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Original Article

Duplication 8q22.1-q24.1 associated with bipolar disorder and speech delay

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Objective: To report a case of a child with bipolar disorder found to have an unbalanced translocation involving the long arm of chromosome 8, a region that has been previously implicated in genome-wide linkage scans.

Case report: A 7-year-old boy with a complex psychiatric symptom presentation including attention deficits, distractibility, impulsivity, pressured speech, sleep disturbance, aggressive behavior, and hypersexuality diagnosed with bipolar disorder. He also showed evidence of borderline intellectual and adaptive functioning and had mild dysmorphic features with a duplication of distal 8q that arose as an unbalanced chromosomal translocation due to a maternal 15p;8q insertion.

Conclusions: This finding of an unbalanced translocation provides further evidence to support previous linkage studies of a potential causative gene on 8q for bipolar disorder.

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Family history is one of the strongest risk factors for the development of child psychiatric disorders (1). Progress continues to find the genetic basis of these complex disorders using cytogenetic studies, linkage analyses, and whole-genome scans. Craddock et al. recently reviewed the current knowledge of the various chromosomal regions, loci, and possible genes involved in bipolar disorder (2). We report a patient with bipolar disorder who was found to have an unbalanced translocation with breakpoints at 8q and 15p, resulting in a duplication of the 8q region.

Several independent genome-wide linkage scans for bipolar disorder have suggested linkage to the distal region of chromosome 8q (3–8). McInnis et al. demonstrated significance for non-parametric linkage (NPL) of 3.13 ($p < 0.003$) and parametric linkage with a logarithm of the odds (LOD) score of 2.1 at 8q24 (5). This group later expanded their analyses and found an NPL of 3.25 ($p = 0.001$) and a LOD score of 3.32 at this locus (6). In a separate study, Cichon et al. also showed linkage to 8q24 with a two-point LOD score of 3.619, a multipoint HLOD score of 3.01 ($\alpha = 0.66$), and an NPL of 3.56 ($p = 0.00029$) (3). Genome scan meta-analysis by Segurado et al. suggests that bipolar disorder is only weakly linked to 8q (9). Suggestive evidence to 8q was also found by Dick et al. with a LOD score of 2.46 ($p < 0.10$) (7). A recent report by McQueen et al. provided additional evidence for a locus on 8q (8). Their analysis comprised the largest investigation of its type for bipolar disorder to date and yielded a LOD score of 3.40 on chromosome 8 at 151 cM.

Through the association of bipolar disorder in a patient with an unbalanced translocation involving the distal long arm of chromosome 8, we provide further evidence supporting previous

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linkage data for chromosome 8q and discuss potential candidate genes in this region. We also discuss the observation of the increased incidence of autoimmune thyroiditis in patients with bipolar disorder. A susceptibility gene for autoimmune thyroiditis has also been reported in the 8q region.

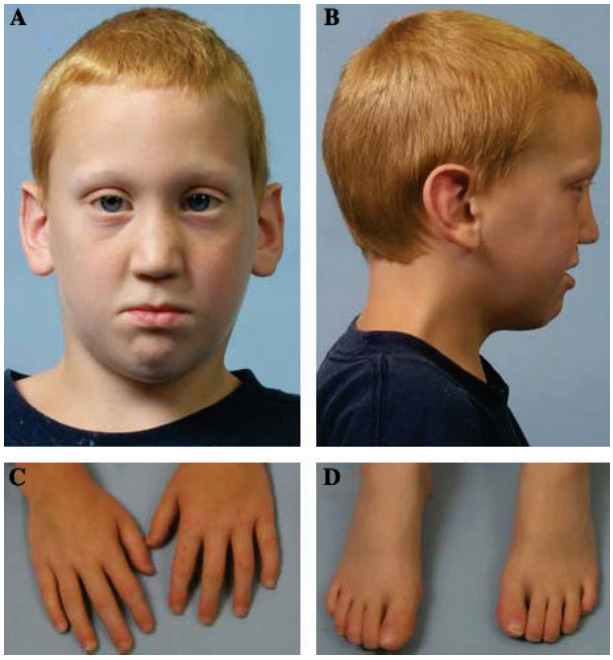
Clinical report

A 7-year-old Caucasian boy was born at 42 weeks estimated gestational age to a 19-year-old gravida 3, para 0, spontaneous abortion 2 mother following an uncomplicated pregnancy. Breech presentation required external version. Delivery occurred via normal spontaneous vaginal delivery. Birth weight was 4.8 kg (>95th percentile).

Motor milestones were met on time. However, receptive and expressive language delays were present as well as developmental deficits in adaptive and cognitive functioning. Reportedly, a hearing deficit was discovered and corrected after the placement of pneumatic equalization tubes. The patient had received previous diagnoses of attention deficit hyperactivity disorder and major depressive disorder, severe without psychotic features from his outpatient child psychiatrist.

Systematic family psychiatric history was collected from the mother with the use of a family lineage chart. Based upon the mother's report, the patient's maternal family psychiatric history is significant for attention deficit hyperactivity disorder (uncle), dyslexia (uncle and mother), and probable mood disturbance with mania (uncle). The mother described her uncle as having a history of hyperactivity and impulsivity with an accompanying mood disturbance similar to the patient's. The patient's younger maternally-related half-sister is normal. Maternal family medical history is significant for spontaneous abortions of male offspring. Paternal psychiatric and medical history is unknown.

Inpatient hospitalization of the patient occurred at 7 years of age for aggressive and hypersexual behaviors. At that time, physical examination showed a head circumference of 52 cm (50th percentile) with bitemporal narrowing (Fig. 1A,B). Height was 135.8 cm (>95th percentile) and weight was 30.4 kg (90–95th percentile). Eyes were hypoteloric with mildly upslanting palpebral fissures (Fig. 1A). There was a thin vermillion border and retrognathia (Fig. 1A,B). Fifth fingers and toes had bilateral clinodactyly (Fig. 1C,D). Nails were hypoplastic and there were broad first toes bilaterally.



LOW RESOLUTION COLOUR FIG

5 *Fig. 1.* (A) Face, (B) profile, (C) hands, and (D) feet of propositus.

Neurological examination was normal. However, the patient exhibited deficits in speech, fine motor performance, and social skills. Psychological testing during the hospitalization on the Kaufman Assessment Battery for Children [K-ABC, (10)] revealed a Mental Processing Composite of 74 (mean = 100, SD = 15) in the borderline range of functioning. Previous testing at age $5\frac{1}{2}$ years on the K-ABC revealed a Mental Processing Composite of 86, in the low average range, suggesting that he was currently evidencing a regression in cognitive functioning possibly secondary to his psychiatric disturbance. His speech evidenced an articulation defect, which combined with his highly pressured pattern of speech, was often indecipherable. He was conversant but his stream of thought was disorganized and tangential. His thought processes were highly concrete. He demonstrated difficulty sustaining attention with a high level of hyperactivity and distractibility. He had poor emotional regulation, low frustration tolerance, physical aggression toward peers, destruction of property, and non-compliance. In contrast, he was indiscriminately friendly, hypersexual, and socially inappropriate toward adults. He displayed a pattern of emotional lability that ranged from being sad and withdrawn to elated and impulsive.

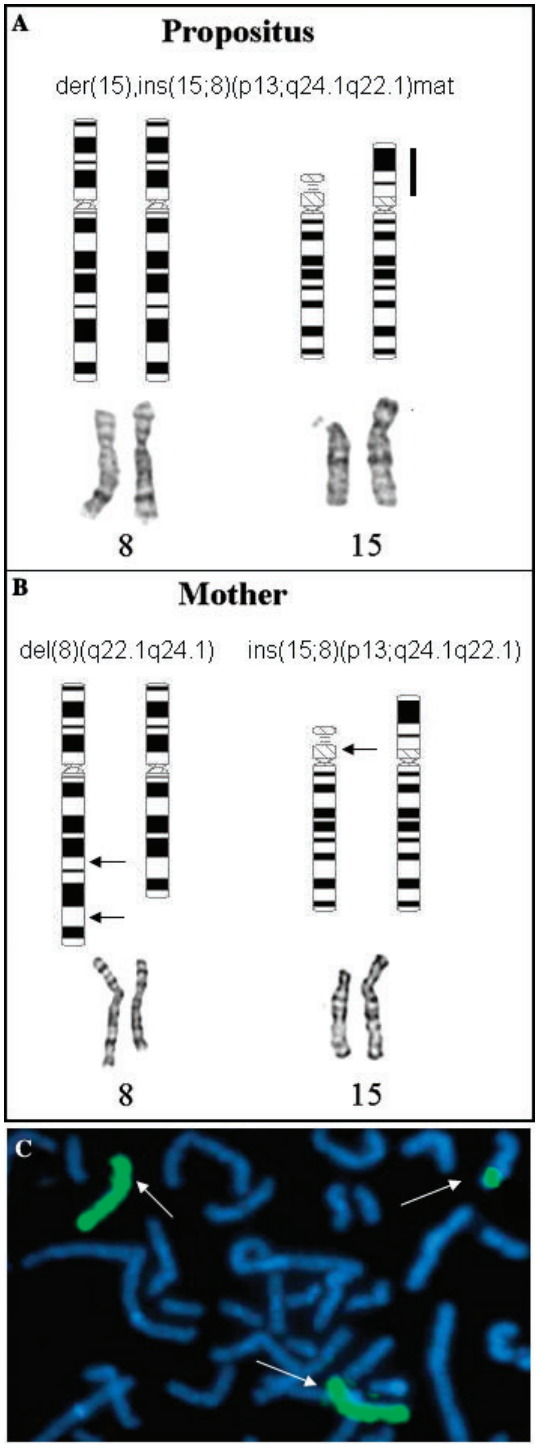
A diagnosis of bipolar 1 disorder was confirmed using the Parent Version of the Kiddie Schedule for Affective Disorders and Schizophrenia-Present State and Lifetime Version [KSADS-PL, (11)]

administered by a trained and reliable child psychiatrist.[1] The mother confirmed symptoms consistent with the patient's previous diagnosis of a major depressive episode, severe without psychotic features, including depressed mood, anhedonia, lethargy, feelings of worthlessness, suicidal ideation, irritability, and sleep disturbance. On admission, the patient met DSM-IV-TR criteria for a manic episode of more than 1 week's duration during which he demonstrated a mood disturbance consisting of symptoms of irritability, decreased need for sleep, pressured speech and excessive talking, flight of ideas and racing thoughts, psychomotor agitation, distractibility and impulsivity, and increased sexualized behavior. His mood disturbance was sufficiently severe to cause marked impairment in functioning necessitating hospitalization.

Due to the acute onset of manic symptoms, the patient was started on risperidone 0.5 mg orally daily that was titrated to 1.5 mg daily. Four days later, because the patient's manic symptoms had not subsided, he was started on lithium 300 mg orally daily increasing to a total of 750 mg daily (300 mg every morning and 450 mg every evening). His lithium level was 0.8 mmol/L after 5 days at this dose. During the course of treatment, the patient evidenced symptoms of akathesia. Hence, risperidone was discontinued and a course of olanzapine was initiated reaching a final dose of 7.5 mg orally daily. Mood stabilization was achieved within 10 days following a steady-state lithium level of 0.8 mmol/L.

Cytogenetic analysis

Cytogenetic analysis revealed a 46,XY,ins(15;8)(p13;q24.1q22.1)mat karyotype (Fig. 2A). The patient's mother and half-sister were balanced translocation carriers with a 46,XX,del(8)(q22.1-q24.1),ins(15;8)(p13;q24.1q22.1) karyotype (Fig. 2B). Overall, the mother and half-sister carried an inverted segment of distal chromosome 8 material on chromosome 15. The propositus inherited partial 8q trisomy from his carrier mother. The rearrangement observed in the propositus was confirmed using whole chromosome 8 paints (Fig. 2C), chromosome 8-specific subtelomere fluorescence *in situ* hybridization (FISH) analysis, and locus-specific FISH analyses with ETO (8q22) and the c-Myc oncogene (8q24).



5 *Fig. 2.* (A) Partial karyotype of the propositus with a bar illustrating the duplicated region of chromosome 8 on the derivative chromosome 15. (B) Partial karyotype of the mother with arrows on the normal chromosomes 8 and 15 illustrating the translocated segments. (C) Whole chromosome 8 paints (green) demonstrating partial trisomy.

[1]The child psychiatrist was trained for 10 weeks through live and videotaped demonstrations of the K-SADS-PL. Following these demonstrations, she was required to videotape her own administrations of the instrument until she reached 100% reliability of administration and scoring with the senior training psychiatrist.

Table 1. Genes localized to chromosome 8q22-q24

Gene	Locus	OMIM (19)
Core-binding factor, alpha subunit 2 (*CBFA2T1*)	8q22	133435
Dihydropyrimidinase (*DPYS*)	8q22	222748
Potassium voltage-gated channel, delayed-rectifier, subfamily S, member 2 (*KCNS2*)	8q22	602906
v-myb myeloblastosis viral oncogene homolog (avian)-like 1 (*MYBL1*)	8q22	159405
Outer dense fiber of sperm tails 1 (*ODF1*)	8q22	182878
Syndecan 2 (heparan sulfate proteoglycan 1, cell surface-associated, fibroglycan) (*SDC2*)	8q22	142460
Ubiquinol-cytochrome c reductase binding protein (*UQCRB*)	8q22	191330
Polymerase (RNA) 2 (DNA directed) polypeptide K (*POLR2K*)	8q22.2	606033
Brain and acute leukemia, cytoplasmic (*BAALC*)	8q22.3	606602
Potassium channel, subfamily V, member 1 (*KCNV1*)	8q22.3	608164
Regulating synaptic membrane exocytosis 2 (*RIMS2*)	8q22.3	606630
Collagen, type XIV, alpha 1 (undulin) (*COL14A1*)	8q23	120324
Solute carrier family 26, member 7 (*SLC26A7*)	8q23	602479
Ribonucleotide reductase M2 B (TP53 inducible) (*RRM2B*)	8q23.1	604712
Ectonucleotide pyrophosphatase/phosphodiesterase 2 (*ENPP2*)	8q24.1	601060
Nephroblastoma overexpressed gene (*NOV*)	8q24.1	164958
v-myc myelocytomatosis viral oncogene homolog (avian) (*C-MYC*)	8q24.12	190080
Ribosomal protein L30 (*RPL30*)	8q24.13	180467

OMIM = Online Mendelian Inheritance in Man.

Discussion

Translocations have long been used to localize potential areas of causative genes in diseases, including psychiatric illnesses. For example, Brandon et al. identified the susceptibility gene, Disrupted In Schizophrenia 1 (DISC1), for schizophrenia through a balanced t(1;11)(q42;q14) translocation (12). The relationship between the mood disorder observed in this patient and his genotype is intriguing. Specifically, this patient was diagnosed with bipolar 1 disorder, had a family history of probable mood disorders (although unconfirmed), and was found to have an unbalanced translocation resulting in three copies of a small region of 8q (partial 8q trisomy).

Wildenauer and Schwab summarized many potential loci for psychiatric disorders that included linkage to various regions on 8q (13). Genome-wide linkage scans have suggested strong evidence for linkage of bipolar disorder to the long arm of chromosome 8, specifically 8q24 at marker D8S256 (LOD score of 3.6, HLOD 2.39, NPL 3.13) (3, 5–7), 8q at 151 cM (LOD score of 3.40) (8), and 8q13 (LOD score of 2.06) (4). The partial trisomy of the 8q region in this patient may be strongly related to his psychiatric phenotype. Previous clinical reports and entries in various cytogenetic databases of partial trisomy 8q have focused mainly on the physical characteristics of these patients with no mention of bipolar disorder. It may be that these cases are described quite early in childhood and not followed long enough to determine whether or not psychiatric disorders develop.

Several other genes in the 8q region have been thought to contribute to psychiatric illness. The high-affinity cAMP-specific phosphodiesterase gene (*HCP1*), mapped to 8q13-q22 has been implicated in determining mood and behavior (14). Search of the human genome database between 8q22.1 and 8q24.1 found multiple genes with variable amounts of expression in the brain as shown in Table 1 (15). Avramopoulos et al. suggested other potential genes including thyroglobulin (TG), a voltage-gated potassium channel (KCNQ3), and brain adenylate cyclase (ADCY8) (6).

Interestingly, although the breakpoints of the rearrangements observed here is not specifically involved, the *myo*-inositol monophosphatase 1 gene (*IMPA1*), mapped to 8q21.13-q21.3, has been thought to play a role in lithium treatment of bipolar disorder (16). This may be of future interest in the research on the role of upstream factors involved in bipolar disorder.

There are several disorders that have been mapped to 8q22-8q24 (Table 2). Among these, Hashimoto thyroiditis is most interesting. It has long been observed that patients with bipolar disorder have a higher incidence of autoimmune or Hashimoto thyroiditis (17). The reason for this has been unclear and is suggested to be related to the possible effects of the treatment of bipolar symptoms with lithium. Recently, Shirasawa et al. found a susceptibility gene for autoimmune thyroid disease, *ZFAT* (zinc-finger gene in AITD suscep-

Table 2. Review of disorders associated with the 8q22-q24 region

Disorder	Chromosome	OMIM (19)
Cohen syndrome	8q22-q23	216550
Klippel-Feil syndrome (segmentation syndrome 1)	8q22.2	148900
Glaucoma 1	8q23	602429
Hashimoto thyroiditis	8q23-q24	140300
Spastic paraplegia 8	8q23-q24	603563
Epidermolysis bullosa simplex, Ogna type	8q24	131950
Epidermolysis bullosa with muscular dystrophy	8q24	226670
Benign neonatal epilepsy 2	8q24	121201
Benign adult myoclonic epilepsy type 1	8q24	601068
Childhood absence epilepsy 1	8q24	600131
Langer-Giedion syndrome (trichorhinophalangeal syndrome type 2)	8q24.11-q24.13	150230
Multiple exostoses type 1	8q24.11-q24.13	133700
Trichorhinophalangeal syndrome type 1	8q24.12	190350
Trichorhinophalangeal syndrome type 3	8q24.12	190351

OMIM = Online Mendelian Inheritance in Man.

tibility region), in 8q23-q24 (18). This further supports the possibility of a gene for bipolar disorder in this region.

In this report, we present a patient with bipolar disorder and a duplication of 8q22.1-q24.1. Further evaluation of the breakpoints and genes in this region will help elucidate the role of this region in the genetic susceptibility for bipolar disorder.

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