Childhood-onset schizophrenia case with 2.2 Mb deletion at chromosome 3p12.2–p12.1 and two large chromosomal abnormalities at 16q22.3–q24.3 and Xq23–q28

Danielle Rudd¹,², Michael Axelsen², Eric A. Epping², Nancy Andreasen² & Thomas Wassink²

¹Interdisciplinary Graduate Program in Genetics, University of Iowa, Iowa City, Iowa
²Department of Psychiatry, University of Iowa, Iowa City, Iowa

Correspondence
Danielle Rudd, Interdisciplinary Graduate Program in Genetics, University of Iowa, Iowa City, IA 52242. Tel: 319-335-7743; Fax: 319-353-3003; E-mail: danielle.s.rudd@gmail.com

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Introductions
Childhood-onset schizophrenia (COS) describes an individual meeting the adult DSM criteria for schizophrenia, but with onset of psychosis before the age of 13 [1–3]. Childhood-onset schizophrenia is rare, comprising less than 1% of all schizophrenia cases [1, 2, 4, 5]. Compared to adult-onset schizophrenia, which often has an acute onset of disease, COS is more typically characterized by an insidious onset of psychosis in the context of a history of language and motor delays that lead to a marked deterioration in functioning [2, 3, 6–8]. Additional premorbid symptoms in COS can include social abnormalities, a variety of cognitive deficits, and behavioral disturbances [3, 6, 9].

Schizophrenia vulnerability appears to be largely determined by genetic factors and COS conforms to this pattern. Studies of environment have found no evidence for an increased role of nongenetic factors in etiology [8]; instead, COS cases have a higher frequency of large chromosomal abnormalities than is typically found in adult onset cases [8–12]. There is very little information available in the current literature highlighting individual patients because COS is such a rare condition. Here, we describe the use of chromosomal microarray (CMA) technology to discover two large de novo chromosomal duplications and an inherited 2.2 Mb deletion in a Caucasian female with COS.

Clinical Report
At the time of examination by our research center, the patient was an 18-year-old female referred to us because of a clinical history consistent with COS. The patient was the second-born of six siblings to healthy nonconsanguineous parents. Both the pregnancy and delivery were normal with a birth weight of 6 lbs. Parents described the patient as walking at 14 months, and though they could not recall exactly when she began to speak, they reported that it was within a normal developmental time frame.
Despite meeting these milestones, the parents also reported that the patient had a difficult time with independent locomotion, falling frequently, being “clumsy”, and having generally poor motor coordination. The parents also reported a long history of deficits in age-appropriate social skills. The patient had a limited range of social interaction compared to her siblings and developed few friendships with same-age peers. She seldom engaged in conversations, was considered for a diagnosis in the autism spectrum and in sixth grade was identified by school personnel as having “a behavioral impairment”. Academically the patient did well in early elementary school, scoring High Average in most performance areas on the Stanford Achievement Tests. She then experienced deterioration so that by sixth grade she began receiving special education services because she was no longer able

Figure 1. (A) The 2.2 deleted region of Chr3p12.2–p12.1. Top individual is the case subject, and bottom is the father. (B) Deletion does not overlap any genes.
to perform basic math or reading skills. At this time a sharp regression in motor skills was also noted.

At age 12 the patient was diagnosed with COS by a local psychiatrist. At age 16 the patient was referred to a regional medical center for a more extensive psychiatric evaluation which yielded the same diagnosis and she was seen in our center at the age of 18. Neuropsychological testing at that time showed a verbal IQ of 70, performance IQ of 65, and full-scale IQ of 67. The patient had global deficits including impairments in memory, language, and visual spatial skills with severe impairments in attention and concentration. The patient often appeared to be attending to internal stimuli. During assessment tasks, she would look away from test material then look back to the examiner and giggle or laugh. She would occasionally make inappropriate and bizarre comments and also exhibited inappropriate affect, exhibiting at various times giggling, laughter, crying, and agitation, all without clear stimuli. She was distractible, impulsive and would stare into space and whisper to herself under her breath as if attending to voices. She exhibited avolition, paucity of speech, and occasional echolalia. She had significant difficulties with abstract reasoning and problem solving and her judgment was poor. Based on this history and examination, the patient was given a diagnosis of COS of the disorganized type with an additional diagnosis of mild intellectual disability.

Materials and Methods

Chromosomal microarray Study

Peripheral blood samples from the patient, her mother and father were collected with informed consent through

Figure 2. (A) The 16.7 Mb duplicated region on chr16q22.3–q24.3. (B) Duplication overlaps 163 genes.
Figure 3. (A) The 43 Mb deletion of chromosome Xq23–q28. (B) The 43 Mb deletion of chromosome Xq23–q28.
a protocol approved by the University of Iowa IRB. This research has been conducted in accordance with the Declaration of Helsinki. DNA was extracted using a standard salt precipitation technique and run on Affymetrix SNP 6.0 arrays (Affymetrix, Santa Clara, CA) according to the recommendations of the manufacturer. Raw intensity data from the Affymetrix 6.0 arrays was analyzed for copy number changes using the publicly available analysis software program Affymetrix Genotyping Console 4.0 (Affymetrix). Copy number variant parameters included a 10 probe minimum and a quality control MAPD value <0.34. All CNVs were manually annotated using the UCSC Genome Browser (UCSC Mar. 2006 (NCBI36/hg18) assembly) (http://genome.ucsc.edu/). The CMA study showed three large chromosomal abnormalities: a 2.2 Mb deletion of chromosome 3p12.2–p12.1 that was

| Gene name | Gene description |
|-----------|------------------|
| ATP2C2    | Associated with speech and language impairment. |
| JPH3      | Brain specific expression and appears to have an active role in certain neurons involved in motor coordination and memory. |
| CDH15     | Defects in this gene are the cause of Huntington disease-like type 2. |
| FA2H      | Associated with neurodegeneration with brain iron accumulation. |
| ZNRF1     | Plays a role in the establishment and maintenance of neuronal transmission and plasticity. Regulates Schwann cells differentiation by mediating ubiquitination of GLUL. Promotes neurodegeneration by mediating 'Lys-48'-linked polyubiquitination and subsequent degradation of AKT1 in axons: degradation of AKT1 prevents AKT1-mediated phosphorylation of GSK3β, leading to GSK3β activation and phosphorylation of DPYSL2/CRMP2 followed by destabilization of microtubule assembly in axons. |
| CNTNAP4   | This gene product belongs to the neurexin family, members of which function in the vertebrate nervous system as cell adhesion molecules and receptors. |
| DYNLRB2   | High expression in brain. |
| GAN       | Deletion of this gene associated with autism. |
| CMIP      | Associated with speech and language impairment. Deletion of this gene associated with autism. |
| CDH13     | This gene encodes a member of the cadherin superfamily. The protein lacks the cytoplasmic domain characteristic of other cadherins, and so is not thought to be a cell-cell adhesion glycoprotein. This protein acts as a negative regulator of axon growth during neural differentiation. Expressed at higher levels in adult brain than in developing brain. Associated with working memory and ADHD. Previous association with autism and schizophrenia. |
| NECAB2    | Widely expressed, highest levels in cerebellum, brain cortex, hippocampus, pons, putamen, and amygdala. Highly expressed in neurons, but also present in glial cells. Slightly higher expression in the dorsolateral prefrontal cortex of schizophrenic patients compared to control individuals. |
| KIAA0513  | Widely expressed, highest levels in cerebellum, brain cortex, hippocampus, pons, putamen, and amygdala. Highly expressed in neurons, but also present in glial cells. Slightly higher expression in the dorsolateral prefrontal cortex of schizophrenic patients compared to control individuals. |
| ZDHHC7    | Palmitoyltransferase with broad specificity. Palmitoylates SNAP25 and DLG4/PSD95. May palmitoylate GABA receptors on their gamma subunit (GABRG1, GABRG2, and GABRG3) and thereby regulate their synaptic clustering and/or cell surface stability. |
| SLC7A5    | Involved in the transport of L-DOPA across the blood-brain barrier, and that of thyroid hormones triiodothyronine (T3) and thyroxine (T4) across the cell membrane in tissues such as placenta. Plays a role in neuronal cell proliferation (neurogenesis) in brain. Involved in the uptake of methylmercury (MeHg) when administered as the L-cysteine or D,L-homocysteine complexes, and hence plays a role in metal ion homeostasis and toxicity. May play an important role in high-grade gliomas. Mediates blood-to-retina L-leucine transport across the inner blood-retinal barrier which in turn may play a key role in maintaining large neutral amino acids as well as neurotransmitters in the neural retina. |
| ZFPML1    | Mainly expressed in hematopoietic tissues. Also expressed in adult cerebellum, stomach, lymph node, liver, and pancreas. |
| TCF25     | A member of the basic helix-loop-helix (bHLH) family of transcription factors that are important in embryonic development. In the embryo, widely expressed with highest levels in brain. |
| TUBB3     | This gene encodes a class III member of the beta tubulin protein family. Beta tubulins are one of two core protein families (alpha and beta tubulins) that heterodimerize and assemble to form microtubules. This protein is primarily expressed in neurons and may be involved in neurogenesis and axon guidance and maintenance. |
| ZNFF78    | This gene is a candidate gene for autism and variable cognitive impairment in the 16q24.3 microdeletion syndrome. |
| ANKRD11   | Mutations in this gene have been associated with KGB syndrome, which is characterized by macrodontia, distinctive craniofacial features, short stature, skeletal anomalies, global developmental delay, seizures, and intellectual disability. Deletion has been associated with autism. |
| ACSF3     | Defects in ACSF3 are the cause of combined malonic and methylmalonic aciduria (CMAMMA) [MIM:614265]. A metabolic disease characterized by malonic and methylmalonic aciduria, with urinary excretion of much larger amounts of methylmalonic acid than malonic acid, in the presence of normal malonyl-CoA decarboxylase activity. Clinical features include coma, ketoacidosis, hypoglycemia, failure to thrive, microcephaly, dystonia, axial hypotonia and/or developmental delay, and neurologic manifestations including seizures, psychiatric disease and/or cognitive decline. |
inherited from the father (Fig. 1A), a de novo 17.6 Mb duplication of chromosome 16q22.3–q24.3 (Fig. 2A), and a de novo 43 Mb deletion of chromosome Xq23–q24 (Fig. 3A). None of the three chromosomal abnormalities were found in control individuals according to the Database of Genomic Variants.

Follow-up molecular confirmation was performed with a NimbleGen 2.1 million probe whole-genome tiling array (Promega, Madison, WI) and processed according to the instructions of the manufacturer. The NimbleGen arrays were scanned using a GenePix 4000B scanner (Molecular Devices, Sunnyvale, CA), signal intensity data were analyzed using NimbleScan software (NimbleGen), and CNV calling was performed using Nexus software (BioDiscovery, El Segundo, CA). All three CNVs were identified on the NimbleGen array.

Discussion

The general course of this patient’s clinical history is consistent with what little information is available for cases of COS. The patient had an insidious onset of illness with deterioration in early childhood across multiple domains of functioning including social interaction, behavior, and general intellectual abilities. Psychotic and disorganized symptoms did not present until the age of 12, but have persisted into adulthood. Childhood-onset schizophrenia often initially resembles a pervasive developmental disorder. However, as is the case with this patient, the emergence of psychotic symptoms in pre-teen years that remain across the life span place the diagnosis in the psychotic spectrum [1].

Cases of COS are noted for having a high rate of cytogenetic abnormalities (10.6%) compared to the general population (0.85%) and adult-onset cases [9, 13, 14]. An early study examined differences between COS patients with and without cytogenetic abnormalities and found that those with aberrations had lower performance IQs and more impairments of premorbid language, motor, and social development [9]. De novo CNVs are associated with schizophrenia [15], specifically with COS [16]. These findings are consistent with our patient who received special education and exhibited behavioral and social abnormalities. The patient described here had Verbal IQ = 70, Performance IQ = 65, and Full Scale IQ = 67, which are considered low [3].

This patient harbored three large chromosomal abnormalities: a paternally inherited 2.2 Mb deletion of chromosome 3p12.2–p12.1, a de novo 17.6 Mb duplication of chromosome 16q22.3–q24.3, and a de novo 43 Mb deletion of chromosome Xq23–q24. The paternally inherited 2.2 Mb deletion at chromosome 3p12.2–p12.1 does not contain any genes (Fig. 1B). Partial trisomy 16 is rare, most likely because of lethality, and phenotype associations are complicated by the frequent presence, as in our case, of additional monosomies or trisomies [17]. Patients with proximal 16q duplications are often characterized by a variable phenotype of developmental and speech delay, learning difficulties, and behavioral problems [18]. More distal duplications, as in our patient, are associated with an even wider array of developmental and organ system abnormalities [19]. The 16.7 Mb duplicated region of chromosome 16q22.3–q24.3 in our patient contains 163 genes (Fig. 2B). Twenty of the genes in the region are of interest due to previously associations with schizophrenia or autism, high or specific brain expression, or an association with other neuropsychiatric disorders (Table 1).

The region on the X chromosome deleted in this patient is categorized as one of two critical regions responsible for normal ovarian function (Fig. 3B) [20, 21]. Specifically, the Xq26.2–q28 region is proposed to be associated with premature ovarian failure [20]. There is no definitive association between Xq perturbations and cognitive impairment. There are a few reports of patients with large Xq disruption and an associated cognitive impairment, however, those patients had translocations that affected other autosomal chromosomes [20].

This case report is an important contribution to the medical genetics field because it adds to a very small body of literature on the potential underlying genetics of COS. To date, there are very few reports of cases of COS that can be attributed to chromosomal abnormalities. We contribute to this body of literature by describing a young female patient with COS and three large chromosomal abnormalities.

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Conflict of interest

None declared.

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