

15q13.3 Duplication in Two Patients With Childhood-Onset Schizophrenia

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We report two cases of paternally inherited 15q13.3 duplications in carriers diagnosed with childhood-onset schizophrenia (COS), a rare neurodevelopmental disorder of proposed polygenic origin with onset in children before age 13. This study documents that the 15q13.3 deletion and duplication exhibit pathogenicity for COS, with both copy number variants (CNVs) sharing a disrupted *CHRNA7* gene. *CHRNA7* encodes the neuronal alpha7 nicotinic acetylcholine receptor ($\alpha 7nAChR$) and is a candidate gene that has been suggested as a pathophysiological process mediating adult-onset schizophrenia (AOS) and other neurodevelopmental disorders. These results support the incomplete penetrance and variable expressivity of this CNV and represent the first report of 15q13.3 duplication carriers exhibiting COS. Published 2016. This article is a U.S. Government work and is in the public domain in the USA. *American Journal of Medical Genetics Part B: Neuropsychiatric Genetics* published by Wiley Periodicals, Inc.

Key words: neurodevelopmental disorders; childhood-onset schizophrenia; microduplication; 15q13.3; *CHRNA7*

INTRODUCTION

Copy number variations (CNVs) are rare chromosomal rearrangements that have been shown to increase the risk of several neurodevelopmental disorders and congenital anomalies. Patients with childhood-onset schizophrenia (COS) exhibit a particularly high rate of rare CNVs that disrupt genes involved in neuronal development and regulation [Walsh et al., 2008; Ahn et al., 2014]. One of the CNVs believed to have a causal influence on the development of psychiatric disorders is the 15q13.3 *deletion*, which occurs at a higher rate than duplications. The deletion increases risk of developmental delay (DD) [Sharp et al., 2008], adult onset schizophrenia (AOS) [Consortium, 2008; Stefansson et al., 2008], COS [Ahn et al., 2014], epilepsy [Helbig et al., 2009], bipolar disorder (BPD) [Leonard and Freedman, 2006], and autism spectrum disorder (ASD) [Miller et al., 2009]. Penetrance of this CNV was estimated independently at 40% (95%CI [21, 72]) and 44% (95%CI [29, 63]) [Kirov et al., 2014; Tropeano et al., 2014]. Though the heterogeneous phenotypic presentation and penetrance of the 15q13.3 *deletion* syndrome has been fairly well-established, the clinical significance and pathogenicity—the presentation of neurodevelopmental disorders—of the corresponding *duplication* at the 15q13.3 locus is less under-

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stood, due in part to its relative rarity. A recent review of 15q13.3 CNV literature found 241 reported deletions and 79 reported duplications [Gillentine and Schaaf, 2015].

The existing reports of the 15q13.3 duplication reveal incomplete penetrance and variable expressivity. To date, the duplication has been associated with ASD [Miller et al., 2009; van Bon et al., 2009], BPD [van Bon et al., 2009; Szafranski et al., 2010], intellectual disability (ID) [van Bon et al., 2009], AOS [Szatkiewicz et al., 2014], DD [Miller et al., 2009], behavioral disorders [Miller et al., 2009], language impairment [Miller et al., 2009; Pettigrew et al., 2015], attention deficit hyperactivity disorder (ADHD) [Williams et al., 2012], Tourette syndrome (TS) [Melchior et al., 2013], obsessive compulsive disorder (OCD) [Miller et al., 2009; Melchior et al., 2013], and epilepsy [Beal, 2014]. The heterogeneity of this duplication parallels the well-known pleiotropic effects found for other CNVs, where presumably shared abnormalities early in brain development result in increased risk of developing neuropsychiatric disorders. Given the rarity of the 15q13.3 duplication and continually expanding pleiotropy, the relationship between this CNV and psychiatric disorders remains incomplete.

Here, we report two cases of paternally inherited 15q13.3 duplications found in an ongoing longitudinal study of 136 COS patients.

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With a worldwide lifetime risk of 1%, schizophrenia is a debilitating brain disorder with substantial personal and societal costs [Szatkiewicz et al., 2014]. It is characterized by hallucinations, delusions, flattened/inappropriate affect, and cognitive impairment, typically manifesting most strongly in late adolescence to early adulthood [American Psychiatric Association, 2000]. COS is a rare variant, defined as schizophrenia occurring before age 13 [Addington and Rapoport, 2009; Ahn et al., 2014]. Compared to later onset schizophrenia, COS typically follows a history of poorer premorbid functioning with a higher incidence of pre-psychotic neurodevelopmental abnormalities. We compare the frequency of the 15q13.3 duplication in COS to that seen in AOS, ASD, ADHD, and ID, and describe how these findings inform our search for the still unknown genetic mechanisms underlying risk-inducing CNVs.

MATERIALS AND METHODS

The probands are participants in an ongoing longitudinal study of 136 nationally recruited patients meeting the criteria for schizophrenia in the DSM-III-R/DSM-IV [American Psychiatric Association, 2000] before age 13 [Ahn et al., 2014]. Several steps were taken to combat diagnostic false positives. Only those with clear positive symptoms (e.g., delusions or hallucinations) were included in the study, while excluding those with severe receptive or expressive language disorders or IQ scores less than 70. Structured psychiatric interviews were conducted with the patients and first-degree relatives including the K-SADS to assess for lifetime and current psychiatric disorders. For details please see [Kumra et al., 1996; Shaw et al., 2006]. The diagnosis was further confirmed during a 3-month in-patient observation, including a 3-week medication-free period. Where possible, data was collected on probands, siblings, and parents. For the purposes of this study, siblings were considered “healthy” if they did not meet criteria for any schizophrenia or schizophrenia spectrum; other non-psychotic disorders were allowed for the sibling controls. This study was approved by the Institutional Review Board of the National Institute of Mental Health. All participants provided written assent/consent, and written informed consent from a parent or legal guardian for minors.

Genotyping and CNV Calling

The genotyping and analysis pipeline is described in more detail elsewhere [Ahn et al., 2014]. Samples which passed quality control procedures were included in CNV analysis using CNVision software [Sanders et al., 2011], which combines predictions of the PennCNV version 16 June 2011 [Wang et al., 2007], QuantiSNP v.2.3 [Colella et al., 2007], and GNOSIS [Sanders et al., 2011]. Only CNVs identified by at least two algorithms passed the analysis. All CNVs were visually inspected with Nexus copy number (<http://www.biodiscovery.com>). Because of the high positive predictive value of transmitted CNVs, if the overlap by length of CNV was at least 80% in a family member, the CNV was considered validated.

CNV Analysis

Rates of the CNV in COS patients and healthy full siblings were computed and compared with rates in publically available samples

of other clinical populations (AOS, ASD, ADHD, and ID) and their controls using Fisher's exact test, adjusted for multiple comparisons with the Bonferroni correction. Analyses were performed using R statistical computing software [R Development Core Team, 2010], and two-sided P -values $< 5.56 \times 10^{-3}$ were considered significant. CNVs were examined using UCSC Genome Browser build 37/hg19.

RESULTS

A total of 136 COS probands and 135 of their healthy, full siblings passed QC. For comparison of the rates of 15q13.3 duplications between COS probands and healthy controls, 77 probands had at least one healthy (i.e., non-psychotic), full sibling, totaling 116 siblings. Two of the 136 COS patients paternally inherited the 15q13.3 duplication. Proband 1 inherited a 503.5 kbp duplication spanning bp 32,012,361 to 32,515,849 from her father with no reported clinical diagnoses, though with a history of transient hallucinations and poor memory (see pedigree, Fig. 1A; CNV illustration, Fig. 2). The duplication contains the whole *CHRNA7* gene. Proband 1 has two siblings who are 15q13.3 duplication carriers, one diagnosed with TS and the other with dyslexia. Proband 2 inherited a 600.2 kbp duplication spanning bp 32,019,919–32,620,127 from his father diagnosed with BPD and who had a history of alcohol abuse (see pedigree, Fig. 1B; CNV illustration, Fig. 2). This duplication contains the whole *CHRNA7* gene. Proband 2 has one sibling who is a 15q13.3 duplication carrier and was diagnosed with ADHD.

The rate of the duplication in COS (1 in 68) was significantly greater than in AOS (1 in 4719, $P = 0.0023$), AOS controls (1 in 2860, $P = 0.0031$), ASD controls (1 in 2739, $P = 0.0019$), and ID controls (1 in 2777, $P = 0.0025$). The rate of the 15q13.3 duplication in COS was not significantly different from that in COS “healthy” siblings (1 in 39, $P = 1.0$), ASD (1 in 927, $P = 0.01$), ADHD (1 in 100, $P = 0.65$), ADHD controls (1 in 351, $P = 0.077$), and ID (1 in 788, $P = 0.015$; see Table I).

Clinical Assessment of Proband 1

The proband, NSB 3248, was the third child of non-consanguineous parents and a full-term but difficult pregnancy, due to stressful events and hyperemesis; there was no exposure or history of drugs, tobacco, and alcohol during pregnancy. Vaginal delivery proceeded without further complications. Birth weight was at 3,740 grams (75th centile), and length 50 cm (90th centile). Developmental milestones were within normal limits. At age 9, she scored an FS-IQ of 124. However, she began exhibiting sudden-onset cognitive changes, immaturity, distractibility, and impaired social interaction, disrupting her ability to function at school. She stopped speaking and communicated only in signs with little eye contact. She was transferred to her school's special education program. At age 10, she was diagnosed with schizophrenia, experiencing visual and auditory hallucinations, as well as severely worsening social impairment. Weight was reported at 57.6 kg (92nd centile), height 157.2 cm (78th centile), and OFC 5.2 cm (75–98th centile). She was reported to have no dysmorphic features or other physical abnormalities; high-resolution karyotype, thyroid function, and mag-

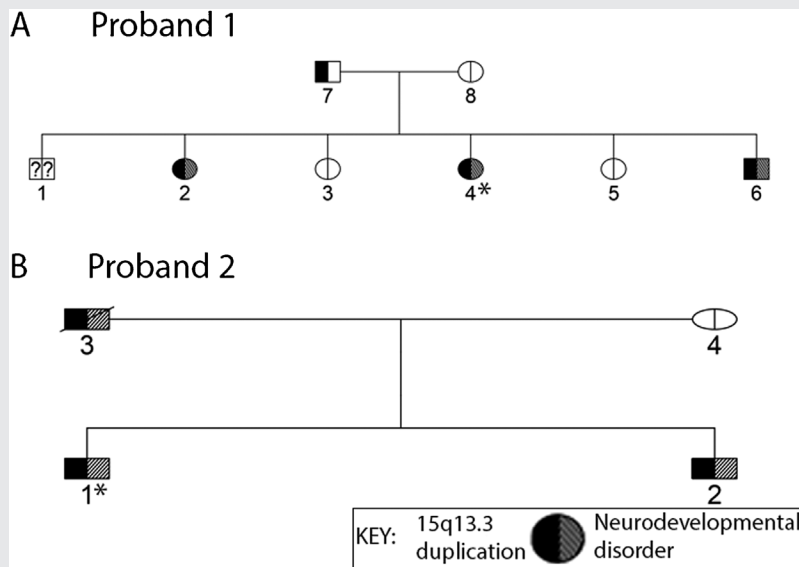


FIG. 1. (A) 1: Too young to be tested; 2: dyslexia; 4: COS; 6: Tourette syndrome. (B) 1: COS; 2: ADHD; 3: BPD and history of alcohol abuse.

netic resonance imaging (MRI) were reported normal. When admitted to the NIMH study at age 12, she exhibited additional psychotic behaviors, as well as flattened and inappropriate affect. She responded moderately well to clozapine (450 mg). At a 1-year follow-up, she exhibited more social interaction at home and in her special education program; she was maintained on clozapine. However, her hallucinations continued and she exhibited occasional outbursts and inappropriate touching at school.

Clinical Assessment of Proband 2

The proband, NSB 852, was the first child of non-consanguineous parents and an uneventful pregnancy. There was no exposure or

history of drugs and alcohol during pregnancy, but there was for tobacco (1 pack/day). Vaginal delivery proceeded without complications, with birth weight at 3,090 grams (10 to 25th centile). Developmental milestones were within normal limits. From birth to age 5, he witnessed significant domestic violence from his biological father, who left the family when the proband was 5. At age 7, problems with hyperactivity, distractibility, and social impairment were noted at school, at which time he scored a FS-IQ of 103 and was diagnosed with ADHD. He was hospitalized at age 11 for suicidal ideation, aggression towards peers, and threats of violence towards himself and others, and was diagnosed with major depression with psychotic symptoms. It was determined that he had been experiencing visual and auditory hallucinations for the

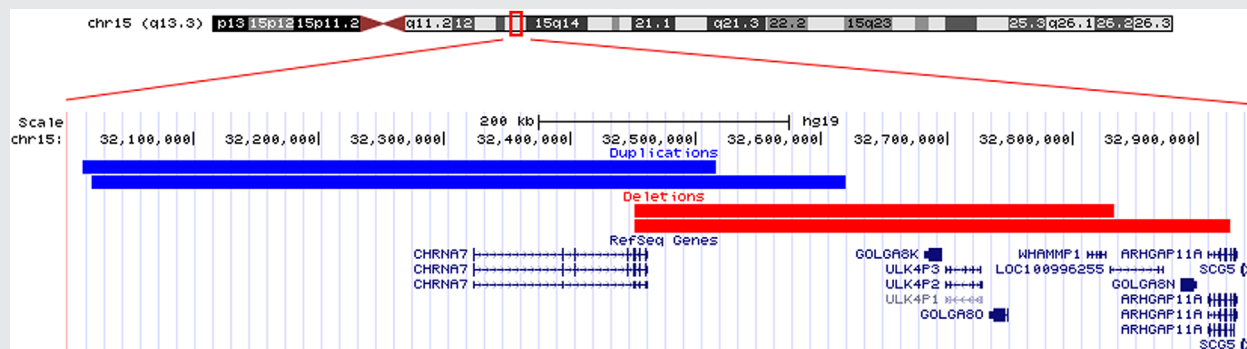


FIG. 2. The two 15q13.3 duplications and two deletions in COS patients share a region of overlap that includes the last two introns and one exon of every RefSeq CHRNA7 isoform. [Color figure can be seen in the online version of this article, available at <http://wileyonlinelibrary.com/journal/ajmgb>].

TABLE I. Comparing Rates of Duplications at 15q13.3 in Childhood-Onset Schizophrenia to Other Clinical Populations and Their Controls

Source	Population	Cases	Total	Frequency	P
COS	COS	2	136	1 in 68	
	Healthy Siblings	3	116	1 in 39	1.0 ^a
Szatkiewicz et al. (2014)	AOS	1	4,719	1 in 4,719	2.3×10^{-3} ^b
	Control	2	5,720	1 in 2,860	3.1×10^{-3} ^b
Moreno-De-Luca et al. (2013)	ASD	34	31,516	1 in 927	0.01
	Control	5	13,696	1 in 2,739	1.9×10^{-3} ^b
Williams et al. (2012)	ADHD	9	896	1 in 100	0.65
	Control	7	2,455	1 in 351	0.077
Cooper et al. (2011)	ID	20	15,767	1 in 788	0.015
	Control	3	8,330	1 in 2,777	2.5×10^{-3} ^b

Fisher's exact test comparing COS 15q13.3 duplication frequency to that in COS "healthy" (i.e., non-psychotic), full sibling pairs, adult-onset schizophrenia (AOS), autism spectrum disorder (ASD), attention deficit hyperactivity disorder (ADHD), and intellectual deficiency (ID), as well as their corresponding control groups. Adjusted for multiple comparisons with Bonferroni correction.

^aP-value from Fisher's exact test, using 77 COS probands and their 116 healthy, full siblings.

^bResults significant at $P < 0.0056$.

past year. At age 12, he was re-hospitalized for mood lability and vague aggressive ideation. He had hysterical crying spells, complained of being possessed with spirits or ghosts, and reported feeling controlled by forces from the outside; he was diagnosed with schizophrenia. He showed severe social impairment and had problems sleeping. He was noted to have prominent ears and large hands and feet. Fragile X DNA test, chromosome analysis, high-resolution banding, and electroencephalogram (EEG) were reported normal. At age 14, he was admitted to the NIMH COS study. In a 20-year follow-up, he was living independently, employed, and in a committed romantic relationship, responding very well to clozapine. When anxious however, he still experienced some visual hallucinations.

DISCUSSION

Our results implicate the 15q13.3 duplication and COS for the first time, expanding the understanding of the genetic risk factors underlying this rare form of schizophrenia and further demonstrating the pleiotropy of 15q13.3. These cases are of interest because the pathogenicity of the 15q13.3 duplication has been in doubt for AOS [Szafranski et al., 2010; Girirajan et al., 2012; Kirov et al., 2014]. Even with the necessarily small size of our rare COS population, the 15q13.3 duplication shows a higher rate in COS patients than observed for AOS patients (see Table I), as also seen for other COS CNVs [Ahn et al., 2014]. Stratifying by age of onset has been useful in medicine for identifying causal genetic variants; that we found a significant difference between the rate of this CNV in COS and AOS supports the importance of studying very early onset disorders. There are likely to be other CNVs or genetic factors which play a role, yet, that was not observed in these particular probands with current methods. The rate, however, is not significantly different to that in COS healthy (i.e., non-psychotic), full siblings because both of our probands carrying the inherited duplication share it with their "healthy" siblings who had non-psychotic neurodevelopmental disorders which were previously associated with the CNV (see Fig. 1), suggesting the duplication's incomplete penetrance for COS. In a review of 15q13.3

duplications of this size (D-CHRNA7-LCR-BP5), only 10.4% (7/67) of cases had normal phenotypes [Gillentine and Schaaf, 2015]. Similarly, in our two 15q13.3 duplication case families, the rate of neurodevelopmental disorders occurring in siblings who are 15q13.3 duplication carriers is 3/3 (100%) (see pedigree, Fig. 1). These findings support prior reports of this CNV being associated with Tourette syndrome [Melchior et al., 2013], ADHD [Williams et al., 2012], and language impairment [Pettigrew et al., 2015]. Interestingly, Proband 2 was diagnosed with COS and his sibling was diagnosed with ADHD, both inheriting the duplication from their father who was diagnosed with BPD. These multiple presentations support the variable expressivity of the CNV. Moreover, that Proband 1's father did not have a diagnosis of a neurodevelopmental disorder (though did report a history of transient hallucinations and poor memory) supports the duplication's incomplete penetrance. The rate of the duplication in COS was not significantly different to that in ASD, ADHD, and ID. This result could be a consequence of our conservative adjustment for multiple comparisons, but nevertheless it underlines the duplication's variable expressivity. These newly reported cases affirm the strong pleiotropic effect of this CNV, adding COS to the expanding list of associated psychiatric disorders.

The CNVs observed for COS at 15q13.3 contain the CHRNA7 gene, which encodes neuronal alpha-7 nicotinic acetylcholine receptors ($\alpha 7$ nAChRs). CHRNA7 is a front-running candidate gene for AOS, but its role in COS is not well understood due to the relative rarity of both the duplication and COS [Leonard et al., 2002; Ross et al., 2005; Stephens et al., 2009]. CHRNA7 has also been linked to other neurodevelopmental disorders, such as BPD, ADHD, epilepsy, Alzheimer's disease, and Rett syndrome [Sinkus et al., 2015]. Other genes, such as GREM1 and OTUD7A are also found at 15q13.3, but have not been associated with neurodevelopmental disorders. Additionally, many genes at this locus, such as the GOLGA8 family, ULK4P family, and uncharacterized LOC100996255/100131315 genes, have unknown function. CNVs at the 15q13.3 region likely arise due to its high susceptibility to non-allelic homologous recombination (NAHR), a problem in gene repair that occurs during meiosis.

CNVs disrupting *CHRNA7* are associated with poor episodic memory [Sinkus et al., 2015] and the P50 inhibitory deficit, a deficit in sensory gating that may underlie unconscious filtering of environmental interference [Gault et al., 1998; Beal, 2014; Sinkus et al., 2015]. Acetylcholine endogenously stimulates $\alpha 7$ nAChR, a five-unit ligand-gated ion channel found both pre- and post-synaptically, and results in the flux of Na^+ , K^+ , and Ca^{++} cations that mediate release of neurotransmitters including GABA, glutamate, acetylcholine, and dopamine [Sinkus et al., 2015]. Regulation of this receptor is complex, with over a dozen mechanisms regulating function and expression currently known. *CHRNA7* mRNA and protein are expressed most highly in nuclei involved in cognitive processing, such that expression of the gene is thought to play an important role in learning and the immune system. Particularly, $\alpha 7$ nAChR's role in calcium signaling influences synaptic plasticity, learning, and memory [Gillentine and Schaaf, 2015]. Patients with schizophrenia do not exhibit the inhibitory mechanism that normally follows the first response to stimuli (e.g., auditory clicks) [Leonard and Freedman, 2006]. In animal models, when $\alpha 7$ nAChR was blocked, the animals lost ability to inhibit auditory response. The *CHRNA7* gene also plays a protective role in inflammation, preventing cytokine expression after inflammatory events [Araud et al., 2011] and agonists for the *CHRNA7* receptor have anti-inflammatory roles [Beal, 2014]. Finally, 15q duplications have been associated with the abnormal organization of the hippocampus shown by anatomic brain MRI measures [Boronat et al., 2015] and superior olivary complex [Lukose et al., 2015]. The abnormal organization of the hippocampus is particularly notable because it is one of the regions of highest expression for $\alpha 7$ nAChR in postmortem brain studies [Gault et al., 1998].

The mechanism of how CNVs confer risk of developing psychiatric disorders is unknown. While deletions and duplications at the 22q11.2 locus appear to function in a dosage sensitive manner with deletions increasing risk and duplications protecting against schizophrenia [Rees et al., 2014], our findings suggest that both deletions and duplications at the 15q13.3 locus are pathogenic and operate by disturbing genetic pathways underlying neurodevelopment through abnormal *CHRNA7* gene dosage. This is supported by the fact that both previously reported cases of the 15q13.3 *deletion* in COS as well as the 15q13.3 *duplications* reported here occur at overlapping sites containing the last two introns and one exon of the *CHRNA7* gene (see Fig. 2) [Ahn et al., 2014]. Though it is assumed that duplications of *CHRNA7* lead to increasing $\alpha 7$ protein abundance and altered calcium signaling, it has yet to be shown in human studies. Further studies are necessary to verify *CHRNA7*'s role in developing COS.

The incomplete penetrance and variable expressivity of the 15q13.3 duplication represents a substantial challenge for affected families and their genetic counselors. This study contributes to the expanding number of neurodevelopmental disorders associated with the duplication, underlining the necessity of well-documented cases and therapeutics. Interestingly, both of our COS 15q13.3 duplication carriers responded well to clozapine. One of clozapine's main targets is blocking the 5HT₃ serotonin receptor, which releases high levels of acetylcholine, the main ligand of $\alpha 7$ nAChRs [Sinkus et al., 2015]. Higher concentrations of clozapine inhibit

$\alpha 7$ nAChRs. Further studies are needed to determine whether *CHRNA7* copy number affects pharmacological response.

A limitation of this study is that our sample exhibits greater racial heterogeneity compared to that, for instance, of the all-Swedish population of Szatkiewicz et al. (2014). Broader phenotyping may increase overall penetrance. Population studies ideally free of ascertainment bias are needed to further document this. While the comparisons of rate across clinical populations are complex, these findings are nevertheless highly suggestive of the strong genetic role of large, rare CNVs like the 15q13.3 duplication underlying the risk of developing COS.

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