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Research paper

Familial aggregation and heritability of the melancholic and atypical subtypes of depression

Femke Lamers [a,1], Lihong Cui [a], Ian B. Hickie [b], Catherine Roca [a], Rodrigo Machado-Vieira [c], Carlos A. Zarate Jr.[c], Kathleen R. Merikangas [a,*]

[a] Genetic Epidemiology Research Branch, Intramural Research Program, National Institute of Mental Health, Bethesda, MD, USA
[b] Clinical Research Unit, Brain & Mind Research Institute, University of Sydney, Camperdown, NSW, Australia
[c] Experimental Therapeutics and Pathophysiology Research Branch, Intramural Research Program, National Institute of Mental Health, Bethesda, MD, USA

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ABSTRACT

Background: The heterogeneity of mood disorders has been a challenge to our understanding of their underlying biologic and genetic pathways. This report examines the specificity of the familial aggregation of atypical and melancholic subtypes of depression and their clinical correlates in a large community based family study of affective spectrum disorders.
Methods: The sample includes 457 probands and their directly interviewed adult first degree relatives from the National Institute of Mental Health (NIMH) Family Study of Affective Spectrum Disorder. Depression subtypes were based on best estimate diagnoses using information from semi-structured diagnostic interviews by experienced clinical interviews and multiple family history reports.
Results: Atypical depression in probands was significantly associated with the atypical subtype of depression in relatives (OR 1.75 [95%CI 1.02–3.02], p=0.04), independent of proband and relative comorbid disorders. Melancholic depression in probands was not associated with melancholic depression in relatives (OR 1.25 [95%CI 0.62–2.55], p=.53). The familial heritability of the atypical subtype was 0.46 (95% CI 0.21–0.71), whereas that of the melancholic subtype was 0.33 (95%CI 0.21–0.45). Melancholic depression was associated with greater severity in terms of treatment, global functioning, suicide attempts, comorbid disorders, and an earlier age at onset of depression.
Limitations: The subsample of interviewed relatives necessary to assess specific subtypes of depression reduced the power to detect the specificity of mood disorder subtypes.
Conclusion: The results indicate that the atypical subtype should be incorporated in future treatment, genetic and other etiologic studies of major depression. Findings further suggest that melancholic subtype may be an indicator of clinical severity of depression.

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1. Introduction

Although there has been substantial progress in our understanding of the biological processes and environmental exposures associated with mood disorders, application of newer technologies such as neuroimaging and molecular biology have not resulted in major breakthroughs. One of the major sources of the lack of progress is the well-established heterogeneity of major depression. In fact, this is the chief explanation cited for the lack of identification of genetic markers in the largest collaborative genetic study of major depression (Verbeek et al., 2012; Wray et al., 2012). Consequently, there has been substantial effort devoted to the identification of subtypes of depression based on symptoms, age of onset, comorbidity patterns, treatment response and biologic and environmental correlates (Baumeister and Parker, 2012). Aside from psychotic features, the subtypes that have persisted in the standardized diagnostic criteria are the atypical and melancholic subtypes (DSM-5).

Family and twin studies have been particularly informative in establishing the validity of depressive subtypes because of their underlying assumption regarding within family homogeneity (Sullivan et al., 2000). Previous family (Stewart et al., 1993) studies have provided support for the validity of the atypical subtype of major depression. Likewise, a large twin study of depressive subtypes yielded higher concordance rates for the atypical subtype in monozygotic (OR=5.4) than for dizygotic (OR=1.0) twins (Kendler et al., 1996). By contrast, previous family (Klein et al., 2002; Maier

* Correspondence to: 35 Convent Drive, MSC 3720 Bldg 35A, Room 2E410, Bethesda, MD 20892, USA.
E-mail address: Kathleen.merikangas@nih.gov (K.R. Merikangas).
[1] Currently address: Department of Psychiatry and EMGO Institute for Health and Care Research, VU University Medical Center/GGZ inGeest, Amsterdam, the Netherlands.

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et al., 1991) and twin studies (Kendler, 1997) have not found specificity of the melancholic depression, nor for the earlier construct of endogenous depression (Andreasen et al., 1986b; Leckman et al., 1984; Weissman et al., 1986; Zimmerman et al., 1986), with some exceptions (McGuffin et al., 1996). In fact, the increased rates of major depressive disorder in general in relatives of probands with melancholic compared to non-melancholic depression suggest that the melancholic subtype may be in indicator of greater severity of depression.

Aggregation of the findings across these studies is complicated by the application of a wide range of definitions including "endogenous" depression based on Research Diagnostic Criteria (RDC) (Spitzer et al., 1978), and varying definitions of the melancholic subtype based on the DSM-III criteria (American Psychiatric Association, 1980) and 'autonomous' depression (Nelson and Charney, 1980). Moreover, none of these studies have investigated simultaneously the familial specificity of atypical and melancholic depression.

The goals of this report are: 1) to evaluate the specificity of the familial aggregation and heritability of the atypical and melancholic subtypes of depression; and 2) to examine the clinical correlates of these two subtypes of depression in a large community-based family study of mood spectrum disorders.

2. Materials and methods

2.1. Sample

The sample for this study is derived from the National Institute of Mental Health (NIMH) Family Study of Affective Spectrum Disorders, a large community based controlled family study of probands with the full range of mood disorders. Probands (N=457) were recruited from a community screening of the greater Washington, D.C. metropolitan area, other local sources through the NIH Clinical Center general volunteer referral core, local health newsletters and announcements, or from screens or participants in the NIMH Mood and Anxiety Disorder Program to enrich the sample for mood disorders. The community sample, designed to be a non-clinical sample of persons with and without mental health disorders, was ascertained by mail contact through a marketing list of households within 50 miles of Washington, D.C. Inclusion criteria were the ability to speak English and availability and consent to contact at least two living first degree relatives. The study was approved by the Combined Neuroscience IRB at the National Institutes of Health (NIH). All participants provided written informed consent. More details of the family study methods are presented elsewhere (Merikangas et al., 2014).

After systematic enumeration of the full pedigree, all available adult and child relatives were contacted regarding study participation. Seventy-three percent of the probands had at least one first degree adult relative with a diagnostic interview (n relatives=559). Seventy-one percent of the first degree relatives who were alive and could be located were enrolled in the study; of these relatives, 73% were directly interviewed. Family history information was systematically collected from probands and interviewed relatives regarding a total of 1523 living and deceased adult first degree relatives, yielding a total of 2082 first degree relatives. Multiple family history reports were available for 36% of the relatives. Non-interviewed relatives were less likely to have lifetime psychiatric diagnoses and were slightly older than interviewed relatives.

For the familial aggregation analyses, only adult, interviewed first degree relatives were included (n=559) because of the decreased reliability of family history reporting of the specific criteria necessary to assess the subtypes of major depression. In the heritability analyses, probands and all interviewed relatives with data on melancholic or atypical depression were included (n=1208 and n=1350, respectively).

2.2. Procedures

2.2.1. Interview

Standard family study methodology was employed including direct interviews of probands and relatives by experienced clinicians, systematic enumeration of all relatives including children and blind assessment of relatives (Merikangas et al., 2014).

2.2.2. Diagnostic assessments

The NIMH Family Study Diagnostic Interview for Affective Spectrum Disorders was based on the adaptation of the diagnostic interview used in prior family studies of anxiety disorders and substance use disorders at the Yale University School of Medicine Genetic Epidemiology Research Unit (Merikangas et al., 1998a, 1998b). The diagnostic interview ascertains diagnostic criteria for current and lifetime DSM-IV-TR disorders, but does not adhere to strict diagnostic criteria for skip-outs based on frequency or duration at the probe level in order to capture subthreshold phenomenology across the key domains of psychopathology for multiple diagnostic systems (Angst et al., 1984, 2005). The interview included all symptoms for melancholic and atypical depression as listed in the DSM-IV. The NIMH Family Study Family History Interview was used to assess a family history of psychiatric disorders based on modifications of the family history interview from previous family study research (Merikangas et al., 1998a, 1998b). The interview was based on the core structure of the Family History-Research Diagnostic Criteria (FH-RDC) developed for the collaborative family study of affective disorders (Andreasen et al., 1986a). Best estimate diagnoses of major depressive episode (MDE) for this study were based on all available information by a team of experienced clinicians (psychologists and a psychiatrist) using a best estimate procedure (Leckman et al., 1982). The current analyses defined lifetime atypical and melancholic depression according to DSM-IV-TR criteria. Briefly major depression with atypical features is characterized by significant weight gain or increase in appetite and hypersomnia; and accompanied by a feeling of "leaden paralysis (i.e., heavy, leaden feelings in arms or legs)" and tendency towards interpersonal rejection sensitivity. However, most studies in the field focus on the physical symptoms that characterize the atypical subtypes. Major depression with melancholic features require: loss of pleasure in all, or almost all, activities; and lack of reactivity to usually pleasurable stimuli plus at least 3 of the following: distinct quality of mood that differs from that associated with loss or similar; depression regularly worse in the morning; early morning awakening; marked psychomotor retardation or agitation; weight loss; or excessive or inappropriate guilt.

Clinical correlates of depression that were collected in the diagnostic interview include: lifetime history of treatment for depression, suicide attempts (yes/no), age of onset of depression, comorbid disorders (mania/hypomania, alcohol and drug use disorders, anxiety disorders [panic disorder, generalized anxiety disorder (GAD), social phobia]) and lifetime Global Assessment of Functioning (GAF). Although mania/hypomania comorbid with an MDE are considered as bipolar disorder in the DSM-IV, in the current study we considered these two subgroups as separate entities based on our earlier work that demonstrated independence of their familial transmission (Merikangas et al., 2014).