

Mood Disorders in Individuals With Distal 18q Deletions

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We examined 36 participants at least 4 years old with hemizygous distal deletions of the long arm of Chromosome 18 (18q-) for histories of mood disorders and to characterize these disorders clinically. Since each participant had a different region of 18q hemizyosity, our goal was also to identify their common region of hemizyosity associated with mood disorders; thereby identifying candidate causal genes in that region. Lifetime mood and other psychiatric disorders were determined by semi-structured interviews of patients and parents, supplemented by reviews of medical and psychiatric records, and norm-referenced psychological assessment instruments, for psychiatric symptoms, cognitive problems, and adaptive functioning. Sixteen participants were identified with lifetime mood disorders (ages 12–42 years, 71% female, 14 having had unipolar depression and 2 with bipolar disorders). From the group of 20 who did not meet criteria for a mood disorder; a comparison group of 6 participants were identified who were matched for age range and deletion size. Mood-disordered patients had high rates of anxiety (75%) and externalizing behavior disorders (44%), and significant mean differences from comparison patients ($P < 0.05$), including higher overall and verbal IQs and lower autistic symptoms. A critical region was defined in the mood-disordered group that included a hypothetical gene, C18orf62, and two known genes, *ZADH2* and *TSHZ1*. We conclude that patients having terminal deletions of this critical region of the long arm of Chromosome 18 are highly likely to have mood disorders, which are often comorbid with anxiety and to a lesser extent with externalizing disorders.

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Key words: depression; bipolar disorder; Chromosome 18; 18q-; hemideletion; mood disorders; *ZADH2*; *TSHZ1*

INTRODUCTION

Understanding the biology of mood disorders by identifying the causative genes has met with limited success. Chromosome 18 has been linked to mood disorders since 1994 [Berrettini et al., 1994]. In

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subsequent years, evolving technologies and methodologies from multiple research groups have confirmed the original finding. However, these additional studies have not honed in on a single region with increasing precision. Instead they appear to have fragmented the chromosome into multiple smaller linkage regions. Even today it is not clear how many different genes on Chromosome 18 may be influential in the development of depressive or bipolar disorders.

We propose a different approach, which is to start with a population that has a known genetic commonality and then describe the behavioral aspects of this special population. We are studying a unique population with a shared genetic abnormality: a hemizygous deletion of distal 18q. However, the exact region

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of hemizyosity is different in each person. This shared genotype allows us to do two things. First, it gives us confidence that the phenotype has at least one component of a shared etiology. Second, it allows us to define the endophenotypes segregating with depressive or bipolar disorders. This combination of a high likelihood of shared genetic etiology and the ability to identify endophenotypes should provide a more robust diagnostic criterion for mood disorders. In addition, the biological mechanism leading to a phenotype in this population is a consequence of gene hemizyosity. Therefore, the underlying biological mechanism leading to a phenotype is haploinsufficiency.

In this study, we had several goals. First, we sought to identify a gene or genes on 18q associated with mood disorder by defining a common hemizygous region in the affected individuals. Second, we compared the affected individuals to others in our cohort with similar sized hemizygous deletions who were at least as old as the youngest affected individual. We expected that this comparison would provide clues to comorbidities and/or endophenotypes and would provide insight about the biological underpinnings of mood disorders with a Chromosome 18q cause. Additionally, these investigations would help to identify potentially unique characteristics of mood disorders in people with 18q deletions.

METHODS

Participants

Participants in the current study were children at least 4 years old, adolescents and adults diagnosed with a deletion of the long arm of Chromosome 18 (18q-) who all underwent detailed psychiatric assessments as part of a comprehensive research assessment at a center for participants with Chromosome 18 abnormalities ($n = 36$). All genotypes were confirmed with microarray comparative genomic hybridization using the Agilent system as described previously [Heard et al., 2009]. Participants eligible for the current study's analysis had to be at least 4 years old, and either they or a parent or guardian had to have sufficient cognitive and language skills to be able to complete a mental health interview, and to participate in neuropsychological testing. Additionally, participants were evaluated by various medical specialists, including a geneticist, endocrinologist, cardiologist, physical therapist, neurologist, and neurotologist over a 3- to 4-day evaluation during a visit to San Antonio. From among 36 patients with 18q- evaluated who met the above criteria, 16 were identified with lifetime histories of mood disorders. In these 16, a critical region of deletion on 18q was identified, as reported below. From the group of 20 who did not meet criteria for a mood disorder, a comparison group of 6 was identified who were in the same age range and had deletions within the same broad region of 18q.

This study was approved by the Institutional Review Board of the University of Texas Health Science Center at San Antonio. A detailed review of the potential risks and benefits of participating in the study was first done in a phone call by one of the staff involved in the research study, and then in person by one of the investigators. Subjects and parents who agreed to participate in these assessments were asked to sign a consent form to indicate their assent (in

participants less than 18) or consent (in participants at least 18) to continue in the study.

Psychiatric Assessments

All participants underwent a detailed mental health assessment that included a general interview of the participant and at least a parent or guardian by a psychiatrist. Additionally, participants were given a structured or semi-structured psychiatric interview by a psychiatrist or by a Master's level psychometrist trained to administer the interview by the supervising psychiatrist. Child and adolescent participants were interviewed with the Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version (K-SADS-PL) [Kaufman et al., 1997], the Diagnostic Interview for Children and Adolescents (DICA-IV) Windows Version [Reich et al., 1997] or the Mini International Neuropsychiatric Interview for Children and Adolescents (MINI-KID) [Sheehan et al., 2010]. Adult participants were interviewed with the DICA, the Mini International Neuropsychiatric Interview Plus version for adults (MINI Plus) [Sheehan et al., 1998], or the Diagnostic Interview for Genetic Studies (DIGS) [Nurnberger et al., 1994]. Parents were interviewed with KSADS-PL, the MINI-KID, the MINI Plus, or the Family Interview for Genetic Studies (FIGS) [Maxwell, 1992]. Final diagnoses were determined on a consensus basis using input from all interviewers, after a review of all available interview data and observations during the assessments, as well as medical and psychiatric records provided by the participants and parents, according to DSM-IV-TR criteria [American-Psychiatric-Association, 2000].

Autism Spectrum Symptoms and Diagnoses

Because research has suggested that individuals with constitutional hemizyosity of 18q have a higher risk of autistic-like behavior [O'Donnell et al., 2010], study participants were evaluated for the possibility an autism spectrum disorder. Such diagnoses were determined using parent reports on the Autism—Tics, AD/HD and other Comorbidities inventory Full Version (A-TAC: FV) [Anckarsater et al., 2007] along with a clinical interview by the study psychiatrist of both the parent and study participant. The A-TAC is a comprehensive parent interview focusing on child autism spectrum disorders, with questions answered in a lifetime perspective relative to peers of the same age. It contains three sections that review the main domains of autism spectrum disorder symptoms as defined in DSM-IV-TR: abnormalities in communication, social interaction, and stereotypical or inflexible behaviors. The A-TAC has been validated for assessing autism spectrum disorders when administered over the phone by laypersons [Hansson et al., 2005; Larson et al., 2010], and in a recent large-scale genetic study [Lichtenstein et al., 2010]. In the current sample, the A-TAC was completed by a Master's level psychometrist or by a child and adolescent psychiatrist by phone or by e-mail, after the on-site evaluation. Study participants here were classified by whether or not they met diagnostic criteria for any autism spectrum disorder, as the above validation studies have not supported the ability of the A-TAC to discriminate among the various types of autism spectrum disorders.

Assessment of Cognitive Ability and Diagnosis of Mental Retardation

All subjects underwent cognitive testing by a pediatric neuropsychologist, doctoral students trained and supervised by the neuropsychologist or a Master's level psychometrist also trained and supervised by the neuropsychologist. Measures used to assess cognitive ability were chosen based on the subjects' ages and developmental levels from multiple measures. These measures included: the Bayley Scales of Infant Development, 2nd edition (BSID-II) [Bayley, 1993]; the Mullen Scales of Early Learning (Mullen) [Mullen, 1995]; the Differential Abilities Scales (DAS) [Elliott, 1990]; the Wechsler Intelligence Scale for Children-Third Edition (WISC-III) [Wechsler, 1991]; and the Wechsler Adult Intelligence Scales, Third and Fourth Editions (WAIS III and IV) [Wechsler, 1997, 2008].

Diagnosis of cognitive disability was made according to DSM-IV-TR criteria, which requires assessed cognitive abilities (Full Scale IQ below 70) and concurrent deficits in adaptive functioning.

Assessment of Emotional and Behavioral Difficulties

Parents/caregivers also completed the Behavioral Assessment System for Children First or Second Edition (BASC or BASC-2) [Reynolds and Kamphaus, 1992, 2004]. Behavior is rated along the following dimensions: Externalizing Behaviors (e.g., problems with hyperactivity, aggression, and conduct); Internalizing Behaviors (e.g., problems with anxiety, depression, and somatization); and Behavioral Symptoms (atypicality, withdrawal and attention problems).

Adaptive Skills

In order to evaluate the impact of mood disorders on behavioral functioning as well as to verify the presence of concurrent behavioral deficits when cognitive disability was present, the adaptive skills of all participants regardless of age were measured by a parent or guardian using the Vineland Adaptive Behavior Scales Parent/Caregiver Rating Form (Vineland) [Sparrow et al., 1984] or the Vineland Adaptive Behavior Scales, Second Edition Parent/Caregiver Rating Form (Vineland-II) [Sparrow et al., 2005]. Both measures assess adaptive behavior in four domains: Communication, Daily Living Skills, Socialization, and Motor Skills. They also provide a composite score summarizing the individual's performance across all four domains.

RESULTS

Our goals were to identify individuals with hemizygous deletions of distal 18q who also had a history of a mood disorder, and to identify a common region of hemizygosity in this population. Additionally, we wanted to characterize this group clinically regarding comorbid disorders and levels of cognitive and behavioral function.

To determine a common region of hemizygosity, 16 individuals with lifetime histories of mood disorders were identified from a total of 36 subjects with 18q deletions who had psychiatric inter-

views. Among these 16, 14 were diagnosed with a lifetime history of unipolar depressive disorders and 2 had bipolar disorders. Table I lists the behavioral characteristics of these 16 participants. This group had mean age of 21 years old (range: 12–42 years old), and 11 (69%) were female. Not all participants had structured interviews that would enable us to diagnose disorders of childhood, so the denominators and proportions are adjusted accordingly. Anxiety disorders in lifetime depressed group were common at 75%, and included anxiety disorders not otherwise specified ($n = 5$), generalized anxiety disorders ($n = 4$), social phobias ($n = 2$), separation anxiety disorders ($n = 2$), post-traumatic stress disorders ($n = 2$), obsessive compulsive disorders ($n = 2$), panic disorder ($n = 1$), and specific phobias ($n = 1$). Of note, several in the anxiety disorder NOS group had phobic or obsessive compulsive symptoms not impairing enough to meet full DSM-IVTR criteria for specific phobia or obsessive compulsive disorder. Seven in the lifetime mood disorders group (44%) had a comorbid externalizing disorder, including five with disruptive behavioral disorders not otherwise specified characterized by explosive outbursts, two with oppositional defiant disorders, and one with conduct disorder. A total of five (36%) had a diagnosis of an attention deficit hyperactivity disorder (ADHD). Seven of the 13 (54%) for whom A-TAC data were available were diagnosed with autism spectrum disorders. Four (24%) had mental retardation. The group's mean IQ was within the low average range of intelligence, and level of function based on Vineland scores was also in the low average range. The depressed group, as expected, had a clinically significant level of depressive, anxiety and internalizing symptoms on the BASC.

We wished to determine whether other behavioral characteristics were more common in the mood disordered group as compared to the non-mood disordered group. However, within our cohort, each individual had a different deletion and therefore potentially somewhat different hemizygous genes. The major consequence is that those with larger deletions were typically more cognitively impaired and therefore more difficult to assess for mood disorders. Consequently, there could be individuals in the non-mood disordered group who, because of lower cognitive abilities, displayed a mood disorder in a way not recognized as such. In order to control for the sizes of different deletions and still compare other characteristics of the mood disordered and non-mood disordered group, we selected from the non-mood disordered group only those individuals whose deletion sizes and age ranges fell within the same range as those in the mood disordered group ($n = 22$). The data depicting the region of hemizygosity for these (16 mood disordered and 6 non-mood disordered) individuals are shown in Figure 1.

The selection of this comparison group lessened the potential for the potentially confounding effects of larger deletion (i.e., greater degree of cognitive disability) and younger age (i.e., shorter time period to exhibit the phenotype). The clinical data from these six individuals are also summarized in Table I. Given the small number of non-mood control participants, we had limited power to detect any statistically significant differences between these groups. Differences in proportions having intellectual disability, anxiety disorders, and oppositional or conduct disorders did not reach significance, nor did levels of internalizing, anxiety, somatic, or depressive symptoms. Even so, participants with a lifetime history

TABLE I. Comparison of Subjects With and Without Lifetime Histories of Mood Disorders

	Overall (N = 22)	Lifetime mood disorder (n = 16)	No lifetime mood disorder (n = 6)	P
Age in years	21 ± 6	22 ± 7	18 ± 2	
Adult age, n (%)	18 (82)	13 (81)	5 (83)	
Female sex, n (%)	16 (73)	11 (69)	5 (83)	
Non-White race, n (%)	4 (18)	3 (19)	1 (17)	
Psychotic disorder	3 (14)	3 (19)	0 (0)	
Any ADHD diagnosis ^a	7 (37)	5 (36)	2 (40)	
Any externalizing disorders	8 (36)	7 (44)	1 (17)	
Alcohol use disorder	1 (5)	1 (6)	0 (0)	
Drug use disorder	1 (5)	1 (6)	0 (0)	
Any anxiety disorder	14 (64)	12 (75)	2 (33)	
Eating disorders	2 (9)	1 (6)	1 (17)	
Enuresis by full DSM-IV-TR criteria ^a	6 (32)	4 (29)	2 (40)	
Encopresis by full DSM-IV-TR criteria ^a	2 (11)	1 (8)	1 (20)	
Any autism spectrum disorder ^b	12 (63)	7 (54)	5 (83)	
Mental retardation	7 (32)	3 (19)	4 (67)	
Intelligence quotient				
Verbal	83 ± 19	91 ± 16	63 ± 10	0.001
Performance ^c	84 ± 13	85 ± 13	78 ± 13	
Overall	77 ± 16	82 ± 16	64 ± 12	0.02
BASC-II				
Internalizing	58 ± 14	61 ± 14	52 ± 11	
Somatization index	54 ± 11	54 ± 11	53 ± 12	
Anxiety	56 ± 12	59 ± 13	49 ± 8	
Depression scale	61 ± 16	65 ± 17	53 ± 12	
Vineland				
Communication	67 ± 19	70 ± 16	60 ± 26	
Daily living skills	69 ± 18	71 ± 17	65 ± 23	
Socialization	69 ± 18	73 ± 15	60 ± 23	
Adaptive behavioral composite	67 ± 17	70 ± 13	58 ± 22	
Autism symptoms on ATAC ^b	7 ± 3	6 ± 3	9 ± 2	0.02

Unless noted otherwise, numbers in columns are means ± standard deviations.

Only *P*-values <0.05 are shown.

^aNot assessed in two subjects with and one subject without lifetime mood disorders who were interviewed with only the FIGS.

^bNot assessed in three subjects with lifetime mood disorders having missing ATAC data.

^cNot assessed in one subject without lifetime mood disorders who was non-verbal.

of a mood disorder had significantly higher means for overall and verbal IQs, and lower total counts of autistic symptoms.

Our approach to identifying the key genes was to determine the common hemizygous region in everyone with the phenotype. Because it is not unusual to identify people with a genetic disease genotype without manifestations of the disease (i.e., non-penetrance), we did not use individuals without the phenotype to determine critical regions. Within the group of 16 with a history of a mood disorder, the two individuals whose breakpoints defined the critical region were participant 18q-155C and 18q-202M. This critical region extends from 70,983,612 to 71,626,363 bp (hg18). Figure 2 shows the region of shared hemizyosity between these two individuals whose deletions defined the critical region. This region is shown in relation to the data from previous genetic studies. Both sets of data are aligned with the UCSC Genome Browser known genes in the region. Our identified critical region lies within the linkage regions identified by two other groups [Coon et al., 1996; Freimer et al., 1996]. The critical region includes two known genes, *ZADH2* (zinc binding alcohol dehydrogenase domain 2) and

TSHZ1 (teashirt family zinc finger 1) as well as a hypothetical gene C18orf62.

We have reported previously that 12.6% of participants with a simple terminal or interstitial deletion of 18q from among 95 subjects for whom parent of origin was available had a deletion of their maternally inherited chromosome [Heard et al., 2009]. Because there are previous reports of a parent of origin effect for mood disorders associated with Chromosome 18, we determined the parental origin of the derivative Chromosome 18 for each participant with and without lifetime mood disorders for whom DNA samples from both parents were available. Table II summarizes the findings from this analysis. All 5 patients (100%) whose deletions were maternal in origin, and 8 of 14 subjects (57%) whose deletions were paternal in origin, had experienced a lifetime mood disorder (FET *P* = 0.13). The remaining six subjects whose deletions were paternal in origin (i.e., whose maternal copy of Chromosome 18 was intact) comprised the group without a lifetime mood disorder. This suggests that the gene linked to lifetime mood disorders in our sample has a greater effect on a mood disorder

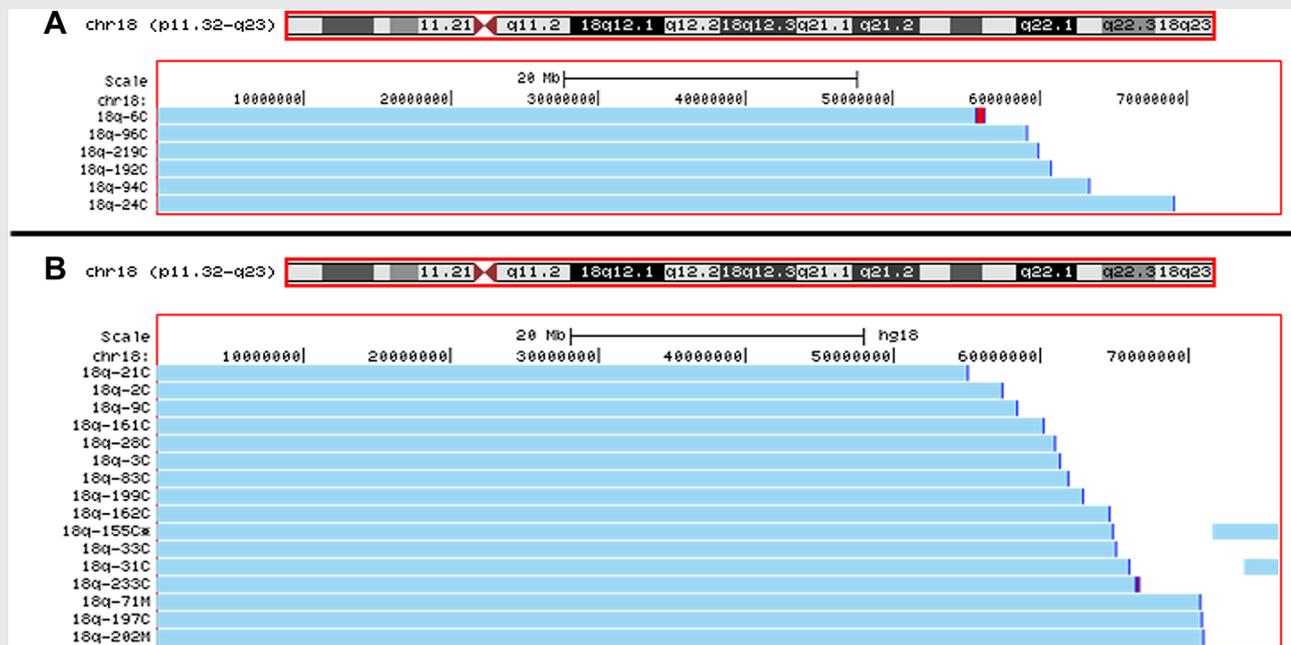


FIG. 1. aCGH data from study participants indicating their net copy number loss on Chromosome 18. Participant study numbers are shown to the left. Panel (A) includes aCGH data from the individuals in the study who did not have a history of a mood disorder. The gray (blue) bar indicates the region of normal copy number, while the gaps indicate the hemizygous region. The darker line at the end of each bar indicates the breakpoint region for each individual's deletion. The dark gray (red) bar at the end of the chromosome for participant 18q-6C indicates a trisomic region. Panel (B) includes the cCGH data from the study participants who had a history of a mood disorder depicted in the same manner as in panel (A).

when the deletion is of maternal origin, meaning that the single remaining active gene is of paternal origin.

Among the comparison group with no history of a mood disorder, all six were also hemizygous for the critical region. This suggests that, as with many genetic conditions, the presence of the genotype is not 100% penetrant and therefore not sufficient alone to cause the phenotype. In our cohort, all 22 individuals were hemizygous for the critical region, yet only 16 had a lifetime history of a mood disorder, suggesting a penetrance of 73%.

DISCUSSION

The original finding by Berrettini et al. [1994] linking Chromosome 18 to bipolar disorder has evolved from the identification of the pericentromeric region of Chromosome 18 to an 18p telomeric region [McInnes et al., 1996; Escamilla et al., 2001; Segurado et al., 2003; Nwulia et al., 2007], a pericentromeric region [Stine et al., 1995; Berrettini et al., 1997; Detera-Wadleigh et al., 1999; Nothen et al., 1999; Segurado et al., 2003; Fallin et al., 2004], and a more distal region of 18q. Whether the distal 18q region can be further subdivided to include more than one gene playing a role in mood disorders is not yet clear.

The linkage data on distal 18q encompass the distal half of the long arm and spans a 24.8 Mb region [Stine et al., 1995; Coon et al., 1996; De Bruyn et al., 1996; Freimer et al., 1996; McInnes et al., 1996; McInnis et al., 2003; McMahon et al., 1997, 2001;

Nothen et al., 1999; Verheyen et al., 1999; Schulze et al., 2003; Segurado et al., 2003; Fallin et al., 2004; Park et al., 2004; Nwulia et al., 2007]. Additionally, in a genome wide association study (GWAS), Goossens et al. [2003] analyzing the DNA from the same family as Verheyen et al. [1999], reported an association between SNPs within the *DSEL* gene and affected individuals. A second GWAS study [Howrigan et al., 2011] identified a significant SNP 17.6 Mb proximal and within the region identified by Park et al. [2004]. The regions of 18q implicated by these studies and their relationship to each other as well as to our data are shown in Figure 2.

Each of these studies in the literature began with the identification of a proband with Bipolar I (BP-I). However, additional family members who were categorized as affected included those with a broader range of diagnoses, including bipolar II (BP-II) (having lifetime histories of major depression and hypomania) and recurrent depressive disorders. Interestingly, several linkage studies focused on BP-II [MacKinnon et al., 1998] and early-onset major depressive disorder (MDD) Zubenko et al. [2003] and Camp et al. [2005] also identified regions entirely within the bipolar region on 18q. More recently, Shi et al. [2011] used GWAS to identify two SNPs with the strong evidence for association with early-onset MDD in this same region. One SNP is 75 kb upstream of *DSEL* (18q22.1) and the second is more proximal between *MEX3C* and *DCC* (18q21.2). Also relevant to the present study is that 35% of those with MDD in the Shi study had anxiety, yet the investigators

TABLE II. Parent of Origin of Chromosome 18 Defect Is Associated With Lifetime Mood Disorder

	Lifetime mood disorder?		Total
	No	Yes	
Parental origin			
Paternal			
Count	6	8	14
% Within parental origin	42.9	57.1	100.0
% Within lifetime mood disorder	100.0	61.5	73.7
% of total	31.6	42.1	73.7
Maternal			
Count	0	5	5
% Within parental origin	0.0	100.0	100.0
% Within lifetime mood disorder	0.0	38.5	26.3
% of total	0.0	26.3	26.3
Total			
Count	6	13	19
% Within parental origin	31.6	68.4	100.0
% Within lifetime mood disorder	100.0	100.0	100.0
% of total	31.6	68.4	100.0

FET *P*-value = 0.13.

in the overall sample had intellectual disability and/or autism spectrum disorders, as would be expected, relative to the general population. Curiously, among the participants who had developed lifetime mood disorders, we observed a lower level of cognitive disability and autism spectrum symptoms than in those who had not developed a mood disorder. This suggests that for patients who have deletions of the long arm of Chromosome 18, a certain level of cognitive and psychosocial function may increase their risk of developing a mood disorder, whereas those having more intellectual impairments and autistic symptoms may be relatively protected from having such disorders. On the other hand, it is also possible that our psychiatric interviews were not sensitive to mood or anxiety disorders in those having intellectual impairment or limited insight abilities.

A second goal of this study was to understand the genetic component of mood disorders in this condition. Since everyone with an 18q deletion has a unique region of hemizyosity, it is possible to exploit this fact and identify a small common region of hemizyosity in the affected subset of people with 18q deletions. Here we identified a 643 kb region of 18q23 that is hemizyous in everyone with a history of a mood disorder. This region includes two known genes and one hypothetical gene.

One gene in the critical region is the teashirt family zinc finger 1 gene (*TSHZ1*). Data from the heterozygous knock-out mouse model implicated this gene in craniofacial and middle ear abnormalities [Core et al., 2007], including the midface hypoplasia and aural atresia phenotypes common in people with hemizyosity of this gene [Cody et al., 2009]. Recently, Feenstra et al. [2011] identified the *TSHZ1* gene as the cause of this phenotype.

The second gene is the zinc binding alcohol dehydrogenase domain gene (*ZADH2*) which is not well described. However, it is one of the genes found to be under-expressed compared to

controls in the brains of people with autism [Voineagu et al., 2011]. Two studies suggest that there may be vulnerability genes in common between autism and other types of mood disorders, specifically bipolar disorders, making this a feasible candidate gene [Munesue et al., 2008; Ragnath et al., 2011].

There are two other genes that are hemizyous in some but not all of the individuals in our cohort; *BCL2* and *DSEL* (circled in Fig. 1). These genes may also play a role on the manifestation of mood disorders. However, it is important to remember that the linkage and GWAS studies identify associations to genes or regions without regard to the genetic mechanism of disease causation. For example, a gene may be causative of a disorder by a dominant negative mechanism and be identified as causative by linkage or GWAS. A condition caused by this mechanism would not cause disease by haploinsufficiency, which is the mechanism of disease in our cohort.

There are numerous previous studies suggesting a paternal parent of origin effect for 18q related bipolar disorders [Stine et al., 1995; McMahan et al., 1997; Lambert et al., 2002; McInnis et al., 2003; Fallin et al., 2004]. Lan et al. [2007] found that families with paternal inheritance showed evidence for a major gene effect compared to the families with maternal inheritance, which supported a multifactorial model. Conversely, Nwulia et al. [2007] found no evidence for imprinting. Interestingly, Luedi et al. [2005] predicted human imprinted genes based on their murine homologs and predicted that *SERPINB2* (at 59 Mb) would be maternally expressed. Although the *SERPINB2* gene lies within the distal 18q region associated with bipolar disorder it is not within our critical region. Additionally, most data supporting a parent of origin effect suggest the causative gene would be paternally expressed.

In our cohort, all the individuals with a maternally inherited deletion were in the mood disordered group. While our cohort is

underpowered to identify a parent of origin association with mood disorders, especially given the relatively infrequent number of subjects with maternal deletions, this finding is interesting because it contrasts with the findings from the other studies. In our study, the active genes in the hemizygous region of those with maternal deletions are paternal in origin. Our data suggest that vulnerability to a mood disorder may require the paternal allele to be expressed, or that expression of only the maternal allele is required for normal function. Thinking mechanistically about the linkage study findings that showed increased linkage signals to the 18q region when the condition was paternally inherited, the implication is that the maternal allele of the causative gene may be imprinted or silenced in families with paternal transmission of a mood disorder, thereby making mutations within the maternal allele inconsequential. If true, then only mutations in the paternal allele would be passed to the next generation and expressed to result in a high risk for a mood disorder. In patients with maternal deletions, only the paternal allele is present and therefore active. If this mechanism was applicable to the causative genes in our study, then we would expect to see a lower proportion of maternal deletions in the group with than in the group without a lifetime mood disorder, as was observed in the current sample.

Limitations of the current study include the relatively small number of participants in both the lifetime mood disorder and the comparison groups, which limited our power for comparative analyses. However, this sample was drawn from a registry of patients around the world for this disorder. While this study used a combination of standard parent and patient interviews and questionnaires, many of these have not yet been well studied or validated in patients with genetic aberrations and intellectual or language disabilities. We were often compelled to use “not otherwise specified” diagnoses to characterize patients who had clear impairment related to mood, anxiety, or disruptive symptoms without meeting full DSM-IV criteria for the more typical diagnoses. Whenever possible, we obtained data from both the patient and a parent. However, there were some patients of greater intellectual disabilities who were verbally incapable of reporting a history of a mood disorder, and for these we relied more heavily on the parents. It is possible that we under-reported the level of mood disorders in such patients. This in part may explain the difference observed in the patients with lifetime mood disorders being less affected by autism symptoms and having higher overall and verbal IQs. Alternatively, a certain level of cognitive or behavioral function may be required to be diagnosed with a mood disorder. It is also important to point out that some in the comparison group could eventually go on to develop a mood disorder with increasing age. While we identified a critical region associated with lifetime mood disorders in our population, it is important to realize that mood disorders, especially unipolar depressive mood disorders, are typically thought of emerging based on the interactions of genetic and environmental effects, and we did not assess such environmental effects in the current sample. Finally, while our assessment of autism spectrum disorders was done using the combination of parent-reports on the A-TAC and live clinical interviews, and the A-TAC has recently been validated for discriminating patients who have autism spectrum disorders [Hansson et al., 2005; Larson et al., 2010; Lichtenstein

et al., 2010], other measures have more empirical evidence to support their criterion validity for such purposes [see Ozonoff et al., 2005].

There is no reason to assume that mood disorders in individuals with intellectual disability are any less debilitating and life limiting than in people with normal cognitive function. In fact, pharmacological treatment of mood disorders in those with intellectual disability may prove even more life enhancing, given the potential challenges of conventional talk therapies like cognitive behavioral therapy in such patients. Future studies should focus on the development of tools to assess mood disorders in people with impaired intellectual ability, and potential interventions for treating them. Future studies are also needed to compare the 18q- populations to not only persons with chromosomal disorders outside this critical region (in order to compare for possible confounds of intellectual impairment and comorbid medical disorders) but also to persons with mood disorders having high familial loading but no apparent chromosomal disorder.

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