



## Research report

# Association of brain-derived neurotrophic factor (BDNF) haploinsufficiency with lower adaptive behaviour and reduced cognitive functioning in WAGR/11p13 deletion syndrome

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## ABSTRACT

In animal studies, brain-derived neurotrophic factor (BDNF) is an important regulator of central nervous system development and synaptic plasticity. WAGR (Wilms tumour, Aniridia, Genitourinary anomalies, and mental Retardation) syndrome is caused by 11p13 deletions of variable size near the BDNF locus and can serve as a model for studying human BDNF haploinsufficiency (+/−). We hypothesized that BDNF+/− would be associated with more severe cognitive impairment in subjects with WAGR syndrome. Twenty-eight subjects with WAGR syndrome (6–28 years), 12 subjects with isolated aniridia due to PAX6 mutations/microdeletions (7–54 years), and 20 healthy controls (4–32 years) received neurocognitive assessments. Deletion boundaries for the subjects in the WAGR group were determined by high-resolution oligonucleotide array comparative genomic hybridization. Within the WAGR group, BDNF+/− subjects ( $n = 15$ ), compared with BDNF intact (+/+) subjects ( $n = 13$ ), had lower adaptive behaviour ( $p = .02$ ), reduced cognitive functioning ( $p = .04$ ), higher levels of reported historical ( $p = .02$ ) and current ( $p = .02$ ) social

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11p Deletion  
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impairment, and higher percentage meeting cut-off score for autism ( $p = .047$ ) on Autism Diagnostic Interview-Revised. These differences remained nominally significant after adjusting for visual acuity. Using diagnostic measures and clinical judgement, 3 subjects (2  $BDNF+/-$  and 1  $BDNF+/+$ ) in the WAGR group (10.7%) were classified with autism spectrum disorder. A comparison group of visually impaired subjects with isolated aniridia had cognitive functioning comparable to that of healthy controls. In summary, among subjects with WAGR syndrome,  $BDNF+/-$  subjects had a mean Vineland Adaptive Behaviour Composite score that was 14-points lower and a mean intelligence quotient (IQ) that was 20-points lower than  $BDNF+/+$  subjects. Our findings support the hypothesis that BDNF plays an important role in human neurocognitive development.

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## 1. Introduction

Brain-derived neurotrophic factor (BDNF) is a 27 kDa homodimeric protein in the nerve growth factor family of peptides that is widely expressed throughout the central nervous system and, in animal studies, appears to play an important role in regulating neuronal development, synaptic plasticity, and energy balance (Cohen-Cory et al., 2010; Greenberg et al., 2009; Xu et al., 2003). Heterozygous *Bdnf* knockout mice exhibit hyperphagia, obesity, decreased nociception, and impaired learning and social behaviours (Kernie et al., 2000; Lyons et al., 1999; MacQueen et al., 2001). WAGR (Wilms tumour, Aniridia, Genitourinary anomalies, mental Retardation) syndrome is a rare genetic disorder caused by heterozygous chromosome 11p13 contiguous gene deletions of variable size. The genitourinary and ocular manifestations of the syndrome are attributed to hemizyosity for *WT1* and *PAX6*, respectively, but the aetiology of cognitive impairment, which is quite variable among individuals with WAGR syndrome, has not been well elucidated (Clericuzio et al., 2011; Fischbach et al., 2005). The gene encoding BDNF is located at 11p14, only 4 Mb distal to *PAX6*, and hemizyosity for BDNF frequently occurs in subjects with WAGR syndrome (Han et al., 2008). Subjects with WAGR syndrome and other 11p deletions can serve, therefore, as models for studying human BDNF haploinsufficiency.

We previously reported associations of BDNF haploinsufficiency with obesity and reduced responsiveness to pain in subjects with WAGR syndrome, findings that support the role of BDNF in human energy homeostasis and nociception (Han et al., 2008). Extant data to support the role of BDNF in human cognitive functioning have been limited to case series. One case report described obesity and cognitive impairment in a child with a paracentric 11p13p15.3 inversion and functional BDNF haploinsufficiency (Gray et al., 2006). Two case series described a total of 9 subjects with 11p14 deletions involving BDNF who displayed obesity and various neurodevelopmental abnormalities, including intellectual disability, attention deficit hyperactivity disorder, and autism (Ernst et al., 2012; Shinawi et al., 2011). However, no prior study has examined cognitive and behaviour phenotypes using standardized clinical assessments in 11p deletion subjects with BDNF haploinsufficiency versus those with both alleles for BDNF intact.

To determine if BDNF deletion status contributes to the neurocognitive abnormalities of subjects with WAGR

syndrome, we examined the association of BDNF haploinsufficiency with cognitive functioning, adaptive and problematic behaviours, and symptoms of autism in a cohort of 28 subjects with WAGR syndrome. For comparison of neurocognition and brain magnetic resonance imaging (MRI) findings, we assessed subjects with visual impairments due to isolated aniridia, as well as healthy controls. We hypothesized that BDNF haploinsufficiency would be associated with more severe neurocognitive impairments in subjects with WAGR syndrome.

## 2. Methods

### 2.1. Participants

Three groups of subjects were recruited for this study using posted online and local advertisements: (1) individuals with WAGR/11p13 deletion syndrome with prior genetic testing showing karyotype with non-mosaic 11p13 deletion, (2) subjects with isolated aniridia who had prior genetic testing showing mutations of *PAX6*, serving as a contrast group; and (3) healthy control subjects who had no chronic medical conditions. The study was approved by the institutional review board of the Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, MD and is registered at [www.clinicaltrials.gov](http://www.clinicaltrials.gov) as NCT00758108. Written informed consent was obtained from adult subjects who were competent to provide consent and from the parents or legal guardians of children and adults with cognitive impairment. Twenty-two subjects in the WAGR group were described previously in a case series examining hyperphagia and body-mass index (Han et al., 2008). Thirteen of the subjects in the WAGR group also were described in a previous case series examining parent-reported history of intellectual disability and autism spectrum disorder (ASD) diagnoses (Xu et al., 2008). The characteristics of these previously described subjects (along with the rest of the cohort) are shown in [Supplementary Table 1](#).

### 2.2. Deletion mapping for subjects with WAGR syndrome

Deletion boundaries for each subject with WAGR syndrome were determined using oligonucleotide array comparative genomic hybridization using a custom-designed microarray

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