

Segmental uniparental isodisomy on 5q32-qter in a patient with childhood-onset schizophrenia

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Schizophrenia is a severe mental disorder affecting approximately 1% of the world's population. Although the aetiology of schizophrenia is complex and multifactorial, with estimated heritabilities as high as 80%, genetic factors are the most compelling. Childhood-onset schizophrenia (COS), defined as onset of schizophrenia before the age of 13 years, is a rare and malignant form of the illness that may have more salient genetic influence. The first known case of paternal segmental uniparental isodisomy (iUPD) on 5q32-qter in a patient with COS is described, which adds to the previously known high rates of chromosomal abnormalities reported in this sample. iUPD is a rare genetic condition in which the offspring receives two chromosomal homologues from one parent. Segmental UPD is defined as UPD on a portion of a chromosome with biparental inheritance seen in the rest of the homologous pair. Complications owing to this abnormality may arise from malfunctioning imprinted genes or homozygosity of recessive disease-causing mutations. This aberration became apparent during whole-genomic screening of a COS cohort and is of particular interest because 5q has been implicated in schizophrenia by several genomewide linkage studies and positive gene associations. This report, therefore, presents more evidence that schizophrenia susceptibility gene, or genes, may be found on distal 5q.

Schizophrenia is a severe mental disorder affecting approximately 1% of the population worldwide. Many factors are believed to contribute to the aetiology of the illness, but given the high heritability rates (>80%),¹ genetic vulnerability is currently the most compelling factor being examined. Childhood-onset schizophrenia (COS), defined as onset of schizophrenia before the age of 13 years, is a rare and malignant form of the illness that may have more salient genetic influence.^{2,3}

Uniparental disomy (UPD) is a genetic condition in which the offspring receives two chromosomal homologues from a single parent. The most commonly reported occurrence of UPD occurs on chromosome 15 and causes Prader–Willi or Angelman's syndrome. If the UPD is present on a portion of the homologues, the condition is referred to as a segmental UPD, and if the homologues are identical (copies of a single homologue from one of the parents), the condition is known as isodisomy. Segmental isodisomies with a normal karyotype are rarely reported and occur by complex mechanisms. One suggested mechanism begins with recombination in a tetrad that is followed by non-disjunction in meiosis I. This leads to a germ cell with a diploid chromosome that can be fertilised to create a trisomic zygote. This is followed by

Key points

- This is the first report of paternal segmental uniparental isodisomy on 5q32-qter in a patient with childhood-onset schizophrenia (COS).
- COS has a high rate of chromosomal abnormalities.
- The availability of high-density microarray technologies provides opportunity to discover rare genetic events such as uniparental disomies

mitotic crossing-over between a chromosome from each of the parents and an event termed trisomy rescue, in which one of the three homologues is lost to create a seemingly normal, diploid cell.⁴ UPD is a rare condition, and to date there has been only one report of a whole-chromosome UPD on chromosome 5 in a child with spinal muscular atrophy.^{5,6}

The increasing availability of whole-genome scans has provided a more effective means to support and discover rare genetic events such as UPD. We hypothesised that given the extreme severity of the illness in the COS cohort, they would be an ideal population to scan for rare genomic aetiologies using multiple complementary methods, including high-density comparative genomic hybridisation, single-nucleotide polymorphisms (SNPs) and expression microarrays. Here, we describe the first reported case of a paternal segmental uniparental isodisomy on 5q32-qter.

METHODS

Patient recruitment and clinical assessment

Patients meeting the *Diagnostic and statistical manual of mental disorders*—third edition revised/*Diagnostic and statistical manual of mental disorders*—fourth edition (DSM-III-R/DSM-IV)⁷ criteria for schizophrenia or psychosis not otherwise specified were recruited nationwide through an extensive screening process, including a review of more than 1400 charts and in-person screening of >230 subjects. The National Institute of Mental Health Institutional Review Board approved the project and written consent was obtained from parents and assent from minor subjects. The patients who participated were required to have a premorbid full-scale IQ of ≥ 70 and an onset of psychotic symptoms before the age of 13 years. The diagnosis of COS was confirmed by two psychiatrists who achieved good reliability as measured by $\kappa^s = 0.8$ for the first 19 cases diagnosed⁹ through an extensive evaluation that

Abbreviations: COS, childhood-onset schizophrenia; DSM, diagnostic manual for mental disorders; GABA, γ -aminobutyric acid; iUPD, uniparental isodisomy; MRI, magnetic resonance imaging; PCR, polymerase chain reaction; SNP, single-nucleotide polymorphism; UPD, uniparental disomy

included clinical and structured interviews of the children and parents using portions of the Schedule for Affective Disorders and Schizophrenia for School-Age Children^{10, 11} and in-hospital observation during a 1 to 3-week drug-free period. Information on these subjects included cognitive and behavioural ratings of early development, history of drug response, neuropsychological test performance, smooth pursuit eye movements and magnetic resonance images (MRIs).

Proband

The female patient is the first-born of a physically healthy and unrelated couple. She has a healthy brother who is 2 years younger. The patient was breech, but birth was by a planned caesarean section; pregnancy and delivery were otherwise unremarkable. The baby was healthy, and the child reached developmental milestones within normal ranges. No unusual behaviour or problems were noted until the child began school and teachers remarked that she was inattentive and internally preoccupied. At the age of 9 years, her parents noticed avoidant and isolative behaviour, as well as deterioration in hygiene. She was hospitalised during an episode in which she refused to eat and was diagnosed with atypical psychosis and general anxiety disorder. By the age of 11 years she was frankly psychotic, experiencing auditory hallucinations, delusions and an increasing lack of drive and affective flattening.

The patient was screened at the National Institute of Mental Health at 12 years of age, and during the interview she was agitated, actively avoided eye contact with the interviewer, was neologistic and seemed to be laughing and conversing with herself. She was experiencing psychotic symptoms including delusions of reference, and concern with punishment from god and was hearing voices. The interview disclosed anhedonia, as well as impairment in school, relationships and self-care. She had no unusual physical or neurological features and was fully oriented. Neuropsychometric assessment was difficult owing to her mental state, which was disclosed by her scores on the Wechsler Intelligence Scale for Children—Revised of 45 and 46 for verbal and performance IQ, respectively. This was in contrast with a report from her first hospitalisation, which stated “given her average test scores on three of the subtests, it is hypothesised by this examiner that the patient’s abilities are at least in the average range of intelligence”. Unfortunately, actual scores were not reported in her medical records, only a summary statement from the psychologist who administered the test. Also, she was successful in attending regular public school until the time of her first hospitalisation. Standard laboratory tests were carried out, including electroencephalography, MRI and a cytogenetic karyotype on peripheral blood, all of which were normal. She met DSM-III criteria for axis I schizophrenia and major depression, and criteria for an axis II learning disability.

The patient was treated, as an outpatient, with olanzapine and experienced adverse effects caused by the drug. After a failure to respond to multiple other antipsychotics, the patient was treated with clozapine, which produced a moderate, sustained clinical and functional improvement, noted at follow-up when she was 14 years old.

Proband family history

The patient’s family exhibited several disorders. Her mother met DSM-III criteria for axis II histrionic and schizoid personality disorders. The father was diagnosed with axis I major depression and social phobia, as well as axis II schizoid, schizotypal and avoidant personality disorders. The brother, evaluated at the age of 10 years, was found to be mentally healthy and was experiencing no known problems at home or school. His healthy status was

confirmed again during a follow-up interview 3 years later. Further, on the basis of proxy information from the parents, the patient had a paternal uncle and paternal second cousin diagnosed with schizophrenia. The patient also has a paternal second cousin diagnosed with bipolar disorder (fig 1, created with Pelican software¹²).

DNA preparation and genotyping

Genomic DNA was extracted from immortalised lymphoblastoid cells, using the QIAamp DNA Extraction Kit (Qiagen, Valencia, California, USA). Several complementary genomic scans were completed. Firstly, a genomewide microsatellite markers scan with semiautomated fluorescent genotyping was undertaken using the ABI Genescan/Genotyper system (Applied Biosystems, Foster City, California, USA) by comparison of the fragment sizes with an internal standard (LIZ). A total of 21 microsatellite markers on chromosome 5 with an average distance between adjacent markers of 9.6 cM (2–28 cM) and an average heterozygosity of 0.80 (0.73–0.89) were selected from the ABI prism Linkage Mapping Set, V.2.5. Multiplex polymerase chain reaction (PCR) tests were carried out with 10 ng of genomic DNA and 9 µl of True Allele PCR Premix (Applied Biosystems). The PCR amplifications were set up on a Biomek FX robotic workstation (Beckman Coulter, Fullerton, California, USA) and run on MSB 0.25 Thermo Hybrid PCR machines (Franklin, Massachusetts, USA). Cycling conditions were as follows: initial denaturation at 95°C for 12 min, followed by 30 cycles of denaturation at 94°C for 15 s, annealing at 55°C for 15 s and extension at 72°C for 30 s. The PCR products were then pooled and the internal size standard (LIZ) was added. The alleles were detected by electrophoresis on the ABI 3700 DNA Analyzer. The software Genescan and Genotyper (Applied Biosystems) were used to size and call the alleles. All genotypes were scored blind as to phenotype.

Secondly, samples were processed according to the Affymetrix GeneChip Mapping 500K Assay Manual using the Mendel_NSP1_EA arrays¹³ as part of the early access programme through the UCLA site of the National Institutes of Health Neuroscience Microarray Consortium. Genotypes were called in GTYPE software (Affymetrix, Santa Clara, California, USA). Intensity data were analysed in custom scripts in Mathematica (B Merriman).

Microarray gene expression sample preparation

Total RNA was extracted from lymphoblastoid cell lines using a Trizol protocol available from the manufacturer (Invitrogen, Carlsbad, California, USA). RNA (500 ng) was used with the Illumina Total Prep RNA Amplification Kit (Ambion, Austin,

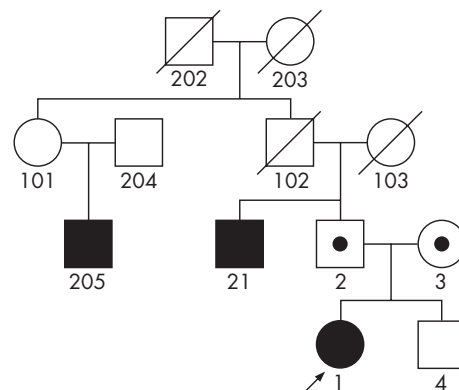


Figure 1 Family affected by schizophrenia and schizophrenia spectrum disorders, including proband with uniparental disomy.

Texas, USA) to prepare RNA with incorporated Biotin-16-UTP (Perkin Elmer, Wellesley, California, USA). cRNA yields were quantified using Invitrogen's RiboGreen, and 1.5 µg of the biotinylated cRNA was hybridised to a Sentrix Human-6 Expression Beadchip (Illumina, San Diego, California, USA), which contained approximately 48 000 known and predicted genes. Washing and scanning were carried out according to the manufacturer's protocol, and a detailed description of the BeadChip system has been provided elsewhere.¹⁴ Samples were coded and run in duplicates, and the results were analysed using the rank invariant normalisation method in the BeadStudio analysis software (<http://www.illumina.com>).

Candidate gene SNP genotyping and transmission disequilibrium test

To follow-up on potential candidate genes in the affected region on 5q, we selected SNPs from previous publications of positive associations with schizophrenia to test for association in the entire COS cohort (n = 88) and their parents (n = 150). Primers and probes were ordered through Assays by Design (Applied Biosystems) for the TaqMan Assay, and we used standard PCR protocols and read plates on the Prism 7900HT. TDTPhase was used to compute phase-known transmission disequilibrium test associations.¹⁵

RESULTS

A comparison of the proband's cognitive abilities as well as volumetric MRIs of the brain indicated that she was among the most extremely affected in our already severely affected cohort of patients with COS. Specifically, her IQ score on admission to the National Institutes of Health was 40, which was the lowest of any of our patients, with only a 7-point improvement at the 3-year follow-up. Further, her overall grey matter was among the smallest in comparison with the other female patients with COS, ranking 13–15 of 15 in every lobe of the brain (details available on request).

The Affymetrix 250K Mendel_Nsp_EA SNP array showed a 35-Mb stretch of homozygosity from 5q32-qter, which encompassed 3400 SNPs. Intensity data indicated that the large interval was diploid as comparable intensity signals were seen across a series of normal diploid controls. Thus, the aberrantly long stretch of homozygosity was not due to chromosomal loss. This was consistent with the normal karyotype results. Therefore, the loss of heterozygosity was most probably attributable to an iUPD.

Multiallelic microsatellite markers, over the region-of-interest defined by the SNP arrays, showed misinheritance at 3 of 4 markers on 5q (fourth marker was uninformative). All questionable genotypes were repeated to rule out genotyping errors. In all cases, the proband apparently inherited an allele from the father, but none from the mother. Genotypes of the healthy sibling were fine (fig 2). Thus, the isodisomic region was paternally inherited. This region is of particular interest because this region of chromosome 5 overlaps with a region implicated in schizophrenia by genome-scan linkage meta-analysis studies.^{16 17} Further, positive associations of SNP alleles in several γ-aminobutyric acid (GABA) receptor genes in the region have been reported.¹⁸ Therefore, we attempted to replicate the reported positive SNP associations by using transmission/disequilibrium test in the entire COS cohort, but none of the SNPs tested showed any association with COS (table 1).

The Sentrix Human-6 Expression Beadchip contains approximately 300 probes corresponding to 253 known and predicted genes in the 35-Mb-affected region on 5q. A direct comparison of expression levels of these genes between the proband and her unaffected brother showed 8 genes that were up regulated and 21 genes that were down regulated,

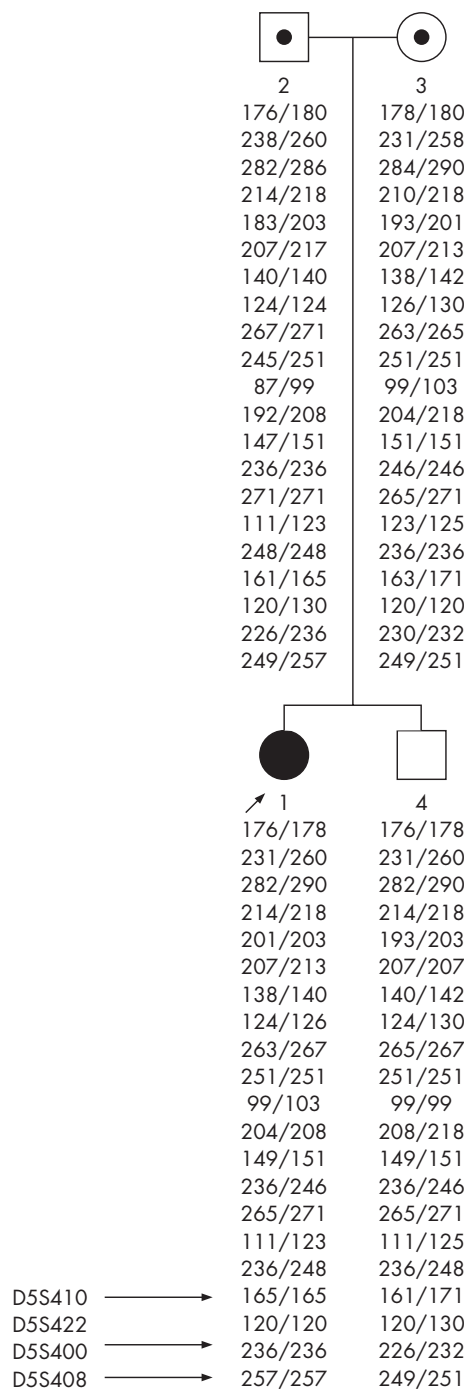


Figure 2 Inheritance errors in affected family using microsatellite markers.

with fold changes ranging from 1.3 to 17 (table 2). Of the genes identified, none were obvious candidates. Unfortunately, we were not able to detect any of the GABA receptor genes in this region at reliable levels, which reflects one of the inherent limitations of using mRNA from lymphocytes rather than brain tissue.

DISCUSSION

We used high-density SNP arrays to reliably search through the genome of people with COS and discovered a paternal segmental iUPD on 5q32-qter in a single patient. To date, only one other case of UPD on chromosome 5 has been

Table 1 Transmission disequilibrium test results of single-nucleotide polymorphisms in candidate genes in the 5q region

Gene	SNP ID	Chromosome 5 location*	Minor allele frequency	COS p value	Petryshen <i>et al</i> ¹⁸ p value	Pimm <i>et al</i> ¹⁹ p value
ENTH	rs10046055	157249595	0.32	0.869	ND	0.002
GABRA6	rs7448515	161113298	0.21	1.000	0.009	ND
GABRA1	rs4464735	161197426	0.48	0.785	0.005	ND
	rs4367330	161217360	0.49	0.793	0.002	ND
	rs4254937	161230514	0.48	0.611	0.002	ND
GABRG2	rs1037715	161248347	0.10	0.655	0.012	ND
	rs11135176	161455134	0.06	1.000	ND	ND
	rs2103475	161467608	0.46	0.555	0.800	ND
GABRP	rs211013	161512019	0.42	1.000	0.540	ND
	rs732157	170143829	0.39	0.084	0.022	ND

ND, not done.

*Locations based on University of California Santa Cruz May 2004.

reported.⁵⁻⁶ This report, therefore, supports a location of some schizophrenia susceptibility gene, or genes, in 5q, as well as provides what may be a novel region of known imprinting. Further, it adds to the body of evidence indicating that the extreme cohort of patients with very early onset of schizophrenia harbour a large number of rare chromosomal abnormalities that are probably associated with the aetiology.

In a 2003 weighted meta-analysis, 5q23.2–q34 was ranked as the second most compelling linkage region for schizophrenia.¹⁶ Subsequent to that meta-analysis, Sklar *et al*¹⁷ found a region on 5q31–5q35 with a non-parametric Linkage Score of 3.28 in a Portuguese sample and successfully replicated the findings in a bipolar population in an attempt to connect it to a psychotic phenotype.¹⁷ Further study of this region showed positive SNP associations with several GABA receptor subunit genes, which are plausible candidates based on prior evidence for GABA system involvement in schizophrenia, in Portuguese and German patients with schizophrenia.¹⁸ Pimm *et al*¹⁹ reported an association with the Epsin 4 gene found on 5q33.3, in a large case–control sample from the UK, and this gene was further implicated by a follow-up study on a Chinese sample that showed an association between Epsin 4 haplotypes and schizophrenia.²⁰ This gene is a schizophrenia candidate owing to its involvement with neurotransmitter vesicle transport and stability in the synapses and neurones.¹⁹ Taken together, these studies provide strong evidence for schizophrenia susceptibility in the region in which we have confirmed an iUPD, a chromosomal abnormality that can be detrimental owing to the homozygosity of autosomal recessively inherited disorders and imprinting.

Imprinting occurs when expression levels are altered due to gene modifications determined by the parent of origin.²¹ We determined that the isodisomy in the proband is paternal, which suggests that paternally imprinted genes in this region will lack expression. Imprinting maps are currently being developed for the human genome, and although there is no conclusive evidence for imprinting in this region, recent projects suggest it is a strong possibility. An expression study using FANTOM2 mouse complementary DNA clones suggests that up to 2101 of 27 663 (7.6%) investigated transcripts are imprinted. The transcripts were mapped to the human genome, and several of the suggested imprinted genes are found in the region of the isodisomy concerned.²² Luedi *et al*²¹ developed a more conservative model and suggest that 2.5% of murine genes are imprinted, 64% of which exhibit maternal expression. Human-based literature also supports the likelihood of imprinted genes in this region, such as research on the SPINK5 gene found on 5q32, which shows disease association with the maternally derived allele.²³ This research is encouraging regardless of the gene involvement

with schizophrenia because imprinted genes typically cluster together.²²

Also of interest is the use of the proband's genome to pinpoint candidate genes, which is possible given the specifics of the isodisomy and the patient's family history. Although both parents of the proband meet criteria for schizophrenia-spectrum disorders, the paternal side of the family presents a history of schizophrenia, which is absent on the maternal side. The isodisomy is paternal, so the father could be a source of a homozygotic recessive mutation responsible for illness in the patient. If the father was heterozygotic for these variants, there is a possible explanation for his meeting criteria for a schizophrenia-spectrum disorder rather than schizophrenia. Full sequencing of the entire region in the proband and her family may be the only way to identify potential disease-causing mutations. Although the possibility of disease contributions lying outside chromosome 5 cannot be ignored, the implications brought about by the family history could implicate a monogenic form of this complex disease.

Although linkage studies have been successful in identifying a few schizophrenia candidate genes, the discovery of a specific chromosomal abnormality in broad linkage regions may be helpful in isolating a specific locus.²⁴ Such abnormalities include the 22q11 deletion and the balanced translocation of chromosome 1, which have provided the strongest genetic predictors of schizophrenia and psychosis.²⁴⁻²⁵ Breakpoint analysis in a segmental isodisomy may also implicate novel genes in the study of schizophrenia. In a 2001 case report, Kotzot *et al*²⁶ discussed mechanisms by which a segmental isodisomy is created when a chromosomal breakage occurs in mitosis and is followed by reduplication. In this case, mitotic reduplication occurs to compensate for the loss by making a replacement segment from the intact homologue. The same group has also proposed mechanisms that involve recombination in meiosis and mitosis that may be responsible for a segmental isodisomy.⁴ These mechanisms provide scenarios in which breakage could have a direct effect on a specific gene. Parental age may also have a role in the occurrence of isodisomies.²⁷ It is noteworthy that the parents of the proband were among the oldest in our cohort at 41 and 37 years of age when she was born.

SUMMARY

Utilisation of high-density SNP arrays has the potential to expose a considerable amount of previously unknown information regarding rates of iUPDs. Prior detection of this genetic condition has relied on time-consuming analysis using microsatellite markers and, as a result, most reports to date have been serendipitous.⁴ Experiments testing the effectiveness of arrays in identifying uniparental disomies

Table 2 Significantly differentially expressed genes on 5q in lymphoblasts between proband and healthy sibling

Illumina	Cytogenetic		Physical		Proband		Healthy sibling		Fold		Difference		
	Location	Location	Location	Signal	Signal	Detection	No of beads	Signal	Detection	No of beads		Change	Score
Underexpressed													
hmm14202-S	5q33.2	154222612	144.169	1.000	1.000	49	379.123	1.000	56	-2.630	-168.06	Gnomon gene hmm14202, RefSeq build 34	
GL_14149707-S	5q33.1	150589673	121.253	1.000	1.000	35	845.239	1.000	43	-2.846	-141.58	CCDC69, coiled-coil domain containing 69	
GL_39725633-S	5q33.2	154222684	433.539	1.000	1.000	49	362.122	1.000	44	-1.989	-114.77	LARP1, La ribonucleoprotein domain family, member 1	
GL_39725635-S	5q35.3	176955409	525.007	1.000	1.000	42	847.703	1.000	39	-1.615	-57.21	TMED9, transmembrane emp24 protein transport domain containing 9	
GL_24496788-S	5q32	145474004	197.888	1.000	1.000	43	329.888	1.000	37	-1.667	-46.50	leucyl-tRNA synthetase	
GL_24307954-S	5q33.3	156800925	214.585	1.000	1.000	33	319.939	1.000	35	-1.491	-28.30	cytoplasmic FMR1 interacting protein 2	
GL_31543450-S	5q35.3	176714602	392.535	1.000	1.000	49	507.164	1.000	67	-1.292	-24.76	px19-like protein	
GL_4507410-S	5q32	149759852	206.366	1.000	1.000	58	277.2	1.000	38	-1.343	-20.10	Treacher Collins-Franceschetti syndrome 1	
Overexpressed													
GL_39995108-S	5q33.1	150676586	196.253	1.000	1.000	52	132.58	1.000	42	1.480	25.29	GM2A ganglioside activator protein	
GL_21265039-S	5q33.2	154326620	1506.14	1.000	1.000	40	1124.47	1.000	36	1.339	25.73	Mitochondrial ribosomal protein L22, nuclear gene encoding mitochondrial protein	
Hs_496717-S	5q33.1	151125780	7490.2	1.000	1.000	45	5659.35	1.000	37	1.324	27.46	Similar to ribosomal protein P1 isoform 2	
GL_20127554-S	5q35.2	175791909	1417.24	1.000	1.000	35	988.662	1.000	26	1.433	30.24	Hypothetical protein HSPC111	
GL_34147516-S	5q32	148856027	948.412	1.000	1.000	60	706.733	1.000	40	1.342	31.38	Casein kinase 1, α -1, down regulated in lung cancer	
GL_29789057-S	5q34	167829133	105.969	1.000	1.000	28	43.3489	0.999	34	2.445	32.06	WWC1, WW, C2 and coiled-coil domain containing 1	
GL_22748634-S	5q35.1	171619676	145.868	1.000	1.000	36	76.826	1.000	53	1.899	34.46	Dendritic cell-derived ubiquitin-like protein	
GL_40556270-S	5q34	162816525	505.192	1.000	1.000	38	327.936	1.000	55	1.541	42.45	NUDC2, NudC domain containing 2	
GL_17017971-S	5q35.1	172329153	1684.97	1.000	1.000	51	1151.58	1.000	41	1.463	44.74	Ribosomal protein L26-like 1	
GL_14141191-S	5q33.1	149804023	30972.8	1.000	1.000	42	20026.4	1.000	46	1.547	49.66	Mannosyl (α -1,3)-glycoprotein β -1,4-N-acetylglucosaminyltransferase, isozyme B	
GL_16915933-A	5q35	179334400	533.294	1.000	1.000	44	326.404	1.000	33	1.634	51.55	UBI1P1, ubiquitin-like domain containing CTD phosphatase 1	
GL_21450801-S	5q33.3	158645113	550.432	1.000	1.000	47	343.021	1.000	35	1.605	51.67	Potassium large conductance calcium-activated channel, subfamily M, β -member 1	
GL_25777641-S	5q34	169786227	106.822	1.000	1.000	37	25.7527	0.998	40	4.148	59.49	THO complex 3, part of the TREX (transcription/export) complex	
GL_14150170-S	5q35.2	175319143	1574.46	1.000	1.000	31	912.292	1.000	37	1.726	59.93	Protein phosphatase 2 [formerly 2A], regulatory subunit B (PR_52), β -isoform	
GL_32307118-I	5q32	145949261	606.349	1.000	1.000	42	348.06	1.000	39	1.742	65.73	Cyclin G1	
GL_40805830-S	5q34	162802038	508.454	1.000	1.000	40	283.965	1.000	49	1.791	67.94	ATX1 anti-oxidant protein 1 homologue (yeast)	
GL_29826339-S	5q32	151159780	1843.69	1.000	1.000	29	950.039	1.000	29	1.941	74.55	Secreted protein, acidic, cysteine-rich (osteonectin)	
GL_4507170-S	5q33.1	151022286	3176.92	1.000	1.000	33	1723.67	1.000	47	1.843	81.10	Drebrin 1, believed to have a role in the process of neuronal growth, developmentally regulated in the bra	
GL_18426914-A	5q35.3	176816524	584.067	1.000	1.000	38	263.163	1.000	50	2.219	107.94	TIMD4, T cell immunoglobulin and mucin domain containing 4	
GL_19923904-S	5q33.3	156281699	471.602	1.000	1.000	25	26.5572	0.998	29	17.758	217.64	Hepatitis A virus cellular receptor 2, T cell immunoglobulin and mucin domain containing molecule	
GL_21314757-S	5q33.3	156493786	563.495	1.000	1.000	46	58.8923	1.000	36	9.568	355.85	Enthoproin [ENTH], Epsin 4	
Genes of interest													
GL_3757713-S	5q33.3	157146388	468.188	1.000	1.000	26	405.09	1.000	19	NA	-5.33	γ -aminobutyric acid (GABA) A receptor, β -2 [GABRB2], transcript variant 1	
GL_12548784-I	5q34	160734293	-0.754852	0.465	0.465	32	5.32896	0.740	24	NA	1.95	GABA A receptor, α -1 [GABRA1]	
GL_4557606-S	5q34	161109522	1.1762	0.571	0.571	39	-7.31738	0.205	49	NA	-3.20	GABA A receptor, α -6 [GABRA6]	
GL_38327553-S	5q34	161258878	6.98615	0.850	0.850	44	10.1125	0.850	23	NA	0.90	GABA A receptor, γ -2 [GABRG2], transcript variant 1	
GL_38788154-I	5q34	161514428	4.25694	0.740	0.740	26	-7.16618	0.208	33	NA	-4.44	GABA A receptor, GABRG2, transcript variant 2	
GL_38788134-A	5q34	161561210	-8.07671	0.109	0.109	24	-6.70604	0.218	36	NA	0.41	GABA A receptor, π -[GABRP]	
GL_7657105-S	5q35.1	170221412	3.16486	0.692	0.692	50	-7.51971	0.199	52	NA	-4.33		

GABA, γ -aminobutyric acid; ENTH, enthoproin.

seem promising,²⁸ and along with other chromosomal abnormalities, isodisomies will probably be key in developing imprinting maps and discovering and confirming regions of risk in many disorders. This case report supports this notion as well as the possibility of finding risk genes and imprinting on 5q.

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REFERENCES

- 1 **Cardno AG**, et al. Heritability estimates for psychotic disorders: the Maudsley twin psychosis series. *Arch Gen Psychiatry* 1999;**56**:162–8.
- 2 **Nicolson R**, Rapoport JL. Childhood-onset schizophrenia: rare but worth studying. *Biol Psychiatry* 1999;**46**:1418–28.
- 3 **Rapoport JL**, Addington AM, Frangou S, Psych MR. The neurodevelopmental model of schizophrenia: update 2005. *Mol Psychiatry* 2005;**10**:434–49.
- 4 **Kotzot D**. Complex and segmental uniparental disomy (UPD): review and lessons from rare chromosomal complements. *J Med Genet* 2001;**38**:497–507.
- 5 **Kotzot D**, Utermann G. Uniparental disomy (UPD) other than 15: phenotypes and bibliography updated. *Am J Med Genet Part A* 2005;**136A**:287–305.
- 6 **Brzustowicz LM**, et al. Paternal isodisomy for chromosome 5 in a child with spinal muscular atrophy. *Am J Hum Genet* 1994;**54**:482–8.
- 7 **Association AP**. Diagnostic and statistical manual of mental disorders—4th Edn. Washington, DC: American Psychiatric Association, 1994.
- 8 **Barcko JJ**, Carpenter WT Jr. On the methods and theory of reliability. *J Nerv Ment Dis* 1976;**163**:307–17.
- 9 **McKenna K**, et al. Looking for childhood-onset schizophrenia: the first 71 cases screened. *J Am Acad Child Adolesc Psychiatry* 1994;**33**:636–44.
- 10 **Kaufman J**, et al. Schedule for Affective Disorders and Schizophrenia for School-Age Children—Present and Lifetime Version (K-SADS-PL): initial reliability and validity data. *J Am Acad Child Adolesc Psychiatry* 1997;**36**:980–8.
- 11 **Ambrosini PJ**. Historical development and present status of the Schedule for Affective Disorders and Schizophrenia for School-age Children (K-SADS). *J Am Acad Child Adolesc Psychiatry* 2000;**39**:49–58.
- 12 **Dudbridge F**, Carver T, Williams GW. Pelican: pedigree editor for linkage computer analysis. *Bioinformatics* 2004;**20**:2327–8.
- 13 **Matsuzaki H**, et al. Genotyping over 100,000 SNPs on a pair of oligonucleotide arrays. *Nat Methods* 2004;**1**:109–11.
- 14 **Kuhn K**, et al. A novel, high-performance random array platform for quantitative gene expression profiling. *Genome Res* 2004;**14**:2347–56.
- 15 **Dudbridge F**. Pedigree disequilibrium tests for multilocus haplotypes. *Genet Epidemiol* 2003;**25**:115–21.
- 16 **Lewis CM**, et al. Genome scan meta-analysis of schizophrenia and bipolar disorder, part II: schizophrenia. *Am J Hum Genet* 2003;**73**:34–48.
- 17 **Sklar P**, et al. Genome-wide scan in Portuguese Island families identifies 5q31–5q35 as a susceptibility locus for schizophrenia and psychosis. *Mol Psychiatry* 2004;**9**:213–8.
- 18 **Petryshen TL**, et al. Genetic investigation of chromosome 5q GABAA receptor subunit genes in schizophrenia. 2005.
- 19 **Pimm J**, et al. The Epsin 4 gene on chromosome 5q, which encodes the clathrin-associated protein enthoprotin, is involved in the genetic susceptibility to schizophrenia. *Am J Hum Genet* 2005;**76**:902–7.
- 20 **Tang RQ**, et al. Family-based association study of Epsin 4 and Schizophrenia. *Mol Psychiatry* 2006.
- 21 **Luedi PP**, Hartemink AJ, Jirtle RL. Genome-wide prediction of imprinted murine genes. *Genome Res* 2005;**15**:875–84.
- 22 **Nikaido I**, et al. Discovery of imprinted transcripts in the mouse transcriptome using large-scale expression profiling. *Genome Res* 2003;**13**:1402–9.
- 23 **Nishio Y**, et al. Association between polymorphisms in the SPINK5 gene and atopic dermatitis in the Japanese. *Genes Immun* 2003;**4**:515–7.
- 24 **MacIntyre DJ**, Blackwood DH, Porteous DJ, Pickard BS, Muir WJ. Chromosomal abnormalities and mental illness. *Mol Psychiatry* 2003;**8**:275–87.
- 25 **Kirov G**, O'Donovan MC, Owen MJ. Finding schizophrenia genes. *J Clin Invest* 2005;**115**:1440–8.
- 26 **Kotzot D**, Rothlisberger B, Riegel M, Schinzel A. Maternal uniparental isodisomy 11q13qter in a dysmorphic and mentally retarded female with partial trisomy mosaicism 11q13qter. *J Med Genet* 2001;**38**:876–81.
- 27 **Kotzot D**. Advanced parental age in maternal uniparental disomy (UPD): implications for the mechanism of formation. *Eur J Hum Genet* 2004;**12**:343–6.
- 28 **Altug-Teber O**, et al. A rapid microarray based whole genome analysis for detection of uniparental disomy. *Hum Mutat* 2005;**26**:153–9.