental Delay, and Obesity

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Genomic copy number imbalances are being increasingly identified as an important cause of intellectual disability and behavioral abnormalities. The typical deletion in WAGR syndrome encompasses the PAX6 and WT1 genes, but larger deletions have been associated with neurobehavioral abnormalities and obesity. We identified four patients with overlapping interstitial deletions on 11p14.1 and extending telomeric to the WAGR critical domain. The minimal overlapping critical chromosomal region was 2.3 Mb at 11p14.1. The deletions encompass the BDNF and LIN7C genes that are implicated in the regulation of development and differentiation of neurons and synaptic transmission. All patients with this deletion exhibit variable degrees of developmental delay, behavioral problems, and obesity. Our data show that ADHD, autism, developmental delay, and obesity are highly associated with deletion involving 11p14.1 and provide additional support for a significant role of BDNF in obesity and neurobehavioral problems. © 2011 Wiley-Liss, Inc.

Key words: microdeletion; developmental delay; ADHD; autism; obesity; WAGR; BDNF; 11p14.1

INTRODUCTION

Global developmental delay (GDD) and intellectual disability occur in 1–3% of the general population, and its cause is unknown in more than one-half of the patients [Moeschler and Shevell, 2006]. Children with learning disability, autism, or attention deficit/hyperactivity disorder are at increased risk for obesity compared to their counterparts without these conditions [Chen et al., 2010; Van Cleave et al., 2010]. Chromosomal abnormalities including submicroscopic deletions and duplications are the most common recognized cause of GDD, intellectual disability, and autism spectrum disorders (ASDs) [Menten et al., 2006; Vorstman et al., 2006; Abrahams and Geschwind, 2008; Vissers et al., 2010]. In addition, recent studies identified significant high prevalence of recurrent copy number variations (CNVs) in obese patients [Bochukova et al., 2010; Walters et al., 2010]. Array-based comparative genomic hybridization (aCGH) is becoming an essential and a routine clinical diagnostic tool and it has increased our ability to detect CNVs in patients with GDD, intellectual disability, ASD, congenital anomalies, and dysmorphism [Stankiewicz and Beaudet, 2007; Shinawi and Cheung, 2008; Miller et al., 2010]. This highly sensitive, whole-genome molecular method allows for comprehensive delineation of unbalanced chromosomal rearrangements, and enables a more precise genotype/phenotype correlation to be established.

The Wilms tumor, aniridia, genitourinary anomalies, and mental retardation (WAGR) syndrome is caused by microdeletions of

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the 11p13 region. The typical deletion in WAGR encompasses the PAX6 and WT1 genes, which are located ~4 Mb centromeric to the BDNF locus at 11p14.1. Larger deletions with atypical centromeric and telomeric breakpoints (BP) have been described in patients with WAGR phenotype in association with intellectual disability and obesity [Marlin et al., 1994; Tiberio et al., 2000; Amor, 2002; Gül et al., 2002; Fischbach et al., 2005]. One way to clarify the underlying genotype-phenotype relationships in these atypical deletions is to construct a deletion map in which we compare the phenotypes of individuals missing different portions of 11p and assign specific features to specific chromosomal regions. This approach was utilized to map clinical features and cognitive phenotypes of several chromosomal deletion syndromes. However, the precise genotype-phenotype correlation of WAGR deletion cases is hampered by the inclusion of PAX6 and other genes within the deleted interval that were implicated in developmental delay and brain abnormalities [Sisodiya et al., 2001; Valenzuela and Cline, 2004]. Therefore, the detection of telomeric deletions not involving the PAX6/WT1 critical interval could shed light on the functional role of other genes on this chromosomal region.

We here report the molecular and clinical characterizations of four patients with novel, non-recurrent interstitial deletions identified by aCGH and involving chromosomal region telomeric to the WAGR critical domain.

CLINICAL REPORTS

Patient #1

This is a male proband who was initially evaluated in our institution (M.S.) at 7 months of age for developmental delay. He was born via induced vaginal delivery at 37 weeks to a 26-year-old G2P1-2, healthy mother and a 29-year-old healthy father, both of Caucasian descent. The patient’s birth weight was 2,920 g (50th centile), his birth length was 49.5 cm (80th centile), and his head circumference at birth was 34 cm (75th centile). The parents had a 3-year-old daughter who was diagnosed with gastroduodenal stenosis that required surgical repair.

After birth, the patient was discharged home with cardiorespiratory monitor because of recurrent episodes of sinus tachycardia that were associated with oxygen desaturation. Echocardiography and Holter monitoring study were unremarkable.

Since first day of life, the patient had generalized hypotonia, feeding difficulties and gastroesophageal reflux which required the Nissen fundoplication procedure twice and G-button placement. He had pyloric stenosis that was surgically repaired at the age of 13 weeks. The patient was diagnosed with congenital glaucoma when he was 4 months of age with intraocular pressures above 40 mmHg. He was treated with four surgical interventions and several intraocular pressure lowering medications to control the glaucoma. The patient underwent urethral diverticulum and bilateral hernia repairs. The patient had severe failure to thrive during first year of life but later on he exhibited an excessive food intake and progressive catch-up of his growth parameters (Fig. 1). The patient had an unusual insensitivity to pains. He sustained four fractures in his arms and legs; two of which were detected only a week after the event. The recurrent fractures were related to osteopenia associated with nutritional vitamin D insufficiency. During first year of life the patient was extremely irritable and colicky. His audiological evaluation was unremarkable.

The patient’s gross motor skills developed normally but he had significant speech delay and was diagnosed with speech apraxia. The patient’s overall cognitive abilities were assessed using the Bayley Scales of Infant Development, III, at 28 months of age and were most like those of a child around the age of 19 months. His receptive

![Fig. 1](image.jpg)
language skills fell at the 20-month-old level, while his expressive
language skills fell at the 12-month-old level. His fine motor skills
were at the 21-month-old level. The results of the Aberrant Behavior
Checklist (ABC) revealed significant increases in the areas
of irritability, lethargy/withdrawal, stereotypic behaviors, and
hyperactivity.

The patient also met criteria for Attention-Deficit Hyperactivity
Disorder (ADHD), Combined Type. He played loudly, was rough
with toys and threw objects across the room. After considering
direct observations, and the reports of his mother, his social
communication was not consistent with a diagnosis of autism.

The physical examination of this patient at 45 months of age
documented no dysmorphic features except for exophthalmos
(Fig. 2A). The head circumference was 50 cm (~35th centile),
weight was 18.7 kg (92nd centile) (Fig. 1), and length was 104 cm
(~80th centile). Neurological examination showed normal tone
and strength of muscles, intact cranial nerves and deep tendon
reflexes.

Patients #2 and #3
Patient #2 was recruited through the South Carolina Autism Project
(#15627) to our exon-focused microarray project which aimed to
evaluate patients with autism for intragenic deletions and duplica-
tions within different candidate genes (see the Methods Section).

The patient was born at 39 weeks gestation with birth weight of
2.6 kg (20th centile), length of 49.5 cm (40th centile), and head
circumference of 33 cm (10th centile). The pregnancy was compi-
lcated by maternal migraine equivalents, uterine cervical cryosur-
gery in the first trimester, and pregnancy induced hypertension. The
patient experienced no neonatal problems but was colicky as an
infant.

Her early motor and speech milestones were normal. At
18 months she appeared overactive and responded inappropriately
to verbal directions. She failed to develop age appropriate play with
toys or with other children. She has had no seizures. Her past
medical history revealed recurrent ear infections and placement of
ear tubes twice in addition to adenoidectomy.

Examination at age 6 years showed height of 121 cm
(>97th centile), weight of 34.5 kg (>97th centile) (Fig. 1), and
head circumference of 51 cm (75th centile). She was ambulatory
and verbal. She had normal facies with stellate-patterned blue eyes,
attached earlobes and everted lower lip (Fig. 2B). There was mild
stiffness of the digits and short fifth fingers. Her strength, tone,
and reflexes were normal. Her statural growth slowed down but
excessive weight gain continued in the teen years: at age 19½ years,
her height was 166 cm (70th centile), and her weight was 119 kg
(>97th centile).

The patient met three of four requirements on the ADI-R for
autistic disorder, but did meet criteria on the Childhood Autism
Rating Scale (CARS). Her IQ and adaptive skills were mildly
impaired [Wechsler Preschool and Primary Scale of Intelligence
(WPPSI) was 61 and Vineland Adaptive Behavior Scale (VABS)
composite was 62]. The patient was diagnosed with ADHD and
placed on Ritalin (methylphenidate), which greatly reduced her
hyperactivity and improved her behavior.

Chromosome analysis, plasma amino acids, urine organic acids,
fragile X syndrome testing, serum adenylosuccinase activity, and
platelet serotonin were normal. Brain imaging was not performed.

Her family history is significant for her father (Patient #3) who
had learning problems and left school at 10th grade. He was
described as a large man (height at 95th centile and weight >97th
centile), moody, and was diagnosed with bipolar disorder. The
father’s sister had two children with learning problems and violent
behaviors, but they were not available for testing (Fig. 3).

Patient #4
The propositus is a 6-year-old male who was born at term via
cesarean section secondary to dystocia to a 26-year-old G2P1,
healthy mother and a 25-year-old healthy father, both of French-
Canadian descent. Prenatal history documented no major compli-
cations or exposures. His birth weight was 3.3 kg (between 25 and
50th centile) and his length was 53 cm (90th centile). There were no
perinatal or neonatal complications after delivery. The patient has
two healthy siblings, and the family history was unremarkable.

FIG. 2. The facial features of Patient #1 [A], #2 [B], and #4 [C].
At 7 months of age, the patient was diagnosed with aniridia, which was complicated by glaucoma and nystagmus. The patient’s motor skills were slightly delayed. He started sitting independently at 13 months and walked at 17 months. His language was delayed, and he started speaking in phrases only at the age of 5 years. Currently he attends a special school for children with developmental delays. The behavioral profile of the patient showed stereotypic behaviors and hyperactivity. The patient was diagnosed with ADHD and placed on Ritalin at the age 4 years. The patient had limited social interactions, and he was very rigid in his routine and ritualistic behaviors. The ADOS and ADI-R documented that he met criteria for ASD.

At age of 4 years 5 months his height was 107 cm (65th centile), his weight was 23.5 kg (>97th centile), his BMI was 20.5 (>97th centile), and the OFC was 50.5 cm (40th centile). The patient exhibited mild dysmorphic features including flat nasal bridge, ogival palate, short neck, and brachydactyly (Fig. 2C). The patient had bilateral aniridia with horizontal nystagmus. His neurological examination was otherwise unremarkable.

MRI of the brain showed slight prominence of the ventricular system. Echocardiography, renal ultrasound, and audiometric evaluation were unremarkable.

**METHODS**

**Targeted Chromosomal Microarray Analysis**

Genomic DNA from Patients #1 and #4 was studied by Chromosomal Microarray Analysis (CMA; Baylor College of Medicine). The CMA Version 6.1 was used for this analysis (http://www.bcm.edu/geneticlabs/cma/tables/44KDisorders.pdf). This is a custom-designed large-insert BAC clone targeted array allowing simultaneous evaluation for copy number losses and gains at large numbers of chromosomal loci [Cheung et al., 2005].

Patients #2 and #3 were recruited through the South Carolina Autism Project and their DNA samples, isolated from lymphoblast cell lines, were tested for deletions and duplications using exon-focused microarrays. These are custom-designed Agilent 44K X 4 platforms for array comparative genomic hybridization (CGH) containing high density probes across exonic and intronic regions of candidate genes (average ~130 probes per gene). There were 83 autism candidate genes (version 1 exon microarray) chosen based on literature support, 234 genes involved in neurological or synaptic function (version 2 exon microarray), and 295 genes with roles in chromatin structure and modification (chromatin array) (see Online Supplemental Material).

**Fluorescence In Situ Hybridization Analysis**

Peripheral blood samples from Patients #1 and 4, and their respective parents were obtained and whole blood lymphocytes were cultured after phytohemagglutinin (PHA) stimulation using standard methods. Fluorescence in situ hybridization (FISH) was performed using standard cytogenetic methods.

**Deletion Mapping by High-Resolution Oligonucleotide Array**

Further characterization of the deletions was performed utilizing the Agilent 244K Whole Human Genome CGH arrays (Agilent Technologies, Inc., Santa Clara, CA) containing 236,000 probes, providing a compiled view of the human genome at an average of 6.4 kb resolution (hg18 assembly). The procedures for DNA digestion, labeling, hybridization, and data analysis were performed essentially according to the manufacturer’s protocol (Agilent Technologies, Santa Clara, CA).
RESULTS

Phenotypic Characterization

The demographic data and the clinical characteristics of the four patients with 11p14.1 deletions are summarized in Table I. The patients were born at term and were appropriate for their gestational age. The first year of life was unremarkable except for Patient #1 who exhibited feeding difficulties, other gastrointestinal problems, and failure to thrive. Two patients had speech delay and all patients had mild to moderate cognitive impairment. Three of four patients needed therapeutic interventions and/or special education at school. None of our patients exhibited seizures, focal neurological findings, or hearing loss. Two of the patients had glaucoma and one had aniridia. None of the patients had striking dysmorphic features, although minor facial dysmorphic findings were documented in two patients. Two patients were diagnosed

<table>
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<th>2</th>
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<td>F</td>
<td>M</td>
<td>M</td>
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<td>WC</td>
<td>WC</td>
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<td>18</td>
<td>26</td>
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<td>31</td>
<td>20</td>
<td>25</td>
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<td>107</td>
<td>104.5</td>
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<td>VD</td>
<td>CS</td>
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<td>3.6 (55th)</td>
<td>3.3 (40th)</td>
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<td>75th</td>
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<td>80th</td>
<td>&gt;97th</td>
<td>95th</td>
<td>65th</td>
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<td>No</td>
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<td>No</td>
<td>Yes (CARS)</td>
<td>No</td>
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<td>Bipolar disorder</td>
<td>ADHD</td>
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<td>Developmental intervention/ special education</td>
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<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Seizures</td>
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<td>No</td>
<td>No</td>
<td>No</td>
</tr>
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<td>nd</td>
<td>nd</td>
<td>Mildly prominent lateral ventricles</td>
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<td>Dysmorphic features</td>
<td>Exophthalmos</td>
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<td>No</td>
<td>Flat nasal bridge, ogival palate, short neck, brachydactyly</td>
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<td>Congenital anomalies</td>
<td>Pyloric stenosis, inguinal hernia, urethral diverticulum</td>
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<td>None</td>
<td>Aniridia</td>
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<td>Miscellaneous</td>
<td>Insensitivity to pain, colicky in infancy</td>
<td>Recurrent OM, colicky in infancy</td>
<td></td>
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</tr>
</tbody>
</table>

ADHD, attention deficit hyperactivity disorder; CS, caesarean section; F, female; OFC, occipito frontal circumference; GER, gastroesophageal reflux; Ht, height; IVD, induced vaginal delivery M, male; na, data not available; nd, not done; nl, normal; OM, otitis media; VD, spontaneous vaginal delivery; WC, white Caucasian.
with autism, three with ADHD and one patient with bipolar disorder. Three of the four patients had weight above the 97th centile. In addition, Patient #1 exhibited an interesting pattern of weight gain. He had severe failure to thrive during first year of life but began gaining excessive weight during second year of life (Fig. 1). In Patient #2 the acceleration in weight gain started also at the beginning of the second year of life (Fig. 1). None of our patients had genital anomalies and the renal ultrasound for Patients #1 and #4 was normal.

**Targeted Chromosomal Microarray Analysis and FISH Studies**

The CMA for Patient #1 revealed a loss in copy number on 11p14.1p14.3, detected with three clones (RP11-20J1, RP11-1L12, RP11-115J23). The FISH studies, using the RP11-1L12 clone as a probe, detected a single signal confirming the heterozygous loss of this chromosomal region. Parental FISH with the same probe was normal in both, indicating the de novo nature of the abnormality [arr cgh 11p14.1p14.3 (RP11-20J1 → RP11-115J23)x1.ish del(11)(p14.2p14.2)(RP11-1L12)dn]. The CMA for Patient #4 revealed a loss on copy number at 11p14.2p13, detected with three clones (RP11-1L12 > RP11-702F20). FISH testing, using the RP11-1L12 clone as a probe, showed a single signal confirming the CMA findings. Parental FISH analysis was normal, confirming that the deletion was not inherited [arr cgh 11p14.2p13(RP11-1L12 → RP11-702F20)x1.ish del(11)(p14.2p14.2)(RP11-1L12)dn].

The exon microarray for Patient #2 showed a loss of all probes covering the BDNF gene, and the deletion was inherited from his affected father (data not shown).

**High-Resolution Genomic Analyses**

The Agilent 244K Whole Human Genome CGH Microarray analysis was used to precisely delineate the BP and the extent of the deletions. The deletion in Patient #1 was found to be approximately 6.6 Mb encompassing the region between 24,628,202 and 31,262,579 bp (hg18; NCBI Build 36.1, March 2006) on 11p14.1p14.3, and therefore it was larger than previously estimated by the CMA. In Patient #2 and #3 the deletion was found to be approximately 2.3 Mb in size extending from 27,257,520 to 29,590,637 bp positions on 11p14.1 (Fig. 4). The size of the deletion in Patient #4 was ~5.6 Mb, extending from 26,111,645 to 31,759,019 bp position on 11p13p14.2.

**DISCUSSION**

It has been noted that individuals with the WAGR contiguous gene deletion syndrome in whom deletions extend telomeric to the critical chromosomal region are often obese and have high incidence of intellectual disability and behavioral problems [Marlin et al., 1994; Tiberio et al., 2000; Amor, 2002; Gül et al., 2002; Fischbach et al., 2005]. This observation led to the speculation that genes involved in the regulation of body weight and critical for brain function may be present within this chromosomal domain. Our data provide an additional support for the significant role of this chromosomal region in obesity and neurobehavioral abnormalities.

In this study we narrowed down the critical chromosomal region associated with this phenotype to 2.3 Mb at 11p14.1 (Fig. 4). This interval contains six well-characterized genes; METT5D1, KIF18A, BDNF, LIN7C, LGRA, and CCDC34.

**METT5D1** and **CCDC34** encode methyltransferase 5 domain containing 1 isoform and CCDC34 coiled-coil domain containing 34 isoform 1, respectively. The precise function of these two genes is unknown and their role in the phenotypic features in our patients is not clear, but in general haploinsufficiency for enzymes such as METT5D1 is usually recessive and not deleterious.

The product of **LIN7C** gene is part of a tripartite complex, which acts as a nucleation site for the assembly of proteins involved in synaptic exocytosis and neuronal cell adhesion [Butz et al., 1998; Feng and Zhang, 2009]. It plays a role in establishing and maintaining the asymmetric distribution of channels and receptors in neurons and in regulating delivery and recycling of proteins to the
correct membrane domains. One study found allelic and haplotype association between LIN7C and ADHD [Lanktree et al., 2008]. It is possible that LIN7C haploinsufficiency plays a significant role in the neurobehavioral phenotype observed in our patients. Identification of loss-of-function point mutations in the LIN7C gene in patients with ADHD and/or autism would provide the strongest evidence for a causative association. KIF18A is a member of the kinesin proteins that are involved in functions related to movements of organelles (e.g., axonal transport) or chromosomes along microtubule [Stumpff et al., 2008] and therefore we cannot exclude it as a candidate gene for the neurobehavioral phenotype.

The product of LGR4 (also known as GPR48), a G-protein-coupled receptor, plays an important role in the development of the anterior segment structure of the eye [Weng et al., 2008]. In addition, the Gpr48+/− mice exhibit early onset glaucoma, which is mediated by dramatic down-regulation of Pitx2 [Weng et al., 2008]. However, no specific phenotype was described for the heterozygous Gpr48+/− mice. In addition, all previously reported patients had deletions that included the PAX6 gene which largely determined their ophthalmological phenotype and there are no data comparing the eye findings on patients with and without LGR4 deletion. Interestingly, two of our patients, Patients #1 and #4, had glaucoma but in Patient #4 it probably complicated a preexisting aniridia. In Patient #4 the deletion is located 3.9 kb from the 3’ end of PAX6 but the PAX6 gene is spared. The presence of aniridia in Patient #4 is consistent with previous data showing that remote 3’ regulatory elements are required for PAX6 expression [Lauderdale et al., 2000]. Although the positional effect can also be relevant for Patient #1, whose deletion is located ~500 kb from the 3’ of PAX6, we cannot exclude the possibility that haploinsufficiency of other genes (e.g., LGR4) is important for the eye phenotype in this patient.

The BDNF gene encodes for brain-derived neurotrophic factor, a member of the nerve growth factor family. It has a critical role in cell differentiation, neuronal survival, migration, dendritic arborization, synaptogenesis, spine development, long-term potentiation, and activity-dependent forms of synaptic plasticity [Greenberg et al., 2009; Lu et al., 2008]. The BDNF protein is widely expressed in the central nervous system during different developmental stages and extending to the adult. Other neuronal-expressed genes such as MECP2 [Jin et al., 2008] and KDM5C (known as JARID1C) [Tahiliani et al., 2007], which are associated with neurobehavioral and cognitive phenotypes, modulate the expression of the BDNF gene.

The association of WAGR with obesity has been previously described and found, in one series, in about 4% of WAGR patients [Fischbach et al., 2005]. BDNF haploinsufficiency was implicated directly with obesity in a study that showed significantly higher BMI throughout childhood in patients with heterozygous BDNF deletions and who had approximately 50% lower serum BDNF concentrations [Han et al., 2008]. The same study found that by 10 years of age, 100% of patients with heterozygous BDNF deletions were obese (BMI ≥ 95th centile for age and sex) as compared with 20% of persons without BDNF deletions [Han et al., 2008]. Another study showed that functional deficiency of BDNF was associated with hyperphagia and obesity in an 8-year-old girl [Gray et al., 2006]. Furthermore, a de novo missense mutation in the receptor for BDNF, NTRK2, which impairs receptor autophosphorylation and signaling to MAP kinase was found in an 8-year-old male with a complex developmental syndrome and severe obesity [Yeo et al., 2004]. Studies in animals showed that Bdnf and its tyrosine kinase receptor Ntrk2 are expressed in several hypothalamic and hindbrain nuclei involved in regulating energy homeostasis, feeding behavior, and weight control. Fetal or early-postnatal deficiency of Bdnf or Ntrk2, in mice results in hyperphagic behavior and dramatic obesity [Xu et al., 2003]. In addition, selective deletion of Bdnf in the ventromedial and dorsomedial hypothalami of adult mice results in hyperphagic obesity [Unger et al., 2007]. Heterozygous bdnf+−/− mice have a normal life span but show aggressiveness and hyperphagia accompanied with obesity [Lyons et al., 1999]. The hyperphagic obesity in these mice occurs in mature but not young Bdnf mutants fed a balanced diet [Fox and Byerly, 2004]. Bdnf mRNA expression in the hypothalamus of Bdnf heterozygous mice showed 50% reduction and the infusion of exogenous BDNF reversed the phenotype [Kernie et al., 2009].

There is previous speculation that BDNF may play a role in behavioral abnormalities and intellectual disability. In one study, 39 out of 54 patients with WAGR syndrome were reported to have intellectual disability [Fischbach et al., 2005]. The same study revealed that 24% of WAGR patients have ADHD and a similar incidence of ASD [Fischbach et al., 2005; Xu et al., 2008] found that deletion of BDNF among patients with WAGR syndrome occurred in 76.5% of patients with autism versus 42.3% in the group without autism suggesting that BDNF may modulate/influence the increased risk of autism in these patients. Hashimoto et al. [2006] showed reduced BDNF levels in adult male patients with autism as compared to age-matched healthy male control subjects. Another study showed that mean levels of BDNF were significantly lower in children with autism as compared to teenagers or adults, or to age-matched healthy controls [Katoh-Semba et al., 2007]. However, other contrasting studies showed an opposite trend [Nishimura et al., 2007] probably reflecting markedly variation of BDNF levels in an age-dependent manner [Nelson et al., 2006]. There is evidence to suggest that BDNF plays a role in the pathophysiology of other psychiatric diseases, including mood disorders and schizophrenia [Hashimoto et al., 2004; Angelucci et al., 2005]. Animal models also support the role of BDNF in neurobehavioral abnormalities. Heterozygous bdnf+−/− mice exhibit deficiencies in learning behavior [Linmarsson et al., 1997] and show aggressiveness [Lyons et al., 1999].

In conclusion, we have found that ADHD, autism, developmental delay, and obesity are common in the deletion involving 1p14.1. Patients with larger deletions exhibit more significant developmental delays and additional clinical phenotypes. Our data provide additional support for the significant role of BDNF in obesity and neurobehavioral problems. The function of LIN7C is intriguing, and its haploinsufficiency may contribute to the behavioral phenotype. Pharmacotherapeutic interventions to enhance the activity or amount of BDNF should be investigated as a treatment in a cohort of individuals known to have this deletion.

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