

# Genotype–Phenotype Association Studies of Chromosome 8p Inverted Duplication Deletion Syndrome

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**Abstract** Individuals diagnosed with chromosome 8p inverted duplication deletion (invdupdel(8p)) manifest a wide range of clinical features and cognitive impairment. The purpose of this study is to employ array CGH technology to define more precisely the cytogenetic breakpoints and regions of copy number variation found in several individuals with invdupdel(8p), and compare these results with their neuropsychological characteristics. We examined the cognitive-behavioral features of two male and two female children, ages 3–15 years, with invdupdel(8p). We noted cognitive deficits that ranged from mild to severe, and adaptive behavior composites that ranged from significantly to substantially lower than adequate levels. CARS scores, a measure of autistic behavior, identified three children with autism or autistic-like features. Three of the four children exhibited attention deficits and hyperactivity consistent with a DSM-IV-TR diagnosis of ADHD. One child showed extreme emotional lability. Interestingly, intellectual disability was not correlated with deletion size, nor was the deletion location associated with the autistic phenotype. On the other hand, the duplication length in 8p21.1/8p22 was associated with cognitive deficit. In addition, a small locus of over-expression in 8p21.3 was common for all three

participants diagnosed as autistic. A limitation of the study is its small sample size. Further analyses of the deleted and over-expressed regions are needed to ascertain the genes involved in cognitive function and, possibly, autism.

**Keywords** Subtelomeric deletion · Inverted duplication deletion 8p21–23 · Intellectual disability · Autism · CGH microarray

## Introduction

It has been estimated that 2.5–3% of all live births will result in some form of intellectual disability (ID). It is also estimated that 30–40% of those infants born with ID will have been produced by some genetic anomaly, the majority of which, at first glance, appear to be idiopathic in nature. Recent studies suggest that approximately 4–9% of individuals with idiopathic ID have subtelomeric rearrangements or deletions (Anderlid et al. 2002; Koolen et al. 2004; Shao et al. 2008; Wu et al. 2010), all of which suggests that approximately 1:1000–1:1500 neonates will show evidence of cognitive deficits arising from subtelomeric deletions. From the results of their analysis of subtelomeric rearrangements, Rooms et al. (2007) argued that no single mechanism seemed to account for these breakpoints, but that diverse molecular processes may produce these outcomes. Other researchers have observed that causes for the high proportion of ID in subtelomeric regions may be due to gene-rich loci residing at the telomeres, concurrent with higher than expected occurrences of chromosomal rearrangements (Bergemann et al. 2005).

Several subtelomeric rearrangements once thought to be rare now appear to be somewhat more common. One such region is associated with the short arm of chromosome 8.

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Florida et al. (1996) found two types of rearrangements: A duplication from the centromere to D8S552, with a deletion from D8S349 to the telomere; second, a duplication from 8p11.2 or 8p21 to D8S552, with a deletion from D8S349 to the telomere. Florida et al. categorized these two types, respectively, as dicentric inverted duplication (dicinvdup(8p)) and inverted duplication (invdup(8p)). Based on cases reported at the time, these researchers estimated the prevalence of either dicentric or monocentric invdup(8p) at 1:22,000–30,000. However, Yu et al. (2010) examined 966 individuals with developmental disorders and found 10 with copy number variants (CNVs) on the short arm of 8p. For either inverted duplication at 8p, the clinical aspects include dysmorphic craniofacial features, e.g., prominent forehead, hypotonia, congenital heart disease, agenesis of the corpus callosum, and ID (Shimokawa et al. 2004). Most often, invdup(8p) arises de novo, however, transmission to offspring from translocation carriers has been observed, often associated with a more variable cognitive phenotype that has included normal adaptive functioning (Sklower-Brooks et al. 1998) or mild developmental delay (Yenamandra et al. 1999; Moog et al. 2000). Shimokawa et al. (2004) found the inherited invdupdel(8p) to be maternal in origin in the five patients they examined.

Interestingly, Stec et al. (2001) noted that the Wolf-Hirschhorn syndrome candidate gene, *WHSC1*, is nearly homologous to the *WHSC1L1* gene that localizes to chromosome 8p11.2. Using CGH microarray technology, Barber et al. (2008) found a 3.75 Mb duplication between 8p23.1 and the olfactory receptor/defensin repeats. Also using microarray technology, Buisse et al. (2009) examined a 13 month old infant with developmental delay and found a smaller, 3.4 Mb, duplication limited to the 8p22 region.

A similar phenotype associated with invdupdel(8p) has been observed among individuals with a partial deletion near the telomere on chromosome 8p (del8p21), and on smaller segments (8p23.1 → ter). Digilio et al. (1998) delineated the features for deletion 8p syndrome, citing growth impairment, craniofacial anomalies, congenital heart defects, genital anomalies, and varying degrees of ID, characteristics found in the invdupdel(8p) phenotype. Often, individuals diagnosed with del8p21 present with a less severe phenotype and mild ID (Fryns et al. 1989; Hutchinson et al. 1992; Wu et al. 1996; Claeys et al. 1997; Hand et al. 2010). Also published is an account of an individual with normal cognitive ability (Gilmore et al. 2001). On the other hand, researchers find ADHD and aggressive behavior among many of those examined (Hutchinson et al. 1992; Wu et al. 1996; Claeys et al. 1997; de Vries et al. 2001). Most often, the deletion arises de novo. However, parents with a balanced translocation (8; 20)(p23; p13) have been shown to transmit the 8p deletion to their offspring (de Vries et al. 2001).

In addition to its previously identified clinical features, inversion duplication on the short arm of chromosome 8 was

found to be associated with autism (Papanikolaou et al. 2006). Marshall et al (2008) examined 427 individuals who had been diagnosed with autism; and, using CGH microarray technology, found 27 instances of de novo alterations, one of which involved the *DLGAP2* gene at locus 8p23.3. Ozgen et al. (2009) cytogenetically examined 4 patients diagnosed with autism and found copy number variants in the invdupdel(8p) region 8p23.1 → p21.1. In addition to the *DLGAP2* gene, these researchers identified two other candidate genes, *MCPHI* and *NEF3*, which may be associated with autism. Glancy et al. (2009) examined a child with autism and detected an inversion duplication 8p23.1–p23.2. Recently, Chien et al. (2010) discovered a 2.4 Mb deletion at 8p23.2 → ter associated with autism in two males they examined.

Apart from the several reports cited, we are unaware of other studies published using CGH microarray technology to associate the molecular-genetic features invdupdel(8p) to its cognitive-behavioral phenotype, nor has there been a systematic investigation of the cognitive-behavioral features associated with invdupdel(8p). Therefore, the purpose of this study was to provide a comprehensive assessment of the cognitive-behavioral features of children with invdupdel(8p), and attempt to establish an association with its molecular-genetic features. Specifically, we employed array CGH technology to define more precisely the cytogenetic breakpoints and CNV regions found in four individuals with this cytogenetic condition, and compare these results with their phenotypic features as assessed by a comprehensive neurobehavioral battery.

## Method

### Subjects

Seven participants who had been previously diagnosed cytogenetically with invdup(8p23) were recruited from various locations in the US. They were enrolled as part of our longitudinal cognitive-behavioral study of children with subtelomeric deletions. Aspects of their cognitive-behavioral features were published previously (Fisch et al. 2010). Parents for two of the seven children declined to have blood drawn for DNA testing. The family of a third child had moved from their residence and could not be located. The remaining four children ranged in age from 3 to 15 years, and were assessed behaviorally and genetically. Two participants were male and two were female.

### Materials

Participants were administered a comprehensive neurobehavioral battery which consisted of five standardized, valid

and reliable instruments to assess behavior. To the extent that they had sufficient language to be tested, participants were administered the Stanford-Binet (4th Edition) (SBFE; Thorndike et al. 1986). In the meanwhile, their parents or caregivers completed the Child Behavior Checklist (CBCL; Achenbach 1991) and Conners Parent Rating Scale-Revised (CPRS-R; Conners 2003). Afterward, parents/caregivers were interviewed using the Vineland Adaptive Behavior Scale (VABS; Sparrow, Balla, and Cicchetti 1984) and Child Autism Rating Scale (CARS; Schopler et al. 1988).

#### *Cognitive-Behavioral Measures*

Where possible, cognitive abilities were assessed using the SBFE. The SBFE contains standard area scores (SAS) for four major areas of assessment: verbal reasoning (VR), abstract/visual reasoning (AVR), quantitative reasoning (QR), and short-term memory (STM). Adaptive behavior skills were assessed with the VABS, which contains four domains: communication, daily living skills (DLS), socialization, and motor skills for children less than 6 years of age. The VABS also contains two scales to assess Maladaptive Behavior.

#### *Attention/Activity*

Activity levels and attentiveness were assessed using the CPRS-R. The CPRS-R examines several scales associated with behavioral genotypes: oppositional, cognitive problems/inattention, hyperactivity, anxiety or shyness, perfectionism, social problems, and psychosomatic problems. More importantly, DSM-IV-TR symptoms/indices specifically associated with attention deficit disorder (ADD) and attention deficit/hyperactivity disorder (ADHD) can be obtained from the CPRS-R. ADD or ADHD scale scores at or above the 95th percentile are consistent with a DSM-IV-TR diagnosis of ADD or ADHD, respectively.

#### *Emotionality/Temperament*

To evaluate the child's emotionality and temperament, parents completed the CBCL. The CBCL assesses emotional behavior along two major dimensions: internalizing, and externalizing behaviors. Internalizing behaviors contain scales that assess the following: withdrawn, somatic complaints, anxious/depressed, social problems, thought problems, attention. Externalizing behaviors contain two scales: delinquent, aggressive. For each of these scales, raw scores are converted into standardized T-scores. T-scores  $\geq 70$  indicate clinically significant aberrant behavior. T-scores between 65 and 69 denote unusually high, subclinical behavior.

#### *Autism*

To ascertain the child's status with regard to autism, the CARS was employed. The CARS consists of 15 subscales associated with DSM-IV criteria defining autistic behavior. Each item is rated from 0 (behavior typical for a child that age) to 4 (extremely abnormal behavior for a child that age). Item scores are summed and summated scores  $\geq 30$  are considered in the autism range. In terms of diagnostic sensitivity and specificity, the CARS is comparable to the ADOS-G, and exhibits slightly higher measure of agreement with the "gold standard" of autism, clinical judgment, than the ADOS-G (Ventola et al. 2006).

#### *Procedure*

To obtain measures of their cognitive abilities, one of us (G.S.F.) administered the SBFE to the participating children. It should be noted that two children presented with extremely limited language skills, or were diagnosed as autistic without language skills. Therefore, they could not be administered the SBFE. However, all participants' parents or caregivers were interviewed using the VABS and CARS; and, all parents and caregivers also completed the CPRS-R and CBCL. Duration for each behavioral assessment was about 2 h. All assessments were scored and compiled by one of us (G.S.F.).

#### *DNA Analysis*

Blood was obtained from all 4 participants and examined at the M.I.N.D. Institute at the University of California, Davis using CGH microarray analysis.

#### *Microarray Analysis*

*Agilent's Human Genome CGH Microarray Kit 244A* These microarrays consist of roughly 236,000 60-mer oligonucleotide probes that cover both exon and intron sequences. These high resolution arrays have an average spatial resolution of 8.9 kB. The entire content is printed on a standard 1"  $\times$  3" slide using Agilent's Sure Print technology.

*Target Preparation* Samples were prepared using the direct method according to the manufacturer's Oligonucleotide Array-Based CGH for Genomic DNA Analysis protocol (Version 6.1, available at <http://www.chem.agilent.com>), to which minor changes were incorporated. Commercially available human male genomic DNA (Promega, Madison, WI) was used as a reference sample. Hybridization took place in a rotisserie oven for 72 h, set to 65°C and the rotation speed at 20 rpm. The washing and scanning of the

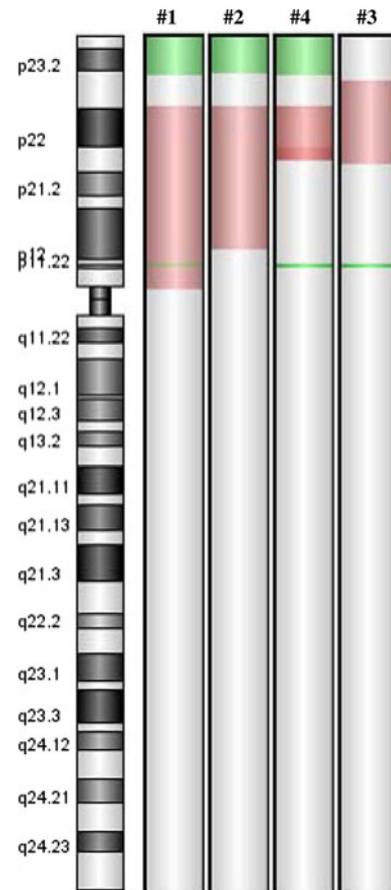
slides took place in an ozone free area to prevent the degradation of the cyanine 5 dye. In turn, the slides were washed according to the wash procedure B. After washing, the slides were dried and then scanned on an Agilent High-Resolution C scanner.

**Data Analysis** Image files generated from the scanner were analyzed using Agilent's Feature Extraction Software 9.1. This software allows a standardize method of extracting data using a standard protocol (CGH\_105\_Jan09). The QC report generated was checked to ensure proper hybridization and placement of the grid by the software. Data generated by the feature extraction tool were loaded into Agilent Genomic Workbench 5.0 to allow visualization of the data. A smoothing average of 10 data points was used.

## Results

### Microarray Analysis

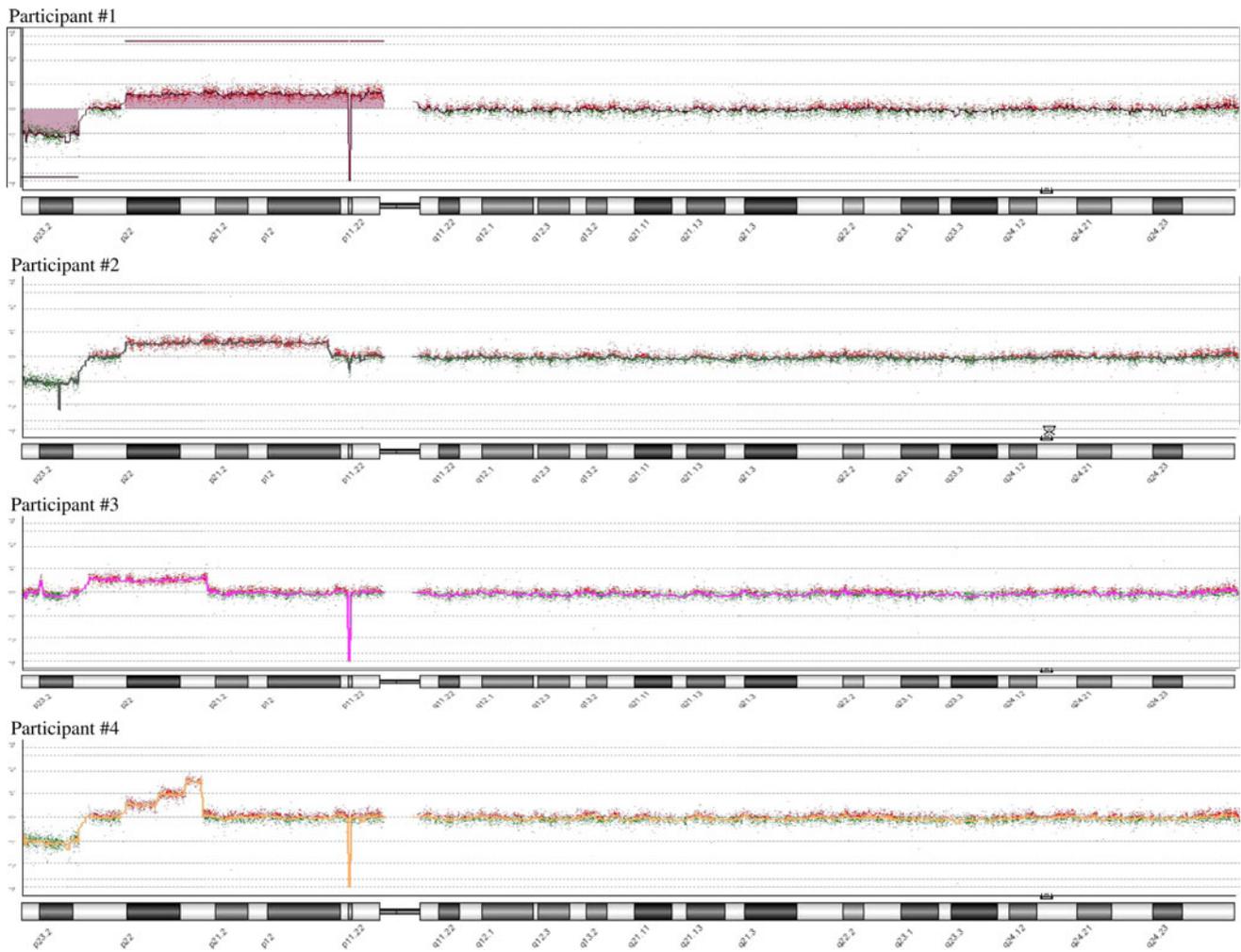
Comparison of the microarray results among the patients showed regions of consistency where chromosomal deletions and duplications occurred (Fig. 1). Three of the 4 participants have terminal deletions with the breakpoints near the boundary between 8p22 and 8p23.1. However, neither the existence of this deletion nor its size correlated with the severity of the clinical outcome. That is, participants #2 and #4 with the deletion were less severely affected than participant #3 without the deletion. Three participants: #1, #4, and #3 have an additional small deletion at 8p11.23p11.22 (39,356,395–39,505,456) that is most likely a CNP (copy number polymorphism) involving *ADAM5P* and *ADAM3A* genes and are non-pathogenic. These three participants have a homozygous deletion of the region, while participant #2 has a heterozygous deletion of the same region. The effect of this deletion is unknown, but was not associated with the level of cognitive deficit. Duplicated segments show greater variability among all participants. A common core duplicated region was found in all four participants that includes all of 8p22 and extends midway into 8p21.3. One participant showed an interesting triple stepwise increase in duplication of adjacent segments within this exact region, with no other duplicated regions involved. Two other participants have duplications that extend from this core region, albeit in opposite directions, and both are more severely affected physically and cognitively (Fig. 2). ISCN physical positions for the aberrations on 8p and approximate copy numbers for participants are presented in Table 1. We did not see other aberrations in pathogenic areas of the genome. Parents of all participants showed normal microarray patterns.



**Fig. 1** CHG microarray of chromosome 8 for participants #1, #2, #4, and #3. Green areas indicate deleted portions of the telomere. Red areas indicate over-expression (color figure online)

### Participant #1

#1 Is a 15-year old female who is relatively tall for her age. Her face was somewhat long and eyes unusually wide open. She often stared at people or into space for long periods. She lacked expressive speech and language; therefore, the SBFE was not administered to her. Her overall VABS score, which is strongly correlated with the SBFE, was <20, and indicated much lower than adequate levels of adaptive behavior. Although she exhibited several autistic-like behaviors, her initial CARS score, 27.5, was in the non-autistic range. However, on re-examination, her CARS score was 35.5, indicating mild-to-moderate autism. Her CPRS-R scores showed that she is in the 99th percentile for hyperactivity, and in the 98th percentile for restlessness and impulsivity. At these levels, her behavior is consistent with a DSM-IV diagnosis of ADHD. Her CBCL results show that all but one of her emotionality and temperament *T*-scores were within the normal range, but her *T*-score for attention 75, is statistically unusual and clinically significant, confirming results obtained by the CPRS-R.



**Fig. 2** Individual participants CHG microarray analysis of chromosome 8

**Table 1** ISCN 2009 physical positions for the aberrations on 8p and approximate copy numbers for participants #1–#4

Participant	ISCN
1	arr 8p23.3p23.1(90,616-6,913,476)X1 dn,8p23.1p11.1(12,547,803-43,647,263)X2~3 dn,8p11.23p11.22(39,356,395-39,505,456)X0
2	arr 8p23.3p23.1(166,252-6,913,476)X1 dn,8p23.1p11.1(12,547,803-37,028,346)X2~3 dn, 8p11.23p11.22(39,356,395-39,505,456)X1
3	arr 8p23.1p21.3(8,117,071-22,366,537)X2~3 dn,8p11.23p11.22(39,356,395-39,505,456)X0
4	arr 8p23.3p23.1(166,252-6,913,476)X1 dn,8p23.1p21.3(12,511,655-21,726,774)X2~5 dn, 8p11.23p11.22(39,356,395-39,505,456)X0

#### Participant #2

#2 Is a 3-year old male with a large head and prominent forehead, who was also big for his age. Otherwise, no other obvious dysmorphic craniofacial features were evident. He was lethargic, did not point or gesture, and made no eye

contact. He did not want his face to be touched. His speech/language was extremely limited therefore, the SBFE was not administered. The VABS, which is strongly correlated with IQ, was 51, and indicated much lower than adequate levels of adaptive behavior. CBCL scores noted subclinical thought problems ( $T = 67$ ) and significant withdrawal

from others ( $T = 74$ ). CPRS-R scores also noted significant anxious/withdrawn behaviors (100th percentile), psychosomatic problems (94th percentile), and emotional lability (95th percentile). These behaviors on the CARS produced a score of 32 (mildly autistic).

#### Participant #3

#3 Is a 13-old female who was severely developmentally and intellectually disabled for her age. Although her expressive speech and language were also severely impaired, her language skills were sufficient for the examiner to administer the SBF. Her test composite, 36, was at the floor value for the SBF. Her adaptive behavior composite score was 20, which is also at the floor value for the VABS, and indicated much lower than adequate levels of adaptive behavior. Her CARS score was 45.5, indicating severe autism. Her  $T$ -scores on the CBCL denoted severe thought problems ( $T = 86$ ), withdrawn ( $T = 74$ ), and social problems ( $T = 75$ ). Scores for cognitive problems, hyperactivity, anxious/shy, perfectionistic, somatic problems, ADHD symptoms, restless/impulsive, and emotionally labile scales on the CPRS-R were all above the 95th percentile.

#### Participant #4

#4 Is a 15-year old male and was the least impaired individual in the sample. His craniofacial features appeared normal. He displayed the clearest expressive speech and language. However, after he had been taken off Ritalin, he began to stutter. His test composite on the SBF, 56, revealed mild intellectual deficits. His adaptive behavior composite on the VABS, 59, indicated lower than adequate levels of adaptive behavior. His CARS score, 21, demonstrated that he was not autistic. Scores on the CPRS-R showed that he was in the 95th percentile for hyperactivity and his scores were consistent with a DSM-IV diagnosis of ADHD. The CBCL noted some thought and social problems, but were not statistically significant.

### Discussion and Summary

We examined the molecular-genetic and cognitive-behavioral features of 2 male and 2 female children, ages 3–15 years, initially diagnosed cytogenetically with invdupdel(8p23). Of the 4 participants we tested using CGH microarrays, 2 exhibited classic invdupdel(8p), the rearrangement in participant #4 corresponds to the invdupdel(8p) mechanism but is more complex than a “classical” invdupdel(8p), while the fourth displayed only the duplication in the region between 8p22 and midway into 8p21.3.

The break point for the deleted region from 8p22→pter was the same for all 3 participants with the deletion, but was not associated with severity of cognitive deficit. On the other hand, the size of the duplicated region did correlate well with the degree of cognitive deficit. The complex structure found in participant #4 is similar to that observed in amplified regions found in cancers and likely results from the mechanism of breakage/fusion/bridge.<sup>1</sup> As a result, the presence of multiple copies may complicate interpretation of the genotype-phenotype analysis.

In their review of chromosome 8p, Tabarés-Seisdedos and Rubenstein (2009) reported that the region contains 484 genes and 110 pseudogenes, and that there are 76 genes from 8p21.1→pter known to be involved with brain function and development, brain disorders, neuropsychiatric disorders, or cancer. They also note that the 8p region is a ‘hotspot’ that contains many CNVs, some of which are associated with autism and schizophrenia. In the deleted portion, 8p22→pter, there are 4 genes associated with brain function and development (*DLGAP2*, *CLN8*, *ARHGEF10*, *mir-124-1*), 3 associated with neuropsychiatric disorders (*ARHGEF10*, *mir-1241-1*, *mir-598*) and 2 associated with cerebral disorders (*MCPHI*, *CTSB*). In the duplicated region, 8p22/8p21.3, there are 15 genes involved with brain function and development (*FGF20*, *ChGn*, *VMAT/SLC18A1*, *GFRA2*, *DOK2*, *NPM2*, *FGF17*, *PPP3CC*, *EGR3*, *ADAM28*, *ADAM7*, *NEF3*, *NEFL*, *GNRH1*, *DPYSL2*, *CLU*, *SCARA3*, *PNOC*, *ZNF395*, *FZD3*, *HMBX1*, *KIF13B*), 12 genes implicated in neuropsychiatric disorders (*PCMI*, *NAT2*, *VMAT/SLC18A1*, *FGF17*, *mir-320*, *PPP3CC*, *EGR3*, *NEF3*, *DPYSL2*, *ADRA1A*, *PTK2B*, *CHRNA2*, *FZD3*), and 14 genes related to cerebral disorders (*FGF20*, *PDGFRL*, *NAT1*, *NAT2*, *LPL*, *GFRA2*, *PHYHIP*, *PPP3CC*, *PEBP4*, *NEFL*, *PNMA2*, *DPYSL2*, *ADRA1A*, *CHRNA2*, *CLU*). Previously, researchers have cited *DLGAP2*, *MCPHI*, and *NEF3* as possible candidate genes for autism (Marshall et al. 2008; Ozgen et al. 2009).

Agenesis of the corpus callosum (ACC) is a frequent finding in individuals with invdupdel(8p) and del(8p) (Hutchinson et al. 1992; Minelli et al. 1993; Yenamandra et al. 1999). In their review of social and behavioral problems tied to ACC, Badaruddin et al. (2007) note that these individuals are often developmentally delayed or effect some form of intellectual disability. In addition, the behavioral, communication, and social problems typically observed in individuals with ACC are linked with pervasive developmental disabilities and autism. Parents of the 2 female participants reported that their children had been diagnosed with ACC, both of whom were also autistic. Behavior consistent with a diagnosis of autism was identified in three of the four children examined.

<sup>1</sup> We thank Reviewer #4 for this interpretation and analysis.

Three of the four children exhibited attention deficits and hyperactivity consistent with a DSM-IV-TR diagnosis of ADHD. One child showed extreme emotional lability. ADHD and aggressive behavior is also often observed among children with del(8p) (Hutchinson et al. 1992; Wu et al. 1996; Claeys et al. 1997; de Vries et al. 2001), but not reported in studies of individuals with invdupdel(8p). Based on previous studies of invdupdel(8p) and del8p21, and the similarities noted in their respective phenotypes, one might have conjectured that the cognitive deficits observed result from the terminal deletion. To the contrary, we found that cognitive deficit was not correlated with deletion size, but to the extent of overexpression in 8p21.1/8p22. Nor was deletion location specifically associated with the autistic phenotype. However, we did note a small region between 8p21.2 and 8p22 in which *NEF3* is expressed, and overexpression occurs in all three participants with autism. Ozgen et al. (2009) reported that *NEF3* is a candidate gene associated with autism.

There are obvious limitations to our study. Our sample size was smaller than we originally sought to analyze using CGH arrays, especially as two of the three children not available for this study had received a diagnosis of autism or PDD-NOS. Consequently, we believe it is imperative for future studies to recruit and evaluate other individuals with invdupdel(8p), to use CGH microarrays and comprehensive neurobehavioral assessment batteries to elucidate the genotype and phenotype, and to ascertain the genes involved in cognitive function and autism.

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