of the kerato-epithelin mutation in individuals with these two corneal dystrophies.

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Identification of an Interstitial Deletion in an Adult Female with Schizophrenia, Mental Retardation, and Dysmorphic Features: Further Support for a Putative Schizophrenia-Susceptibility Locus at 5q21-23.1

To the Editor:

Schizophrenia is a common and complex mental disorder. Family, twin, and adoption studies provide overwhelming but indirect evidence for a significant genetic contribution to the etiology of schizophrenia (Gottesman 1967, 1982, 1991; Murray et al. 1986; Kendler and Diehl 1993; Kendler et al. 1993). Cumulative evidence from genetic linkage studies is now available to suggest that schizophrenia-susceptibility genes may be found in relatively broad regions on chromosomes 22q, 8p, and 6p (Schizophrenia Collaborative Linkage Group 1996*a,* 1996*b*).

Evidence suggesting linkage at the 5q21-31 locus has also been provided independently by two groups (Schwab et al. 1997; Straub et al. 1997), and the implicated region consists of two partially overlapping regions, which extend to a combined distance of 30–40 cM, with the strongest evidence for linkage, under the

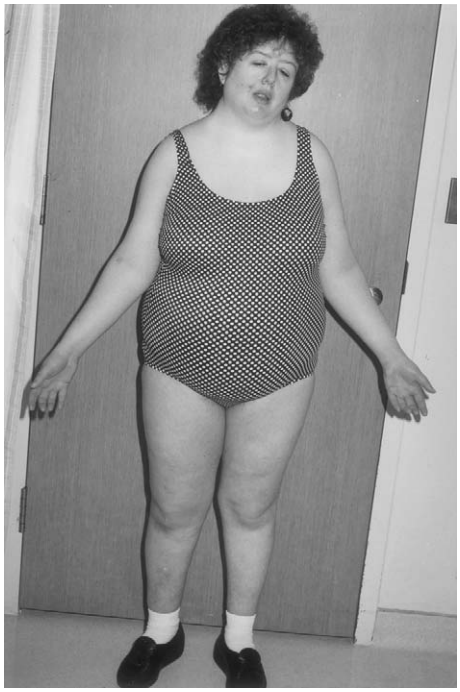

Figure 1 Dysmorphic, mentally retarded, 34-year-old woman with schizophrenia. The photograph shows the facial dysmorphisms, including downward-slanting palpebral fissures, ptosis, narrow nasal bridge, low-set ears, wide neck with low posterior hairline, and tapered fingers.

narrow phenotypic definition, for marker D5S804 (LOD score 3.35) (Straub et al. 1997). It has been proposed (Bassett 1992; Karayiorgou and Gogos 1997) that the search for chromosomal abnormalities in schizophrenic patients with dysmorphic features, learning disabilities, or mental retardation may offer an alternative approach to narrowing a region of interest, as has occurred, for example, with velocardiofacial syndrome (VCFS).

Here we report a 34-year-old moderately retarded woman with schizophrenia and dysmorphic features and with a de novo interstitial deletion of 5q22-23.2 (46,XX,del[5][q22q23.2]). The proband was conceived by a 24-year-old Caucasian woman, of English, Scottish, and German ancestry, and her nonconsanguineous 24-year-old Caucasian husband, of German ancestry. Both were healthy, with no prior history of mental disorder, and there was no known family history of mental disorder. The proband's gestation was relatively uncomplicated, and she weighed 5 lb 13 oz and measured 18½ inches, at birth. She had a poor sucking reflex, was unable to nurse, and required a special feeding nipple. By age 7 mo, she had not yet acquired the ability to sit without support. By age 3 years, she manifested temper tantrums in addition to delays in speech and motor development. Formal testing revealed that the proband's estimated IQ potential was within the mildly retarded range.

She attended special-needs classes, from kindergarten through high school. School reports suggested that, throughout her childhood and adolescence, the proband was hypersensitive, avoided certain social situations, and had marked difficulty relating to peers. Her cognitive development was uneven, as evidenced by her scores on the Wechsler Intelligence Scale for Children, administered when she was 12 years old (verbal IQ scores ranged from 55 on comprehension to 100 on arithmetic, and performance IQ scores ranged from 60 on coding to 90 on block design, with a full-scale IQ of 69). By age 18 years, she was reading at a 6th-grade level and would seek out and read magazines and books in her areas of interest. After graduation from high school, the proband held a number of restaurant and office jobs, with varying levels of success. Her difficulty with interpersonal relationships persisted, and she frequently had conflicts with supervisors and coworkers.

When she was ~25 years old, her family began to notice that she was isolated from peers and that her general level of social functioning had seemed to decline. A year later, the proband began to experience auditory command hallucinations, ideas of reference, and delusions. She believed that newscasters were speaking to her from the television, and she became convinced that she had personal relationships with music celebrities. These symptoms persisted for ~2 mo before treatment was sought. Her agitation increased dramatically as the hallucinations and delusions worsened. She was treated on an outpatient basis and, over the course of 1½ years, was prescribed a series of antipsychotic medications, most of which produced unacceptable side effects. Eighteen months after the onset of her acute psychotic symptoms, a benzodiazapene (Klonopin) was adequately effective for ~4 years. At age 30 years, following a period of symptom exacerbation and medication noncompliance, she was hospitalized, for medication adjustment. She improved temporarily, only to be involuntarily hospitalized 6 mo later. Since that time, the proband has been stabilized with clozapine and fluoxetine and reports that, although the voices continue, they are not intrusive or distressing.

The proband meets lifetime criteria for DSM-IV (*Diagnostic and Statistical Manual of Mental Disorders,* 4th ed.) schizophrenia (American Psychiatric Association 1994). Despite the early diagnosis of mental retardation, uneven cognitive development is seen most typically in childhood-onset psychiatric disorders and is rare in cases of so-called pure mental retardation. The proband's prominent delusional symptoms at age 25 years suggest the paranoid subtype. Currently, she manifests symptoms associated with a residual subtype, including affective flattening, avolition, and alogia in the absence of

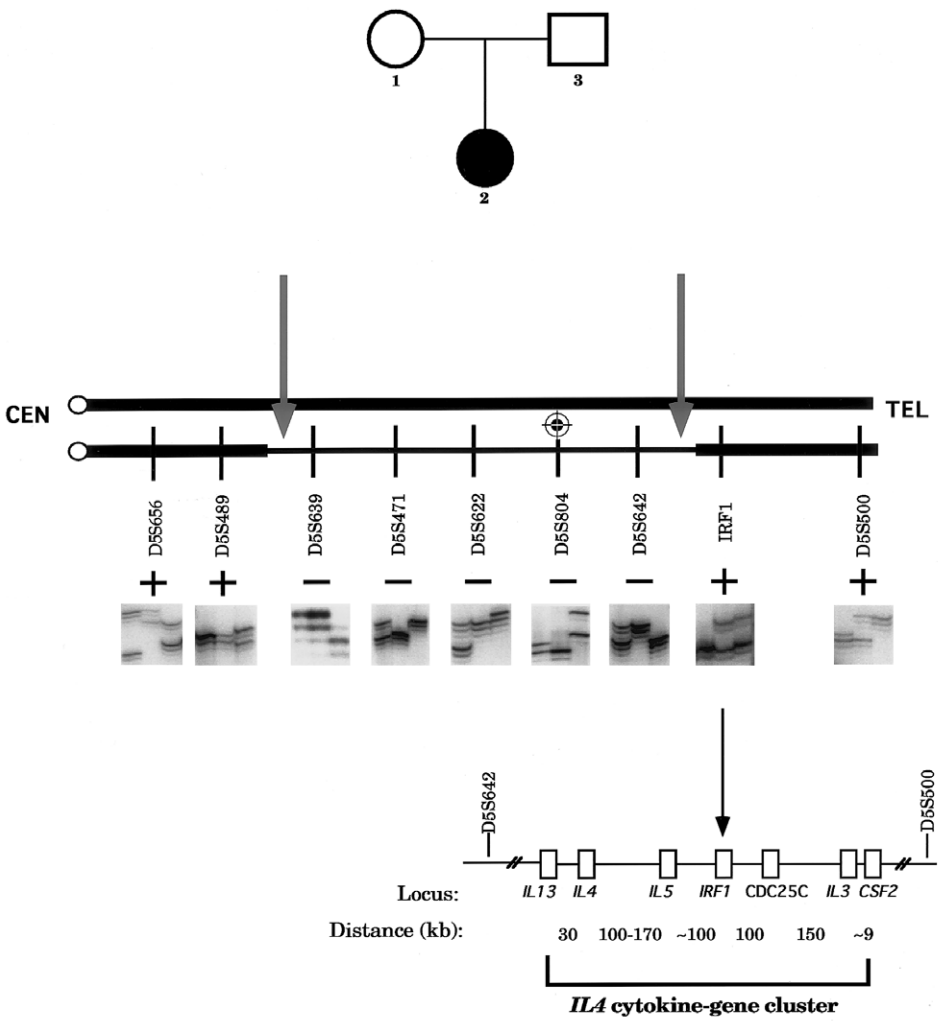

Figure 2 Molecular analysis of the 5q22-23.2 hemizygous deletion in a patient with schizophrenia. Microsatellite markers from the region for which the parents were informative are indicated. An abnormal pattern of allele inheritance in the proband was determined. For all markers, the gel order is as follows: mother (lane 1), proband (lane 2), and father (lane 3). A plus sign (+) indicates the presence of two alleles, and a minus sign (−) indicates the absence of one allele. For markers D5S639, D5S471, D5S622, D5S804, and D5S642, the proband failed to inherit a parental allele (the paternal allele). A normal pattern of inheritance for markers D5S656, D5S489, IRF1, and D5S500 indicated that these markers are located outside the deletion. The arrows indicate the deletion boundaries. Marker D5S804, which has been linked to schizophrenia (Straub et al. 1997), has been shown to map within the deletion. A detailed map of the IL-4 cytokine-gene cluster (Marsh et al. 1994), which could be considered a candidate for schizophrenia, also is presented. We were not able to determine if the genes proximal to IRF1 (namely, IL-13, IL-4, and IL-5) are included in the deletion, since the parents were not informative for the IL-4 marker.

marked hallucinations and delusions. The proband has had an episodic course, with interepisode residual symptoms.

At the time of examination, the proband was 34 years old, measured 5 feet 3½ inches tall, and was obese, weighing 194 lb. She was dysmorphic, with features that included bilateral ptosis, downward-slanting palpebral fissures, and ocular hypertelorism (fig. 1). She had an expressionless face, a narrow nasal bridge, low-set ears, a low posterior hairline, a wide neck, and tapered fingers. Her mouth was small and tent shaped, with a retropositioned jaw. Her head circumference was 56 cm (90%, +2 SD), the palpebral fissures were 2.8 cm (1%, −2 SD), the inner canthal distance was 2.8 cm (25%, −1 SD), and the outer canthal distance was 8.5 cm (50%). Neurological examination revealed mild spasticity with increased tone at the ankles, stiffness, and bilateral downward-going plantar reflexes. Her genitalia were those of a normal female, Tanner stage 5, with widely spaced nipples.

Cytogenetic studies of the proband's peripheral blood lymphocytes, at the 400–550-band level, showed a female karyotype with a small interstitial deletion in the long arm of chromosome 5, extending from band q22 to band q23.2 (46,XX,del[5][q22q23.2]). Maternal and paternal karyotypes were normal at the same resolution level. To define the proximal and distal boundaries of the deletion, we genotyped DNA from the patient and from her parents, using 28 short-tandem-repeat polymorphic (STRP) markers that spanned the implicated region and that could be used to search for abnormal inheritance of alleles. The STRP-marker set consisted of markers D5S495, D5S433, D5S505, D5S492, D5S421, D5S656, D5S659, D5S489, D5S494, D5S404, D5S639, D5S471, D5S657, D5S622, D5S1478, D5S818, D5S804, D5S642, D5S666, D5S458, IL-4, IRF1, IL-9, D5S399, D5S393, D5S500, D5S658, and D5S436. This set included marker D5S804, for which Straub et al. (1997) reported positive LOD scores for an Irish sample, as well as markers IL-9 and D5S399, for which Schwab et al. (1997) reported positive linkage in a German/Israeli sample. Results of our analysis are illustrated in figure 2. We mapped markers D5S639, D5S471, D5S622, D5S804, and D5S642 within the deletion boundaries, since the proband failed to inherit a parental allele for this series of markers on chromosome 5q, consistent with paternal origin of the de novo deletion. The proximal deletion boundary was mapped between markers D5S494 and D5S639, whereas the distal boundary was mapped between markers D5S642 and IRF1. The size of the deletion is ~4–5 Mb.

Marker D5S804 is included in the deletion, whereas markers IL-9 and D5S399 are outside the deletion. Marker IRF1 is also outside the deletion. We were unable to determine the relative position of marker IL-4, since the parents were not informative for this particular marker. Therefore, the possibility still remains that the three interleukin genes that map proximal to IRF1 (IL-13, IL-4, and IL-5) may be included in the deletion.

Additional autosomal abnormalities in schizophrenic patients have been described (Bassett 1992; Karayiorgou and Gogos 1997). Examples include a report of an Asian family in which two family members with schizophrenia were found to have a partial trisomy of chromosome 5, caused by an unbalanced translocation of the long (q) arm of chromosome 5 (Bassett et al. 1988), and a report of cosegregation of psychiatric illness and of a translocation involving chromosome 11q14-21, in a large Scottish pedigree (St. Clair et al. 1990). More recently, Karayiorgou et al. (1995) characterized two hemizygous cryptic deletions at 22q11 in a sample of 100 unrelated schizophrenic patients. In the general population, the frequency of this microdeletion is estimated to be 2/10,000, and no deletions were found in a sample of 200 healthy controls. This locus overlaps with the shortest region of overlap involved in the etiology of VCFS/DiGeorge syndrome (Driscoll et al. 1993), and it actually was shown that 4 (29%) of 14 VCFS children with 22q11 deletions develop schizophrenia or schizoaffective disorder in adolescence and adulthood (Pulver et al. 1994).

As is also the case with the 22q11 microdeletions, the locus identified in this study is located in a chromosomal region implicated independently in schizophrenia susceptibility, through linkage studies of families. However, unlike for the 22q11 microdeletions, for which the independent evidence for linkage was spread over a region including practically the entire long arm of chromosome 22 (Karayiorgou and Gogos 1997), the evidence for linkage on 5q is spread over a more restricted region, but not restricted enough to permit immediate pursuit of gene identification through cloning strategies. Identification of the deletion described here provides independent support for the existence of a schizophrenia-susceptibility locus at 5q21-23 and also may provide additional clues toward identification of the putative 5q schizophrenia-susceptibility gene(s).

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Meiotic Microdeletion Breakpoints in the BRCA1 Gene Are Significantly Associated with Symmetric DNA-Sequence Elements

To the Editor:

Mutation screening by SSCP, protein-truncation test, and subsequent sequencing revealed an 11-bp deletion in exon 11 of the BRCA1 gene segregating in a German breast-cancer family with four affected females and an obligate male carrier manifesting prostate cancer. The deletion, which starts at either nucleotide 3599 or 3600 (GenBank U14680 [http://www.ncbi.nlm.nih.gov/]) and causes premature termination at codon 1166, has been described before and was shown to be disease causing (Struewing et al. 1995). Interestingly, inspection of the DNA-sequence context of 3599/3600del11 led to the identification of two symmetric sequence elements, TAGAT and GAAATAAAG, located immediately upstream of the proximal breakpoint and separated from each other by 6 bp (fig. 1).

Evidence for the involvement of symmetric elements in meiotic microdeletions, on the basis of seven deletional hotspots in five human genes, has been reported elsewhere by one of us (Krawczak and Cooper 1991). Each hotspot either consisted of or was flanked by a symmetric element (GAGAG at codon 245 of the AT3 gene; AATAA and GAAGAAG at codons 340/341 of the F8 gene; TGGAGAGGT and CTCCCTC at codon 31 of the HBA2 gene; GAGGAG at codon 7, TGAGT at codon 41, and ATCACTA at codon 141 of the HBB gene; and GTTTG at codon 178 of the HPRT gene). However, whether symmetric elements play a role in small-deletion mutagenesis in general has remained contentious. Although symmetric elements of $\geqslant 5$ bp were observed in 50 of 60 microdeletions analyzed, this was not found to represent a significant excess over random expectation, and it was concluded that symmetric elements are not a major cause of microdeletions (Krawczak and Cooper 1991). However, reanalysis of a threefold-larger sample (Cooper and Krawczak 1993) indicated that symmetric elements might be overrepresented, by a factor of 1.3, in the vicinity of microdeletion breakpoints.

Review of the sequences surrounding the 108 small deletions in the BRCA1 gene that have been published so far or that have been submitted to the mutation database of the Breast Cancer Information Core (http://www.nhgri.nih.gov/Intramural_research/Lab_transfer/Bic) suggests that breakpoints in the BRCA1 gene are associated with symmetric elements. To assess the statistical significance of this outcome, the distance to the nearest symmetric element of a given length was deter-