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Maternally Derived Microduplications at 15q11-q13: Implication of Imprinted Genes in Psychotic Illness

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Abstract

Objective—Rare copy number variants have been implicated in different neurodevelopmental disorders, with the same copy number variants often increasing risk of more than one of these phenotypes. In a discovery sample of 22 schizophrenia patients with an early onset of illness (10–15 years of age), the authors observed in one patient a maternally derived 15q11-q13 duplication overlapping the Prader-Willi/Angelman syndrome critical region. This prompted investigation of the role of 15q11-q13 duplications in psychotic illness.

Method—The authors scanned 7,582 patients with schizophrenia or schizoaffective disorder and 41,370 comparison subjects without known psychiatric illness for copy number variants at 15q11-q13 and determined the parental origin of duplications using methylation-sensitive Southern hybridization analysis.

Results—Duplications were found in four case patients and five comparison subjects. All four case patients had maternally derived duplications (0.05%), while only three of the five comparison duplications were maternally derived (0.007%), resulting in a significant excess of maternally derived duplications in case patients (odds ratio=7.3). This excess is compatible with earlier observations that risk for psychosis in people with Prader-Willi syndrome caused by maternal uniparental disomy is much higher than in those caused by deletion of the paternal chromosome.

Conclusions—These findings suggest that the presence of two maternal copies of a fragment of chromosome 15q11.2-q13.1 that overlaps with the Prader-Willi/Angelman syndrome critical region may be a rare risk factor for schizophrenia and other psychoses. Given that maternal duplications of this region are among the most consistent cytogenetic observations in autism, the findings provide further support for a shared genetic etiology between autism and psychosis.

Genomic microdeletions and microduplications (commonly termed copy number variants) are now known to contribute to the etiology of schizophrenia (1–4), autism (5, 6), and intellectual disability (7, 8). In schizophrenia and related psychoses, the most robust findings concern microdeletions at chromosomes 1q21.1, 15q11.2, 15q13.3, and 22q11.2 (2–4) as well as the *NRXN1* gene (9) and micro-duplications at chromosomes 16p11.2 (10) and 16p13.1 (11). The finding of a nonspecific relationship between neurodevelopmental phenotypes and specific copy number variants appears to be a general feature. For example, the schizophrenia-related deletion at 1q21.1 has been reported in cases of autism (6) and intellectual disability (7). The same appears to be true for deletions at 15q13.3 (8) and 15q11.2 (12) and duplications at 16p11.2 (6) and 16p13.1 (13). That the same copy number variants associate with schizophrenia, autism, intellectual disability, and other neurodevelopmental disorders indicates a genetic overlap among these seemingly disparate diagnoses.

Aiming to discover novel pathogenic copy number variants, we performed a genome-wide copy number variant scan of 22 Danish schizophrenia patients with an early onset of disease (aged 10–15 years), under the premise that developmental forms of the disorder would be particularly enriched in this group (1). One of the patients carried a 6-Mb duplication of chromosome 15q11.2-q13.1. This duplication involves the Prader-Willi syndrome (Online Mendelian Inheritance in Man [OMIM] number: 176270) and Angelman syndrome (OMIM number: 105830) critical region. These syndromes derive, respectively, from paternal and

maternal chromosomal deletions (as well as other mechanisms [see Discussion section]). Duplications of the Prader-Willi/Angelman syndrome critical region were recognized in several case reports in the mid-1990s as a separate genomic syndrome, the 15q11.2-q13.1 duplication syndrome (OMIM number: 608636), which commonly includes features such as autism, intellectual disability, seizures, developmental delay, and minor dys-morphic features (macrocephaly, down-slanting palpebral fissures, expressionless face), most often when the duplications are maternally derived (14–16). These duplications are currently among the most consistent cytogenetic findings in autism spectrum disorders, estimated to account for 0.5%–3% of all cases (17–19), although the more realistic rate is closer to approximately 0.6%, based on 13 observations in the largest study, which consisted of 2,268 cases (18).

Given the evidence that this region is important in different neurodevelopmental disorders, we investigated the involvement of chromosome 15q11-q13 duplications in schizophrenia and related psychoses in a large European sample consisting of 7,582 patients affected with schizophrenia or schizoaffective disorder and 41,370 comparison subjects. Since we did not have DNA samples for many of the identified carriers' parents, we used a methylation-sensitive Southern hybridization analysis to determine the parental origin of the duplications. This analysis distinguishes between maternally and paternally derived duplications without genotyping the parents of carriers.

Method

Samples and Genotyping

Danish sample (discovery and follow-up assessment)—The Danish sample consisted of 524 patients clinically assigned with a diagnosis of schizophrenia according to ICD-10, without ever having received a diagnosis of mania or bipolar illness (F30-31). Information on all hospital contacts as well as corresponding principal ICD-8 (1969–1994) and ICD-10 (1994–2006) diagnoses was obtained through the Danish Psychiatric Central Register (20). The diagnoses were verified by an experienced psychiatrist using the OPCRIT checklist, with 96% of patients who fulfilled ICD-10 criteria for schizophrenia also fulfilling DSM-IV criteria. The majority (85%) of patients were ethnic Danes, while 15% of patients had one Caucasian parent born in another North European country. The comparison group consisted of 477 healthy subjects from the Danish Blood Donor Corps in the Copenhagen area. Patients with an inpatient admission before age 16 (age: 12–15 years [N=22]) were assessed in the discovery sample, while the remaining patients, as well as all comparison subjects, were assessed in the follow-up sample. The 22 patients from the discovery sample were genotyped on the Illumina HumanCNV370 microarray at deCODE Genetics (Reykjavik, Iceland), and the follow-up sample was genotyped on the Illumina Human610-Quad array, described elsewhere (11) (for further details, see Table 1 in the data supplement accompanying the online version of this article). Copy number variant calling was done using the PennCNV algorithm (21) and verified through visual inspection of log-R ratios and B-allele frequencies in the 15q proximal region.

SGENE-plus study follow-up sample—A total of 3,879 persons diagnosed with schizophrenia or schizoaffective disorder and 35,590 comparison subjects, all from six European populations, were successfully examined for copy number variants at the locus studied in the present analyses. An additional 5,773 genotyped samples of individuals of Icelandic origin were examined but excluded from association analysis because of other psychiatric or developmental disorders (autism, bipolar disorder, attention deficit hyperactivity disorder [ADHD], dyslexia, and alcoholism) and/or first-degree relationships to schizophrenia patients. A full description of the sample and genotyping is provided

elsewhere (11) (also see Table 1 in the data supplement). Copy number variant calling was done using the PennCNV algorithm (21) and verified through visual inspection of log-R ratios and B-allele frequencies in the 15q proximal region.

International schizophrenia Consortium sample—The International Schizophrenia Consortium sample consisted of 3,391 patients with schizophrenia or schizoaffective disorder and 3,181 comparison subjects, all of European descent. Full description of the sample, genotyping, and copy number variant calling is provided elsewhere (3). A total of 661 patients and 670 comparison subjects from Aberdeen, Scotland, overlap between the SGENE-plus and International Schizophrenia Consortium samples and were only counted once in the present study (also see Table 1 in the data supplement).

Cardiff University sample—The Cardiff University sample consisted of 471 affected individuals (schizophrenia patients [N=447]; schizoaffective disorder patients [N=24]) and 2,792 comparison subjects, the latter being from the Wellcome Trust Case Control Consortium. The comparison subjects were volunteers from the National Blood Service and were born in the United Kingdom during 1 week in 1958. Details of the sample as well as genotyping and copy number variant calling are provided elsewhere (4) (also see Table 1 in the data supplement).

Ethical approval was obtained from the local ethics committees at each study site. After complete description of the study to the subjects, written informed consent was obtained.

Methylation-Sensitive Southern Analysis

We performed a methylation-sensitive Southern hybridization on 12 identified carriers to determine the parental origin of 15q11-q13 duplications. This method has previously been applied for this purpose (22). It exploits the different methylation patterns in paternal and maternal chromosomes in this region, and thus parental origin can be established without genotyping parents of carriers. However, this assay cannot distinguish between inherited and de novo duplications. DNA was digested with the XbaI and methylation-sensitive NotI enzymes, and the products ran on agarose gel. We constructed a probe containing the exon alpha of *SNPRN*, which maps to a region duplicated in all 12 carriers (Human Genome [National Center for Biotechnology Information Build 36]: chromosome, 15:22,751,022–22,751,415), and performed a Southern hybridization of the digested DNA using standard techniques. The probe detects a 4.2-kb band from methylated maternal DNA and a 0.9-kb band from unmethylated paternal DNA in the XbaI and NotI digestion. Hybridization intensity was quantified using Kodak 1D Image Analysis Software, v.3.5, (Rochester, N.Y.) and ratios between intensities of paternal and maternal bands calculated to determine dosage after subtracting background emission. Full details of the method and analysis are provided in section 2 of the data supplement.

Results

In addition to one discovery sample patient (case 1), we identified the following 11 15q11-q13 duplication carriers: one male German schizophrenia patient (case 2), one female schizoaffective disorder patient (case 3) and one male schizophrenia patient (case 4) from the United Kingdom, one female Icelandic schizophrenia patient (case 5), one female Icelandic bipolar I disorder patient (case 6), one female Icelandic autism patient (case 7), and five female Icelandic comparison subjects (comparison subjects 1–5). Case patients 6 and 7 were identified from the 5,773 individuals in the Icelandic sample who had a psychiatric or developmental disorder other than schizophrenia or who were first-degree relatives of a schizophrenia patient. These individuals were excluded from case-control

association analysis. Case patients 2, 6, and 7 and comparison subjects 2, 4, and 5 carried duplications corresponding to those found in the Danish discovery sample patient (at breakpoint [BP] 1–BP3 [Table 1, Figure 1]). Case patients 3 and 4 and comparison subjects 1 and 3 carried a slightly smaller duplication corresponding to the Prader-Willi/Angelman syndrome critical region (BP2, BP3), while case patient 5 carried a roughly 9-Mb duplication spanning across BP1–BP4 and a part of the region between BP4 and BP5. The duplications in case patients 2–4 have been reported in previous genome-wide copy number variant studies in schizophrenia (3, 4, 23). However, each of these studies only found one duplication and parental origin was not assessed, and thus the duplications were not discussed specifically in these studies.

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Chromosome 15q11-q13 Duplication				15q11-q13 Duplication Syndrome Features[a]				
Parental Origin	**Transmission Status**	**Breakpoints (build 36)**	**Genotyping Platform**	**Age at Assessment (years)**	**Autistic Features**	**Intellectual Disability**	**IQ**	**Developmental Delay**
Maternal	Unknown	20306549-26208861	Human370CNV	49	[b]	Yes	[b]	Motor
Maternal	Unknown	20306549-26208861	HumanHap300	23	Yes	No	81	Motor, language
Maternal	Unknown	21240037-26208861	Affy500K	45	[b]	[b]	[b]	[b]
Maternal	Unknown	21205736-26360355	Affy5.0	53	[b]	[b]	[b]	[b]
Maternal	Yes	20306549-29344873	HumanHap300	43	[b]	Yes	64–68	Cognitive, social
Maternal	Unknown	20306549-26208861	HumanHap300	13, 58	[b]	[b]	[b]	Social
Maternal	De novo	20306549-26208861	HumanHap300	5	Yes	Yes	56	Motor, language
Paternal	Yes	21240037-26208861	HumanHap300		Unknown	Unknown	Unknown	Unknown
Paternal	Unknown	20306549-26208861	Human370CNV		Unknown	Unknown	Unknown	Unknown
Maternal	Unknown	21240037-26208861	HumanHap300		Unknown	Unknown	Unknown	Unknown
Maternal	Unknown	20306549-26208861	HumanHap300		Unknown	Unknown	Unknown	Unknown
Maternal	Unknown	20306549-26208861	HumanHap300		Unknown	Unknown	Unknown	Unknown

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Parental Origin of Duplications

We performed a methylation-sensitive Southern analysis of all 12 duplication carriers and found that all seven individuals with a neuropsychiatric diagnosis (cases 1–7) carried maternally derived duplications. Comparison subjects 3–5 also carried maternally derived duplications, while comparison subjects 1 and 2 carried paternally derived duplications (Figure 1, Table 1 [also see section 2 in the data supplement]). A two-sided Fisher's exact test based only on the follow-up schizophrenia/ schizoaffective disorder case samples (cases 2–5) showed a nominally significant overrepresentation of maternally derived duplications, relative to comparison subjects (case patients [N=4/7,582] versus comparison subjects [N=3/41,370]: p=0.01, odds ratio=7.3, 95% confidence interval=1.2–50).

Phenotypic Features of Duplication Carriers

It is notable that case patient 6 has severe psychotic features, although the patient met study criteria for bipolar disorder and therefore was not included in the association analysis for schizophrenia/schizoaffective disorder, while case patient 7 was diagnosed with childhood autism, mild intellectual disability, and specific developmental disorder of motor function. Details for all 12 carriers, including primary diagnosis, sex, age at onset, and family history of psychiatric illness as well as the most commonly reported phenotypic features of 15q11-q13 duplications, are summarized in Table 1. Detailed summaries for case patients 1–7 are presented in section 3 of the data supplement.

Some but not all case patients had an early age at onset of psychiatric illness. Case patient 2 was diagnosed with a developmental language disorder and early childhood autism features prior to a diagnosis of schizophrenia at 18 years of age (see section 3 in the data supplement). Case patients 4 and 6 had an age at onset of 16 and 13 years, respectively. Case patient 1 also had an early age at onset, as dictated by the inclusion criteria for the discovery sample. Case patient 5 was diagnosed with schizophrenia at age 21 years, while case patient 3 was first admitted to the hospital for psychiatric illness at age 41 years. We observed a tendency for intellectual disability and developmental delay among the case carriers, since three have mild intellectual disability and five have developmental delay (Table 1). Neuropsychiatric evaluation of the five comparison carriers has not been performed, and therefore we do not know whether they share some features with the case patients. All of the case patients have a family history of psychiatric illness. Unfortunately, we do not have access to DNA samples for most of the affected relatives, and we only know the duplication status for three of these relatives as follows: the mother of case patient 5 has bipolar disorder and carries the 15q11-q13 duplication; the brother of case patient 6 has bipolar disorder but does not carry the duplication; and the sister of case patient 7 had idiopathic seizures in early childhood and has ADHD but does not carry the duplication. This suggests that in these families, the 15q11-q13 duplications are not the sole mechanisms underpinning disease, a phenomenon that has been noted previously (18). We found no additional large (>500 Kb) copy number variants among the 12 15q11-q13 duplication carriers, and therefore we cannot pinpoint a "two-hit" copy number variant model mediating the developmental phenotype, as was suggested for microdeletions at chromosome 16p12.1 in a recent study (24).

Origin of Duplications in Carriers

Both parents of case patient 7 have been genotyped on single nucleotide polymorphism microarrays, and therefore we could determine that the duplication is de novo in this patient. Through analysis of the genotypes in case 7 and in the parents of this patient, we could determine that the duplicated alleles were derived from both chromosomes of the patient's mother, suggesting interchromosomal nonallelic homologous recombination (25) as the mutational mechanism. Furthermore, for comparison subject 1, analysis of microsatellite

genotypes from other family members revealed that the duplication is present de novo in the subject's father, most likely through an interchromosomal nonallelic homologous recombination in the father's germline (see section 4 in the data supplement). This evidence is consistent with the notion that most deletions and duplications in the 15q11-q13 region are mediated through nonallelic homologous recombination between the low copy repeat regions associated with BP1–BP5 (reviewed in 19) (Figure 1) and that large duplications derived through this mechanism most often occur via interchromosomal crossover (26). Medical records for case patient 5 show that the duplication was transmitted to the patient from the mother (established through a clinical genetics analysis of the patient and the patient's mother performed prior to the present study). DNA samples were not available for parents of other carriers, and therefore we could not assess whether the duplications in these individuals are de novo or inherited.

Discussion

Duplications of the Prader-Willi/Angelman critical region are a recognized genomic syndrome (OMIM number: 608636), wherein the most commonly observed features include autism, developmental delay, intellectual disability, seizures, and hypotonia. In most cases where the parental origin of the duplications has been assessed, the syndrome-associated features were present only when duplications were maternally derived (14–16), although a developmental phenotype has been observed in single carriers of paternally derived duplications (reviewed in 19).

In the present study, we report that maternally derived 15q11-q13 duplications may also act as risk factors for schizophrenia and related psychoses. The carriers with psychosis also show known features of 15q11-q13 duplication syndrome and other genomic syndromes (e.g., developmental delay and intellectual disability) (Table 1). However, other features, including seizures and hypotonia, were not observed in the medical records available to us for the carriers. Only one of the carriers with psychotic illness has a previous diagnosis of autism (case 2). The other carriers have no known history of autistic features, and therefore we judge it unlikely that they represent autism patients misdiagnosed as schizophrenia patients.

Although the occurrence of 15q11-q13 duplications in schizophrenia and psychotic illness is rare, and the significance level of association is nominal (p=0.01), the hypothesis for association is supported by two independent lines of evidence. The first comes from observed differences in the clinical manifestation of the various genotypes causing Prader-Willi and Angelman syndromes (27, 28). Angelman syndrome arises from disruptions that lead to a lack of maternally expressed gene product(s), maternally derived deletions of the critical interval, paternal uniparental disomy, and mutations of the key maternally expressed imprinted gene *UBE3A*. Patients with Angelman syndrome have severe to profound mental retardation, microcephaly, seizures, and ataxia and almost always lack speech (29, 30). Prader-Willi syndrome is caused in approximately 70% of cases by deletion of the paternal chromosome for the critical region (27). Most other cases have maternal uniparental disomy, having received two maternal copies of the region, with the paternal chromosome being absent. Rare cases are caused by mutations in the imprinting center, leading to methylation defects. Despite diverse mechanisms, all individuals with Prader-Willi syndrome have in common a lack of paternally expressed gene product(s). Prader-Willi syndrome is characterized by a failure to thrive in infancy, mild learning disabilities, and, on emerging from infancy, an abnormal satiety response to food intake and obsession with food, sexual immaturity, short stature, and a characteristic physical phenotype (31). In addition to these core deficits, individuals with Prader-Willi syndrome are prone to affective disorders, including mood instability, nonpsychotic depression, and psychosis, features not observed in

Angelman syndrome (29, 30). Moreover, and of particular relevance to our finding, Prader-Willi syndrome resulting from maternal uniparental disomy is several-fold more frequently associated with psychotic episodes than the paternal deletion subtype (Table 2). This has been reported in three independent studies from different countries. One study on Prader-Willi syndrome conducted in the United Kingdom identified psychotic illness at a significantly higher rate in 33 patients with maternal uniparental disomy compared with 82 patients with paternal deletions (61.8% versus 16.5%, respectively, $p<0.001$, odds ratio=8.2) (27). Two other studies also reported that the maternal uniparental disomy subtype is associated with mixed symptoms of bipolar mood disorder and psychosis at high frequencies (32, 33). Together, these studies suggest that having two maternal copies of the chromosome (leading to overexpression of maternally derived genes) is the important factor for risk of psychosis in Prader-Willi syndrome, rather than the loss of expression of genes from the paternal chromosome. This is consistent with our observation of overrepresentation of maternally derived duplication of the 15q11-q13 region in schizophrenia and schizoaffective disorder. Interestingly, among the carriers identified in our study, case patient 3 has a schizoaffective disorder, case patient 5 (schizophrenia) has prominent affective symptoms, and case patient 6 (bipolar disorder) also has prominent psychotic features (see section 3 in the data supplement), similar to the common presentations reported by both Vogels et al. (33) and Verhoeven et al. (34).

The second line of evidence comes from the confirmed role of 15q11-q13 duplications in the etiology of autism (17–19). As discussed in the introduction, there is now a strong and growing body of evidence that autism and psychotic illness partially share genetic etiology, with copy number variants that associate with schizophrenia and related psychoses also being observed at elevated rates in autism. Our current finding adds another locus to the list of copy number variants that increase susceptibility to both disorders.

The 15q11-q13 region contains a cluster of imprinted genes (genes that are expressed only when transmitted from either mother or father but not both). Several of these are only expressed from the paternal chromosome, while at least one gene, *UBE3A*, is only expressed from the maternal chromosome and is robustly imprinted in the brain (35). The product of this gene, E6-AP ubiquitin ligase, regulates the degradation of certain proteins in neurons such as the synaptic protein Arc, which promotes the internalization of AMPA receptors at excitatory synapses, thus linking *UBE3A* to regulation of glutamatergic signaling and synaptic development (35). A mouse model lacking *UBE3A* shows impaired long-term potentiation in the hippocampus and, consequently, a learning and memory deficit (36). Another gene in the region, *ATP10A*, encoding an amino-phospholipid-transporting ATPase involved in transporting phosphatidylserine and phosphatidylethanolamine from one side of a lipid bilayer to another, is of unknown imprinting status but is probably maternally expressed in the brain in at least some individuals (possibly depending on gender) (37), while the mouse *ATP10A* is not imprinted in the brain (38).

Chromosome 15 harbors several loci implicated in schizophrenia and other neurodevelopmental disorders. There is a series of low copy repeat regions near the centromere. Such regions are liable to create nonallelic homologous recombination between the parental chromosomes because of the high homology between these repeats, resulting in deletions or duplications of the regions in between (25). There are five well-recognized low copy repeat regions in the 15q11-q13 region (commonly termed BP1–BP5, reviewed in Hogart et al. [19]). Our finding differs from previous findings concerning the 15q proximal region, which have implicated deletions at 15q11.2 between BP1 and BP2 (chromosome 15: 20,306,549–20,777,695) and at 15q13.3 between BP4 and BP5 (chromosome 15: 28,723,577–30,302,218) in schizophrenia (2–4) as well as duplications in general occurring within the BP1–BP5 region in autism, intellectual disability, and schizophrenia (39). The

study by Itsara et al. (39) combined data from different genome-wide copy number variant studies, and in fact the only schizophrenia case reported by these authors is that of case patient 4 in the present study (first reported by the International Schizophrenia Consortium [3]). Our data, together with previous findings of high occurrence of psychosis in the maternal uniparental disomy subtype of Prader-Willi syndrome (40), suggest that maternally expressed gene products in the region between BP2 and BP3 (Figure 1) might be involved in mediating risk of psychosis. Also, our study provides new suggestive evidence of psychotic illness belonging to the phenotypic spectrum of the 15q11-q13 microduplication syndrome (OMIM number: 608636).

A limitation to our study, however, is the rarity of 15q11-q13 duplications in schizophrenia and related psychoses in general, and therefore a follow-up study of individuals with 15q11-q13 microduplication syndrome is needed to estimate the prevalence of psychotic features in adult-hood in the syndrome. Another limitation is the lack of DNA samples from close family members of most of the identified carriers to determine transmission status of the duplications and cosegregation with illness. Also, we have no neuropsychiatric assessment of the carriers identified among comparison subjects. These are individuals who have participated in various genetic studies at deCODE Genetics (diagnosis is provided in Table 1 for the two who participated as patients in a specific disease study). All five subjects were adults at the time of their recruitment, and therefore it is unlikely that they have a severe form of the duplication syndrome. Our study, together with that of Glessner et al. (18), provides a good estimate of the prevalence of maternally derived 15q11-q13 duplications in autism and schizophrenia spectrum disorders as well as in the control population, with a prevalence of 0.5–1 out of 100, 1,000, and 10,000 individuals, respectively.

In conclusion, our findings of schizophrenia and psychotic illness in carriers of maternally derived 15q11-q13 duplications suggest that an excess of maternally expressed gene products in this region may be involved in the etiology of psychosis. Although rare in psychotic illness compared with autism spectrum disorders (0.05% versus 0.6%, respectively), exploration of the effects of this duplication in model systems has the potential to provide insight into the biological processes underlying psychosis.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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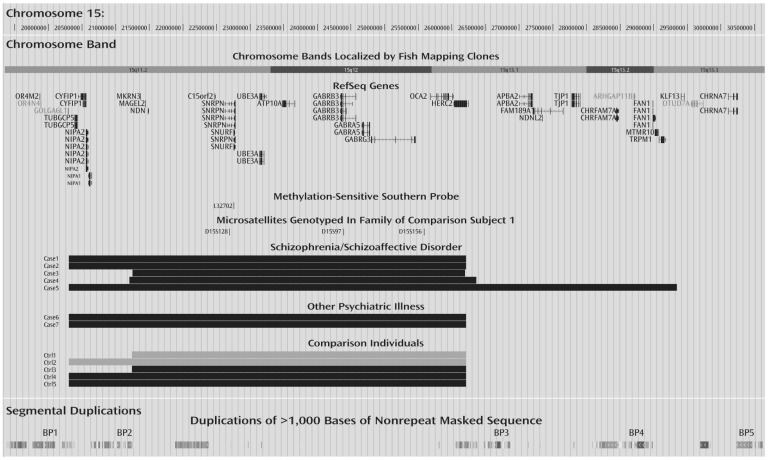

FIGURE 1. The Chromosome 15q11.2-q13.3 region[a]

[a] The data depict chromosomal coordinates according to the National Center for Biotechnology Information Build 36 (top), followed by chromosome bands, annotated genes from the National Center for Biotechnology Information Reference Sequence database, tracks indicating the Southern hybridization probe, microsatellites used to determine duplication origin, tracks indicating the duplications identified in the present study, and segmental duplications in the region, with common breakpoints (BPs) of Prader-Willi and Angelman syndromes (BP1–BP5). All duplications were maternally derived except two of the comparison duplications, which were paternally derived (gray bars). (Figure adapted with permission from the Human [Homo Sapiens] Genome Browser Gateway [http://genome.ucsc.edu/]. Kent WJ, Sugnet CW, Furey TS, Roskin KM, Pringle TH, Zahler AM, Haussler D: The Human Genome Browser at UCSC. Genome Res 2002; 12:996-1006).

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TABLE 1

General and Psychiatric Characteristics, Duplication Details, and 15q11-q13 Duplication syndrome Features in Identified Carriers

Participant	General Features				
	Sex	Diagnosis	Age at Onset (years)	Family History: Psychopathology	Family History: Duplication Status
Case patient 1 (Danish)	Male	Schizophrenia	10	Three brothers with schizophrenia; mother with unknown mental illness	Unknown in all four
Case patient 2 (German)	Male	Schizophrenia	18	One brother with depressive mood	Unknown
Case patient 3 (United Kingdom)	Female	Schizoaffective disorder	41	One daughter with autism, intellectual disability, and schizophrenia	Unknown
Case patient 4 (United Kingdom)	Male	Schizophrenia	16	Mother with schizophrenia and low IQ; one brother with possible schizophrenia and low IQ	Unknown in both
Case patient 5 (Icelandic)	Female	Schizophrenia	21	Mother with bipolar disorder	Yes
Case patient 6 (Icelandic)	Female	Bipolar disorder	13	One brother with bipolar disorder; mother with recurrent depression	No for brother; unknown for mother
Case patient 7 (Icelandic)	Female	Autism	1	One sister with idiopathic seizures and attention deficit hyperactivity disorder	No
Comparison subject 1 (Icelandic)	Female	No known diagnosis			Unknown
Comparison subject 2 (Icelandic)	Female	Preeclampsia			Unknown
Comparison subject 3 (Icelandic)	Female	Alzheimer’s disease			Unknown
Comparison subject 4 (Icelandic)	Female	No known diagnosis			Unknown
Comparison subject 5 (Icelandic)	Female	No known diagnosis			Unknown

[a]Other known features, including seizures and hypotonia, were not reported for any of the case patients and were unknown for comparison subjects.

[b]Not reported.

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TABLE 2

Phenotypic Characteristics and Parental allele Dosage in Different 15q11-q13 rearrangements

Genotype	Paternal Copy[a]	Maternal Copy[a]	Syndrome	Psychotic Rate (%)	Study
Normal	1	1	Normal	3.5	Perälä et al. (40)
Paternally derived deletion	0	1	Prader-Willi syndrome	0–16	Soni et al. (27), Verhoeven et al. (32), and Vogels et al. (33)
Maternal uniparental disomy	0	2	Prader-Willi syndrome	56–62	Soni et al. (27), Verhoeven et al. (32), and Vogels et al. (33)
Maternally derived deletion	1	0	Angelman syndrome	Not observed	Cassidy et al. (29) and Penner et al. (30)
Paternal uniparental disomy	2	0	Angelman syndrome	Not observed	Cassidy et al. (29) and Penner et al. (30)
Maternally derived duplication	1	2	15q11-q13 duplication syndrome	Yes[b]	*b*
Paternally derived duplication	2	1	Normal/unknown	Observed	Hogart et al. (19)

[a]Data indicate copies of the 15q11-q13 critical interval inherited from each parent in individuals with the genotype.

[b]Data taken from evidence provided in the present study, though the frequency at which psychosis is present in maternally derived duplications is unknown.