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Segmental Uniparental Isodisomy on 5q32-qter in a Patient with Childhood-Onset Schizophrenia

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Abstract

Introduction: Schizophrenia is a severe mental disorder affecting approximately 1% of the world's population. Though the etiology 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 age 13, is a rare and malignant form of the illness which may have more salient genetic influence. Uniparental isodisomy (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 due to this abnormality may arise from malfunctioning imprinted genes or homozygosity of recessive disease-causing mutations.

Methods: Whole genome screening using Affymetrix GeneChip Mapping 500K, microsatellite markers and expression with Illumina Sentrix Human-6 Expression Beadchip was completed on DNA and RNA extracted from lymphoblastoid cell lines from the cohort of NIMH COS patients and family members.

Results: The SNP array revealed a segmental UPD on 5q32-qter in a single patient with COS. Microsatellite markers in the affected region confirmed this finding and identified the UPD as paternally inherited. Exploratory analyses of gene expression levels in this region suggested several significant differences between the proband and an unaffected sibling, though none of the differentially expressed genes were obvious candidates.

Discussion: Here we describe the first known case of paternal segmental uniparental isodisomy on chromosome 5, which adds to the previously known high rates of chromosomal abnormalities reported in this patient sample. This is particular interest because 5q has been implicated in schizophrenia by several genome-wide linkage studies and positive gene associations. This patient report, therefore, presents more evidence that some schizophrenia susceptibility gene, or genes, may be found on distal 5q.

Key Points:

- First report of paternal segmental uniparental isodisomy on 5q32-qter in a patient with childhood onset schizophrenia
- Childhood onset schizophrenia has a high rate of chromosomal abnormalities
- More evidence that some schizophrenia susceptibility gene, or genes, may be found on distal 5q
- Availability of high-density microarray technologies provide opportunity discover rare genetic events such as uniparental disomies.

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Introduction

Schizophrenia is a severe mental disorder affecting approximately 1% of the population worldwide. Many factors are thought to contribute to the etiology of the illness, but given 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 age 13, is a rare and malignant form of the illness which 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 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 fertilized to create a trisomic zygote. This is followed by mitotic crossing-over between a chromosome from each of the parents and an event termed trisomy rescue in which one of the 3 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 hypothesized that given the extreme severity of the COS cohort, they would be an ideal population to scan for rare genomic etiologies using multiple complementary methodologies, including high density CGH, SNP 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 DSM-III-R/DSM-IV[7] criteria for schizophrenia or psychosis NOS were recruited nationwide through an extensive screening process, including a review of over 1400 charts and in-person screening of over 230 subjects. The NIMH 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 or above and an onset of psychotic symptoms before the age of 13. The diagnosis of childhood-onset schizophrenia (COS) was confirmed by 2 psychiatrists who achieved good reliability as measured by kappa[8] = 0.8 for the first 19 cases diagnosed[9] through an extensive evaluation that included clinical and structured interviews of the children and parents using portions of the Schedule for Affective Disorders and Schizophrenia for School-Age Children (K-SADS-E and K-SADS-PL)[10,11] and in-hospital observation during a 1-3 week medication-free period. Information on these subjects included cognitive and behavioral ratings of early development, history of medication response, neuropsychological test performance, smooth pursuit eye movements, and MRI scans.

Proband

The female patient was the first-born of a physically-healthy and unrelated couple. She has a healthy brother who is two years younger. The patient was breech, but birth was by a

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planned cesarean section; pregnancy and delivery were otherwise unremarkable. The baby was healthy, and the child reached developmental milestones within normal ranges. No unusual behavior or problems were noted until the child began school and teachers remarked that she was inattentive and internally preoccupied. At the age of 9, her parents noticed avoidant and isolative behavior, as well as deterioration in hygiene. She was hospitalized during an episode in which she refused to eat and diagnosed with atypical psychosis and general anxiety disorder. By the age of 11, she was frankly psychotic, experiencing auditory hallucinations, delusions, and an increasing lack of drive and affective flattening.

The patient was screened at the NIMH at 12 years of age, and during the interview she was agitated, actively avoided eye-contact with the interviewer, neologistic, and appeared to be laughing and conversing with herself. She was experiencing psychotic symptoms including delusions of reference, concern with punishment from god, and hearing voices. The interview revealed 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 due to her mental state revealed by her scores on the WISC-R of 45 and 46 for verbal and performance IQ, respectively. This was in contrast to a report from her first hospitalization which stated "given her average test scores on three of the subtests, it is hypothesized 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. Further, she was successful in attending regular public school up until the time of her first hospitalization. Standard laboratory tests were carried out, including EEG, MRI, and a cytogenetic karyotype on peripheral blood, and all were normal. She met DSM-III criteria for Axis 1 schizophrenia and major depression, and she met criteria for an Axis II learning disability.

The patient was treated as an outpatient with Olanzapine and experienced adverse effects caused by the medication. 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 age 10, 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, based on proxy information from the parents, the patient had a paternal uncle and paternal 2nd cousin diagnosed with schizophrenia. She also has a paternal 2nd cousin diagnosed with bipolar disorder (see Figure 1, created with Pelican software[12]).

DNA preparation and genotyping

Genomic DNA was extracted from immortalized lymphoblastoid cells using the QIAamp DNA Extraction Kit (Qiagen, Inc., Valencia, CA). Several complementary genomic scans were completed. First, a genome-wide microsatellite markers scan with semi-automated fluorescent genotyping was undertaken using the ABI Genescan/Genotyper system by comparison of the fragment sizes with an internal standard (LIZ). A total of 21 microsatellite

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markers on chromosome 5 with an average distance between adjacent markers of 9.6cM (2 – 28cm) and an average heterozygosity of 0.80 (0.73-0.89) were selected from the ABI prism Linkage Mapping Set, version 2.5. Multiplex PCR were performed with 10ng of genomic DNA and 9ul of True Allele PCR Premix (Applied Biosystems, Inc. Foster City; CA, USA). The PCR amplifications were set up on a Biomek FX robotic workstation (Beckman Coulter, Fullerton; CA, USA), and run on MSB 0.25 Thermo Hybaid PCR machines (Franklin; MA, USA). Cycling conditions were as follows: initial denaturation at 95 C for 12 minutes, followed by 30 cycles of denaturation at 94 C for 15 seconds, annealing at 55 C for 15 seconds and extension at 72 C for 30 seconds. 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, Foster City, CA) were used to size and call the alleles. All genotypes were scored blind as to phenotype.

Second, samples were processed according to the Affymetrix GeneChip Mapping 500K Assay Manual using the Mendel_NSP1_EA arrays[13] as part of the early access program through the UCLA site of the NIH Neuroscience Microarray Consortium. Genotypes were called in GTYPE software (Affymetrix, Santa Clara, CA). Intensity data were analyzed in custom scripts within 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, United States). 500 ng of RNA was used with the Illumina Total Prep RNA Amplication Kit (Ambion, Inc., Austin, TX) to prepare RNA with incorporated Biotin-16-UTP (Perkin Elmer, Wellesley, California, United States). cRNA yields were quantified using Invitrogen's RiboGreen, and 1.5 µg of the biotinylated cRNA was hybridized to a Sentrix Human-6 Expression Beadchip (Illumina, Inc., San Diego, CA), which contained approximately 48,000 known and predicted genes. Washing and scanning were performed 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 analyzed using the rank invariant normalization method in the BeadStudio analysis software, www.illumina.com.

Candidate gene SNP genotyping and TDT

In order 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 TDT associations.[15]

Results

Comparison of the proband's cognitive abilities as well as volumetric MRI brain scans indicated that she was among the most extremely affected in our already severe cohort of patients with COS. Specifically, her IQ score upon admission to NIH was 40, which was the lowest of any of our patients, with only 7 point improvement at 3-year follow-up. Further, her overall gray matter was among the smallest in comparison to the other female COS patients, ranking 13-15th out of 15 in every lobe of the brain (details available upon request).

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The Affymetrix 250K Mendel_Nsp_EA SNP array revealed a 35 Mb stretch of homozygosity from 5q32-qter which encompassed 3,400 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 (LOH) was most likely attributable to a uniparental isodisomy.

Multiallelic microsatellite markers, over the region of interest defined by the SNP arrays, revealed misinheritance at 3 out of 4 markers on 5q (4th 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 (See Figure 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 within several GABA receptor genes in the region have been reported [18]. Therefore, we attempted to replicate the reported positive SNP associations using TDT in the entire COS cohort, but none of the SNPs tested showed any association with COS (See Table 1).

Table 1. TDT results of SNPs in candidate genes in 5q region

Gene	SNP ID	chromosome 5 location*	minor allele frequency	COS pvalue	Petryshen et al pvalue	Pimm et al pvalue
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
	rs1037715	161248347	0.10	0.655	0.012	nd
GABRG2	rs11135176	161455134	0.06	1.000	nd	nd
	rs2103475	161467608	0.46	0.555	0.800	nd
	rs211013	161512019	0.42	1.000	0.540	nd
GABRP	rs732157	170143829	0.39	0.084	0.022	nd

*Locations based on UCSC May 2004; nd=not done

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. Direct comparison of expression levels of these genes between the proband and her unaffected brother revealed 8 genes that were upregulated, and 21 genes that were downregulated with fold changes ranging from 1.3 to 17 (See 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 utilizing mRNA from lymphocytes rather than brain tissue.

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

Illumina		cytogenetic	physical	proband			healthy sibling			Fold	Difference	
TargetID	Symbol	location	location	signal	detection	#beads	signal	detection	#beads	Change	Score	Annotation
underexpressed												
hmm14202-S	hmm14202	5q33.2	154222612	144.169	1.000	49	379.123	1.000	56	-2.630	-168.06	Gnomon gene hmm14202 , RefSeq build 34
GI_14149707-S	DKFZP434C171	5q33.1	150589673	121.253	1.000	35	345.129	1.000	43	-2.846	-141.58	CCDC69, coiled-coil domain containing 69
GI_39725633-S	LARP	5q33.2	154222684	433.539	1.000	49	862.232	1.000	44	-1.989	-114.77	LARP1, La ribonucleoprotein domain family, member 1
GI_39725635-S	HSGP25L2G	5q35.3	176955409	525.007	1.000	42	847.703	1.000	39	-1.615	-57.21	TMED9, transmembrane emp24 protein transport domain containing 9
GI_24496788-S	LARS	5q32	145474004	197.888	1.000	43	329.888	1.000	37	-1.667	-46.50	leucyl-tRNA synthetase
GI_24307954-S	CYFIP2	5q33.3	156800925	214.585	1.000	33	319.939	1.000	35	-1.491	-28.30	cytoplasmic FMR1 interacting protein 2
GI_31543450-S	PX19	5q35.3	176714602	392.535	1.000	49	507.164	1.000	67	-1.292	-24.76	px19-like protein
GI_4507410-S	TCOF1	5q32	149759852	206.366	1.000	58	277.2	1.000	38	-1.343	-20.10	Treacher Collins-Franceschetti syndrome 1
overexpressed												
GI_39995108-S	GM2A	5q33.1	150676586	196.253	1.000	52	132.58	1.000	42	1.480	25.29	GM2A ganglioside activator protein
GI_21265039-S	MRPL22	5q33.2	154326620	1506.14	1.000	40	1124.47	1.000	36	1.339	25.73	mitochondrial ribosomal protein L22, nuclear gene encoding mitochondrial protein
Hs.496717-S	Hs.496717	5q33.1	151125780	7490.2	1.000	45	5659.35	1.000	37	1.324	27.46	similar to ribosomal protein P1 isoform 2
GI_20127554-S	HSPC111	5q35.2	175791909	1417.24	1.000	35	988.662	1.000	26	1.433	30.24	hypothetical protein HSPC111
GI_34147516-S	CSNK1A1	5q32	148856027	948.412	1.000	60	706.733	1.000	40	1.342	31.38	casein kinase 1, alpha 1, downregulated in lung cancer
GI_29789057-S	KIBRA	5q34	167829133	105.969	1.000	28	43.3489	0.999	34	2.445	32.06	WWC1, WW, C2 and coiled-coil domain containing 1
GI_22748634-S	DC-UbP	5q35.1	171619676	145.868	1.000	36	76.826	1.000	53	1.899	34.46	dendritic cell-derived ubiquitin-like protein
GI_40556270-S	LOC134492	5q34	162816525	505.192	1.000	38	327.936	1.000	55	1.541	42.45	NUDCD2, NudC domain containing 2
GI_17017971-S	RPL26L1	5q35.1	172329153	1684.97	1.000	42	1151.58	1.000	51	1.463	44.74	ribosomal protein L26-like 1
GI_14141191-S	RPS14	5q33.1	149804023	30972.8	1.000	33	20026.4	1.000	46	1.547	49.66	ribosomal protein S14
GI_16915933-A	MGAT4B	5q35	179334400	533.294	1.000	44	326.404	1.000	33	1.634	51.55	mannosyl (alpha-1,3-)-glycoprotein beta-1,4-N-acetylglucosaminyltransferase, isozyme B
GI_21450801-S	MGC10067	5q33.3	158645113	550.432	1.000	47	343.021	1.000	35	1.605	51.67	UBLCP1, ubiquitin-like domain containing CTD phosphatase 1
GI_25777641-S	KCNMB1	5q34	169786227	106.822	1.000	37	25.7527	0.998	40	4.148	59.49	potassium large conductance calcium-activated channel, subfamily M, beta member 1
GI_14150170-S	THOC3	5q35.2	175319143	1574.46	1.000	31	912.292	1.000	37	1.726	59.93	THO complex 3, part of the TREX (transcription/export) complex
GI_32307118-I	PPP2R2B	5q32	145949261	606.349	1.000	42	348.06	1.000	39	1.742	65.73	protein phosphatase 2 (formerly 2A), regulatory subunit B (PR 52), beta isoform
GI_40805830-S	CCNG1	5q34	162802038	508.454	1.000	40	283.965	1.000	49	1.791	67.94	cyclin G1
GI_29826339-S	ATOX1	5q32	151159780	1843.69	1.000	29	950.039	1.000	29	1.941	74.55	ATX1 antioxidant protein 1 homolog (yeast)
GI_4507170-S	SPARC	5q33.1	151022286	3176.92	1.000	33	1723.67	1.000	47	1.843	81.10	secreted protein, acidic, cysteine-rich (osteonectin)
GI_18426914-A	DBN1	5q35.3	176816524	584.067	1.000	38	263.163	1.000	50	2.219	107.94	drebrin 1, thought to play a role in the process of neuronal growth, developmentally regu
GI_19923904-S	LOC91937	5q33.3	156281699	471.602	1.000	25	26.5572	0.998	29	17.758	217.64	TIMD4, T-cell immunoglobulin and mucin domain containing 4
GI_21314757-S	HAVCR2	5q33.3	156493786	563.495	1.000	46	58.8923	1.000	36	9.568	355.85	hepatitis A virus cellular receptor 2, T cell immunoglobulin and mucin domain containing
genes of interest												
GI_37537713-S	ENTH	5q33.3	157146388	468.188	1.000	26	405.09	1.000	19	n/a	-5.33	enthoprotin (ENTH), Epsin 4
GI_12548784-I	GABRB2	5q34	160734293	-0.754852	0.465	32	5.32896	0.740	24	n/a	1.95	gamma-aminobutyric acid (GABA) A receptor, beta 2 (GABRB2), transcript variant 1
GI_4557606-S	GABRA6	5q34	161109522	1.1762	0.571	39	-7.31738	0.205	49	n/a	-3.20	gamma-aminobutyric acid (GABA) A receptor, alpha 6 (GABRA6)
GI_38327553-S	GABRA1	5q34	161258878	6.98615	0.850	44	10.1125	0.850	23	n/a	0.90	gamma-aminobutyric acid (GABA) A receptor, alpha 1 (GABRA1)
GI_38788154-I	GABRG2	5q34	161514428	4.25694	0.740	26	-7.16618	0.208	33	n/a	-4.44	gamma-aminobutyric acid (GABA) A receptor, gamma 2 (GABRG2), transcript variant 1
GI_38788134-A	GABRG2	5q34	161561210	-8.07671	0.109	24	-6.70604	0.218	36	n/a	0.41	gamma-aminobutyric acid (GABA) A receptor, gamma 2 (GABRG2), transcript variant 2
GI_7657105-S	GABRP	5q35.1	170221412	3.16486	0.692	50	-7.51971	0.199	52	n/a	-4.33	gamma-aminobutyric acid (GABA) A receptor, pi (GABRP)

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Discussion

We have used high density SNP arrays to reliably search through the genome of individuals with childhood-onset schizophrenia and have discovered a paternal segmental uniparental isodisomy on 5q32-qter in a single patient. To date, only one other case of UPD on chromosome 5 has been 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 harbor a large number of rare chromosomal abnormalities that are likely involved in the etiology.

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. found a region on 5q31-5q35 with an NPL 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 revealed 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 schizophrenia samples[18]. Pimm et al. reported association with the Epsin 4 (ENTH) gene found on 5q33.3, in a large case-control sample from the U.K.[19], and this gene was further implicated by a follow-up study on a Chinese sample that showed association between Epsin 4 haplotypes and schizophrenia[20]. This gene is a schizophrenia candidate due to its involvement with neurotransmitter vesicle transport and stability in the synapses and neurons[21]. Taken together, these studies provide strong evidence for schizophrenia susceptibility in the region in which we have confirmed a uniparental isodisomy, a chromosomal abnormality that can be of detriment due to 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[22]. 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 while there is no conclusive evidence for imprinting in this region, recent projects suggest it is a strong possibility. An expression study using FANTOM2 mouse cDNA 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 concerned isodisomy[23]. Luedi et al. developed a more conservative model and suggest that 2.5% of murine genes are imprinted, and 64% of which exhibit maternal expression[22]. 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[24]. This research is encouraging regardless of the gene involvement with schizophrenia because imprinted genes typically cluster together[23].

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. While 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 homozygous recessive mutation responsible for illness in the patient. If the father was heterozygous for these genes, 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

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only way to identify potential disease-causing mutations. Although the possibility of disease contributions lying outside of chromosome 5 cannot be ignored, the implications brought about by the family history could implicate a monogenic form of this complex disease.

While linkage studies have been successful in identifying a few schizophrenia candidate genes, discovery of a specific chromosomal abnormality within broad linkage regions may be helpful in isolating a specific locus[25]. Such abnormalities include the 22q11 deletion and the balanced translocation of chromosome 1, which have provided the strongest genetic predictors of schizophrenia and psychosis[25,26]. Breakpoint analysis in a segmental isodisomy may also implicate novel genes in the study of schizophrenia. In a 2001 case report, Kotzot et al. discuss mechanisms by which a segmental isodisomy is created when a chromosomal breakage occurs in mitosis and is followed by reduplication[27]. 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 play a role in the occurrence of isodisomies.[28] It is of note 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

Utilization of high density SNP arrays has the potential to expose a significant amount of previously unknown information regarding rates of uniparental isodisomies. 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 appear promising[29], and along with other chromosomal abnormalities, isodisomies will likely 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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Figure 1. Family affected by schizophrenia and schizophrenia spectrum disorders, including proband with UPD.

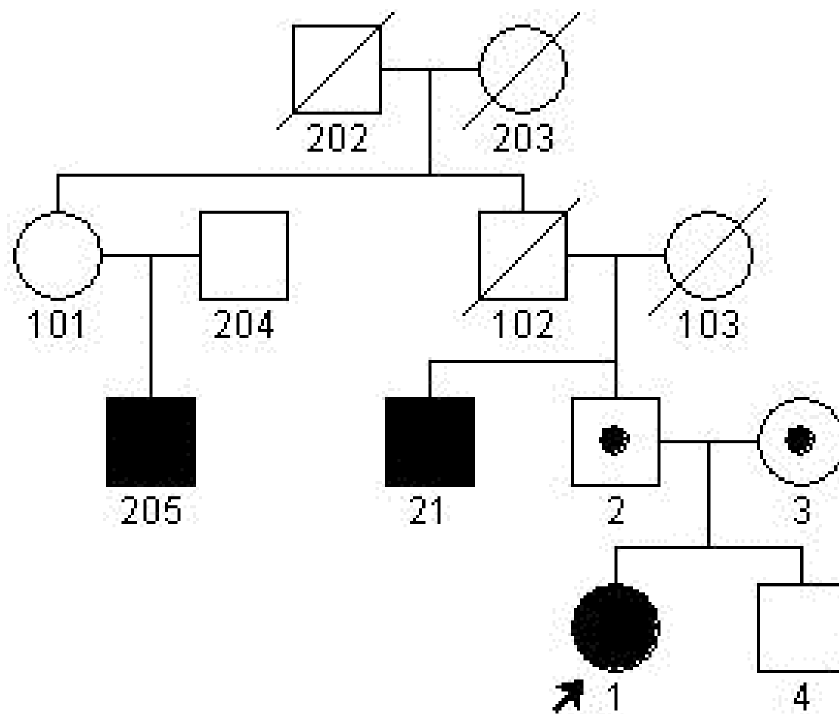

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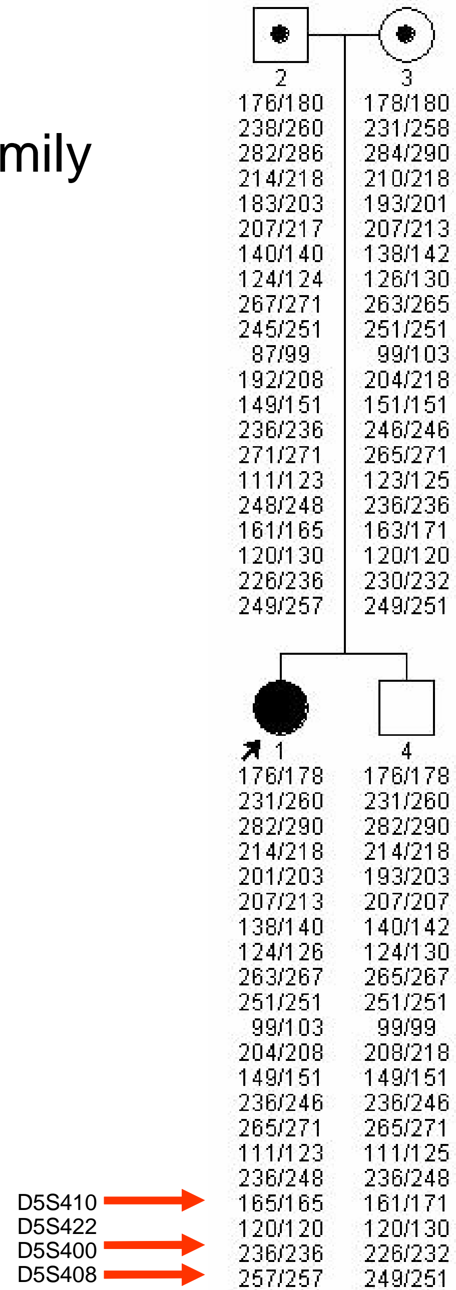
Figure 2. Inheritance errors in affected family using microsatellite markers



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