Biological Psychiatry

Treatment-Resistant Schizophrenia in a Patient With 17q12 Duplication

To the Editor:

Schizophrenia is a severe mental illness with a lifetime prevalence of .7% (1). Treatment resistance is common, with about one third of patients demonstrating resistance (2). A family history of psychosis has been associated with poorer treatment response (3), but the specific genetic predictors of treatment resistance are unknown. We report a case of a young man with 17q12 duplication and treatment-resistant schizophrenia.

A 19-year-old Afro-Caribbean man was referred to our service for treatment-resistant schizophrenia. He was born at full term by vaginal delivery after an uneventful pregnancy to healthy parents. Following immunization at age 2 years, he had an isolated febrile seizure. At age 4 years, he was noted to have speech delay. He attended mainstream primary and secondary school, where, with additional educational assistance, he achieved five passes in the school-leaving examinations (General Certificate of Secondary Education examinations), which is within the average range. He initially presented to regional Child and Adolescent Mental Health Services at age 17 with prodromal psychotic symptoms including low mood, anxiety, and social withdrawal. Deterioration of his mental state and functioning was attributed to recent social stressors. He developed frank psychotic symptoms 1 year later and was referred to a local Early Intervention team. Mental state examination revealed second-person auditory hallucination, bizarre delusions, passivity phenomena, and circumstantiality, along with significant negative symptoms including social and emotional withdrawal. The Positive and Negative Syndrome Scale (PANSS) (4) at the time of the assessment showed a total score of 77 (positive, 24; negative, 15; general, 38). A diagnosis of schizophrenia was made, based on DSM-IV criteria (5).

He was treated with amisulpride and responded initially, showing a 29-point decrease in PANSS total score (total PANSS score after treatment, 48; positive, 14; negative, 9; general, 25), but he relapsed within months despite treatment. Treatment was switched to olanzapine, but response remained inadequate despite sustained treatment over a year, leading to the referral to a secondary service for treatment-resistant psychosis.

His past medical history was unremarkable, and brain magnetic resonance imaging performed at age 17 showed no abnormalities. Following the febrile seizure at age 2, no subsequent seizures occurred according to history provided by the patient, his mother, and review of the general practitioner's notes. The consensus is that febrile seizures are a distinct pathology separate from epilepsy and are not associated with long-term impairment in cognitive function or behavioral abnormalities (6–8). It is unlikely that this isolated febrile fit is associated with the subsequent development of psychotic illness at age 17, but a relationship cannot be excluded.

The Wechsler Adult Intelligence Scale—Fourth UK Edition (9) administered at age 18 revealed that his cognitive abilities were within the "below average" range (full-scale IQ = 70; 95% confidence interval [CI] = 69–79) with more pronounced difficulties in working memory (working memory index, 69; 95% CI = 64–74). Performance in remaining Wechsler Adult Intelligence Scale—Fourth UK Edition subscales was as follows: verbal comprehension index, 74 (95% CI = 69–79); perceptual reasoning index, 73 (95% CI = 68–78); and processing speed index, 84 (95% CI = 79–89).

On assessment at the time of the referral, the patient presented with positive symptoms, including auditory hallucinations in the second and third person, circumstantiality, thought insertion and broadcast, and persecutory and grandiose delusions coupled with significant negative symptoms characterized by social withdrawal and stereotyped thinking. The PANSS showed a total score of 110: positive, 32; negative, 29; general, 49. The Global Assessment of Functioning score was 25. Physical examination and standard blood tests were unremarkable (10). Olanzapine levels were 94 μg/L (reference range, 20–40 μg/L), indicating good compliance.

His illness met criteria for treatment-resistant schizophrenia (10) on the basis of persistent, distressing, and disabling symptoms despite adequate antipsychotic treatment with two different antipsychotics, and a trial of clozapine was recommended. Response to clozapine was partial (PANSS total score, 89; positive, 16; negative, 29; general, 44) with a significant reduction of positive symptoms, but minimal overall improvement in his functioning.

In view of the history, genetic testing was recommended, and informed consent was obtained from the patient and parents. Analysis was conducted at a cytogenetics clinical pathology accredited laboratory as previously described (11,12). Briefly, genomic DNA extracted from peripheral blood was analyzed by array comparative genomic hybridization, using an Agilent 60K array (designs 028469 and 017457; Agilent Technologies, Inc, Santa Clara, California). Feature Extraction and DNA Analytics software packages (Agilent Technologies, Inc) for oligoarrays were used to carry out image quantification, array quality control, and aberration detection, according to the manufacturer's instructions. Array comparative genomic hybridization analysis identified a duplication of about 1.356 Mb in 17q12 (chromosome 17: 34,817,421…36,173,763) in the patient and his unaffected mother.

To our knowledge, this is the first report of a patient with 17q12 duplication and treatment-resistant schizophrenia. This raises the possibility that this copy number variant could be linked to treatment resistance, extending recent evidence suggesting that treatment-resistant schizophrenia is enriched for common risk alleles (13). The 17q12 duplication is a rare copy number variant in the general population. The variability in phenotypic outcome in our report between the unaffected parent and affected offspring is common in genomic disorders and may be explained by factors such as incomplete penetrance, differences in the size of the duplication, and

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epigenetic changes (14). In the 19 cases of 17q12 duplication reported to date, the most common presentations are developmental delay accompanied by learning disability and repetitive behaviors (15). Psychotic symptoms have been previously described in two cases of 17q12 duplication: one in a patient with bipolar affective disorder (16) and one in a patient with auditory hallucinations (17).

Szatkiewicz *et al.* (18) recently showed an association of 17q12 duplication with schizophrenia, observing more duplications in schizophrenia cases (five in the cases and one in the control subjects). This loci encompasses genes that are involved in brain development (19) and the immune system that are localized in mitochondria and the cytoplasm, regions where dysfunction has previously been implicated in schizophrenia (20). Further studies in patients with treatment-resistant schizophrenia are needed to determine if there is a specific link to treatment resistance.

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