REVIEW ARTICLE

The genetics of severe depression

Clio E. Franklin[1], Eric Achtyes[2], Murat Altinay[3], Kala Bailey[4], Mahendra T. Bhati[5], Brent R. Carr[6], Susan K. Conroy[7], Mustafa M. Husain[4], Khurshid A. Khurshid[8], Todd Lencz[9], William M. McDonald[10], Brian J. Mickey[11], James Murrough[12,13], Sean Nestor[14], Thomas Nickl-Jockschat[15,16,17], Sina Nikayin[18], Kevin Reeves[19], Irving M. Reti[1], Salih Selek[20], Gerard Sanacora[18], Nicholas T. Trapp[21], Biju Viswanath[22], Jesse H. Wright[23], Patrick Sullivan[24], Peter P. Zandi[1]✉ and James B. Potash[1]✉

Genome-wide association studies (GWASs) of major depressive disorder (MDD) have recently achieved extremely large sample sizes and yielded substantial numbers of genome-wide significant loci. Because of the approach to ascertainment and assessment in many of these studies, some of these loci appear to be associated with dysphoria rather than with MDD, potentially decreasing the clinical relevance of the findings. An alternative approach to MDD GWAS is to focus on the most severe forms of MDD, with the hope that this will enrich for loci of larger effect, rendering their identification plausible, and providing potentially more clinically actionable findings. Here we review the genetics of severe depression by using clinical markers of severity including: age of onset, recurrence, degree of impairment, and treatment with ECT. There is evidence for increased family-based and Single Nucleotide Polymorphism (SNP)-based estimates of heritability in recurrent and early-onset illness as well as severe functional impairment. GWAS have been performed looking at severe forms of MDD and a few genome-wide loci have been identified. Several whole exome sequencing studies have also been performed, identifying associated rare variants. Although these findings have not yet been rigorously replicated, the elevated heritability seen in severe MDD phenotypes suggests the value of pursuing additional genome-wide interrogation of samples from this population. The challenge now is generating a cohort of adequate size with consistent phenotyping that will allow for careful and robust classifications and distinctions to be made. We are currently pursuing such a strategy in our 50-site worldwide Gen-ECT-ics consortium.

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INTRODUCTION

Major depression is an etiologically multifactorial, genetically heterogeneous disorder that affects ~7% of the US population and causes significant morbidity [1]. For several severe psychiatric disorders, schizophrenia, bipolar I disorder, and autism, large genetic contributions, in the 60–90% range, have been demonstrated [2, 3]. By contrast, such investigation in major depressive disorder (MDD) has yielded estimates of heritability that are far lower, in the 30–40% range [3–5]. It was therefore predicted that, to detect robust signals in genome-wide association studies (GWAS) of MDD, sample sizes would need to be far larger [6]. Among the first MDD GWASs to report statistically significant results was a multi-cohort study that included 121,380 cases and identified 15 genome-wide significant loci [7]. A meta-analysis that included 135,458 cases implicated 44 independent and significant loci, with effect sizes that were quite small at 1.03 and 1.04 [8]. And Howard et al included a remarkably large sample of 660,937 cases in their meta-analysis of GWAS depression results, yielding 102 independent susceptibility variants [9].

A striking element of requiring these enormous sample sizes has been the logistical challenge of how to find depression cases in sufficient numbers. One answer has been to incorporate

[1]Department of Psychiatry and Behavioral Sciences, Johns Hopkins University School of Medicine, Baltimore, MD, USA. [2]Department of Psychiatry, Western Michigan University Homer Stryker M.D. School of Medicine, Kalamazoo, MI, USA. [3]Department of Psychiatry and Psychology, Cleveland Clinic, Cleveland, OH, USA. [4]Department of Psychiatry, University of Texas Southwestern Medical Center, Dallas, TX, USA. [5]Department of Psychiatry and Behavioral Sciences, Stanford University, Stanford, CA, USA. [6]Department of Psychiatry, University of Florida Health, Gainsville, FL, USA. [7]Department of Psychiatry, Indiana University School of Medicine, Indianapolis, IN, USA. [8]Department of Psychiatry, University of Massachusetts Memorial Health, Worchester, MA, USA. [9]Department of Psychiatry, Donald and Barbara Zucker School of Medicine at Hofstra/Northwell, Glen Oaks, NY, USA. [10]Department of Psychiatry and Behavioral Sciences, Emory University School of Medicine, Atlanta, GA, USA. [11]Department of Psychiatry, Huntsman Mental Health Institute, University of Utah Health School of Medicine, Salt Lake City, UT, USA. [12]Department of Psychiatry, Icahn School of Medicine at Mount Sinai, New York, NY, USA. [13]VISN 2 Mental Illness Research, Education, and Clinical Center (MIRECC), James J. Peters VA Medical Center, Bronx, NY, USA. [14]Department of Psychiatry, Temerty Faculty of Medicine, University of Toronto, Toronto, ON, Canada. [15]Department of Psychiatry and Psychotherapy, Otto-von-Guericke University, Magdeburg, Germany. [16]German Center for Mental Health (DZPG), partner site Halle-Jena-Magdeburg, Magdeburg, Germany. [17]Center for Intervention and Research on adaptive and maladaptive brain Circuits underlying mental health (C-I-R-C), Halle-Jena-Magdeburg, Magdeburg, Germany. [18]Department of Psychiatry, Yale University School of Medicine, New Haven, CT, USA. [19]Department of Psychiatry and Behavioral Health, Ohio State University College of Medicine, Columbus, OH, USA. [20]Faillace Department of Psychiatry and Behavioral Sciences, McGovern Medical School, University of Texas Health Care Center at Houston, Houston, TX, USA. [21]Department of Psychiatry, Carver College of Medicine, and Iowa Neuroscience Institute, University of Iowa, Iowa City, IA, USA. [22]Department of Psychiatry, National Institute of Mental Health and Neurosciences, Bangalore, India. [23]Department of Psychiatry and Behavioral Sciences, University of Louisville School of Medicine, Louisville, KY, USA. [24]Department of Psychiatry, University of North Carolina at Chapel Hill School of Medicine, Chapel Hill, NC, USA. ✉email: pzandi@jhu.edu; jpotash@jhmi.edu

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minimally phenotyped individuals found in existing datasets, such as those from 23andMe and the UK Biobank [7, 8]. While these provided ample power, they raise the question of what phenotype exactly is being studied. The positive predictive value of 1-item depression screens for MDD has been shown to be just 55.6%, while those for 2- and 3- item screens are no better [10]. Are the implicated variants truly increasing susceptibility for MDD or clinically relevant depression, or are they risk variants for a non-clinical dysphoria [11]?

One strategy to refocus the search for MDD risk variants on genetic factors with implications for clinical care, is to engage in a sample collection strategy that enriches for the most severe cases. Though the sample size will inevitably be smaller, the hope is that larger effect sizes might mean significant signals could still be detected. This focus on "genetics at the extreme" is analogous to efforts in the study of lung function and osteoarthritis where GWAS yielded 33 novel lung function loci and five novel genome-wide significant osteoarthritis (OA) loci, respectively [12, 13]. The strength of association was higher in four of eight signals that were at or near genome-wide significance in the most severe OA phenotype when compared to a broader phenotypic definition [12]. The Genetics of Electroconvulsive Therapy (Gen-ECT) Study, which involves investigators from the U.S., in collaboration with centers around the world as part of an international consortium--Gen-ECT-ic--formed to implement such a strategy [14]. The study's initial aim was to ascertain patients from ECT clinics, since typically only the most severely ill depressed patients receive this treatment. The inclusion criteria have recently evolved to include other options shown to be effective in the management of severe MDD: ketamine, esketamine and transcranial magnetic stimulation [15].

Clinically, severe depression is defined in the DSM-5-TR and ICD-11 based on characteristics of single episodes, in particular, number and intensity of symptoms, and degree of distress and impairment in functioning they cause [16, 17]. Both classification schemes further divide severe cases into those with or without psychotic features. Illness features are often captured, particularly in clinical trials, by rating scales, such as the Hamilton Depression Rating Scale, where a cutoff score of 23–25 can be used to delineate severe from moderate depression [18]. Some studies have pointed to features that distinguish severe episodes, including suicidal ideation, anhedonia, psychosis and melancholic symptoms [19–21]. Another way of conceptualizing severity focuses on the natural course of illness rather than individual episodes, with earlier age at onset (AAO) of illness, longer duration of episodes, more frequent recurrence, and worse functioning being defining features [22].

As no single factor defining severity in depression has emerged, there have been conflicting views about the best approach to characterizing it. Some have argued for focusing on the intensity, frequency, and/or persistence of symptoms because the functional impact depends on factors extrinsic to the disorder [23]. One study found that "although DSM has been criticized frequently for its definition of depression as a variable combination of nine specific symptoms," the core symptoms emerged as a single factor separate from other related variables, and this factor was associated with overall severity, as measured by several severity scales [24]. Other studies have found correlations across severity of episodes, course of illness features, and functional measures. For example, in a STAR-D study of 4041 people with MDD, earlier AAO was associated with substantial functional impairment and greater illness burden, including more lifetime episodes, more severe episodes, and more lifetime suicide attempts [22].

A concept related to severity is treatment-resistance, the persistence of an episode and/or a lifetime course in which repeated therapeutic interventions have failed to result in sustained remission [25, 26]. The field has yet to develop a consensus definition for treatment-resistant depression (TRD): in fact, TRD was defined differently in every study in this review [26]. This makes it harder to interpret findings across studies. It is also possibile these studies may be capturing patients who are not truly treatment resistant, but are perhaps non-adherent to medication, had an inadequate duration of trial(s), or were trialed on too few medications.

ECT often results in rapid improvements and generally yields high effect sizes in MDD. Patients receiving ECT for MDD often represent a combination of those whose episodes are most severe and impairing. This is reflected in several national treatment guidelines: the British National Institute for Health and Care Excellence (NICE) recommends the use of ECT in patients with "severe" depression in whom their MDD is life threatening, or has not responded adequately to prior attempts at treatment, and the US Food and Drug Administration (FDA) states ECT is indicated in those experiencing a "severe major depressive episode" who are "treatment-resistant or who require a rapid response due to the severity of their psychiatric or medical condition" [27, 28]. One study of 75,429 inpatient admissions for MDD showed that, compared to patients who did not receive ECT, those administered this treatment had higher depression severity, more social withdrawal, more functional impairment, more psychiatric hospitalizations, and more outpatient psychiatrist visits [29]. A study from Denmark of 92,895 patients with MDD found depression severity as determined by ICD-10 severity code was the strongest predictor of being treated with ECT [30]. Another report showed 2243 patients in ECT clinical trials had higher depression severity ratings, per Hamilton Depression Scale, than 3677 patients in pharmacotherapy trials [31]. However, there are several indications for the use of ECT that may not be markers of disease severity, namely when there are medical contraindications for typical antidepressants, and in MDD with catatonic features. We recognize that, though ECT is available to many patients, use of and access to ECT for depression is quite variable across the US and internationally.

We will next review the evidence from genetic epidemiology and from molecular genetics studies concerning whether more severe forms of depression display greater heritability than is detectable in broader samples, and whether they result from genetic variants of larger effect than has heretofore been detected in very large-scale studies of the broader phenotype.

METHODS

We searched PubMed and Scopus for articles relating to the genetics of depression published prior to November 2023. The search terms used were: "depression", "major depressive disorder", "genetic epidemiology", "genetics", "family study", "twin study", "adoption study", "GWAS", "whole genome", "whole exome", "genome-wide association study", "age of onset", "recurrence", "impairment", "treatment resistance" and "electroconvulsive therapy". The reference lists in applicable articles identified in the above search were used to identify additional relevant articles. The following inclusion criteria were applied: original research articles, published in a peer-reviewed journal, written in English, articles including analyses of depression severity subtypes or explicitly addressing a severe depression phenotype. For reasons stated elsewhere in this review, single gene studies were excluded. After the above literature review, we included 20 papers related to genetic epidemiology, 13 GWAS studies, four whole exome sequencing studies and one whole-genome sequencing study.

Given the breadth of different types of study methodologies that we have incorporated into this review and the relatively small number of each of these types of studies, we have pursued a narrative rather than systematic review. As more data accumulates, a future systematic review of the literature will be important.

Severe depression

Genetic epidemiology. When looking at genetic epidemiology studies of severe MDD, it is important to note that most were conducted from the 1970s to the early 2000s. There are fewer recent non-molecular genetic studies of MDD as the field has moved towards GWAS/whole exome studies. Many earlier studies have small sample sizes, limiting their power to detect an association using severity markers. Some note trends that did not reach statistical significance and this may explain some variability in the findings of early studies [32, 33].

The majority of family studies have shown stronger familiality of MDD when the proband has features indicative of a severe form of illness [34–41]. The age cut-off used to define "early age at onset (AAO)" has ranged from <20 to up to 51 years of age [38, 40, 42]. In a family study of 133 probands with MDD, 1518 of their first-degree relatives and 82 controls, Weissman et al. found the risk of MDD was 24.2% in first-degree relatives of probands with an AAO of <20 years, versus only 7.6% in relatives of probands age 40 or older [38]. Conversely, in a study looking at 545 individuals from 65 multigenerational families, Guffanti et al found no significant difference in MDD heritability when comparing AAO < 25 years of age vs >25 [43]. In a study of 75 probands requiring hospitalization for unipolar depression and 763 of their first-degree relatives, Bland et al. found first-degree relatives of probands with >1 episode of depression or an AAO of <51.2 years, the mean AAO in their study population, had a significantly higher likelihood of developing depression, with relative risks of 2.27 and 2.04, respectively [42]. A further study by Weissman et al. distinguished between mild and severe MDD using the criterion of hospitalization for ≥5 days for a depressive episode. They found higher familial rates of depression in both severe and mild MDD, though this definition of severity did *not* yield a significant difference in rates among first-degree relatives between the two groups [35, 44].

Twin studies have also demonstrated increased recurrence risk of MDD in co-twins of probands with severe features of depression, suggesting higher heritability. In a study of male twins, Lyons et al found early-onset MDD, defined as <30 years of age, had a heritability of 0.47. This was far higher than heritability of late-onset MDD, found to be just 0.10 [45]. Conversely, in a study of 646 female twins with a lifetime diagnosis of MDD and their co-twins, Kendler et al. found no significant difference in heritability with AAO [32]. They noted their study sample had few people >40 years of age, restricting their power to detect an association. In subsequent larger studies, looking at both male and female twins, Kendler et al. found earlier AAO of MDD in probands *did* result in an increased risk of MDD in co-twins [46, 47]. When looking at the number of lifetime episodes of depression, studies have found risk of MDD in co-twins increased with number of episodes of depression in probands [47, 48]. The definition of "multiple" episodes has not been consistent across studies. Kendler et al. separated their patient sample into groups based on number of episodes of depression from 1 to >13 and found familial risk was highest in co-twins of probands reporting 7–9 lifetime episodes of depression [48].

Several twin studies have also examined the impact of impairment on heritability. Kendler et al. found a higher degree of impairment (rated as none, moderate and severe) in the proband's worst episode significantly predicted risk of MDD in a co-twin. In this study, severe impairment was defined as "marked impairment in main life task so that respondent was almost nonfunctional" [48]. These results were consistent with those of an earlier twin study by Kendler et al, which found incapacitation predicted a 33% increase in depression risk in co-twins [32]. Another Kendler et al. study used a twin and full/half-sibling design to look at 1,718,863 Swedish twin/sibling pairs. They found increased clinical severity, defined by referral to psychiatric care, receipt of antidepressants or provision of early retirement in response to psychosocial dysfunction, significantly affected risk of MDD in relatives. This report, the only genetic epidemiology study examining the impact of proband treatment with ECT on heritability, found such treatment did not significantly affect relative MDD risk [49].

There are a few studies looking at the impact of MDD with psychotic symptoms vs. without, and results are mixed. A twin study by Torgersen, of 151 index twins and their co-twins, found a higher frequency of MDD in monozygotic co-twins of index twins with psychotic symptoms (40%) compared to in those without (25%), though the subgroups were too small to test for statistical significance [33]. An adoption study by von Knorring et al looking at adoptive and biologic parents of 115 adoptees with a history of affective disorder and 115 controls found no significant difference in heritability between the two MDD subtypes [50]. Using a novel method, Kendler et al calculated family genetic risk scores (FGRS), based on MDD risk in 1st–5th degree relatives, in a Swedish national database of 4,129,002 individuals. MDD both with psychotic features and without were associated with a similar mean MDD FGRS, but MDD with psychotic features was associated with higher schizophrenia and bipolar disorder scores [51].

In conclusion, family and twin studies have shown these markers of MDD severity do indicate increased heritability, with AAO being the most extensively studied. A summary of key results related to this and other clinical markers of severity is provided in Table 1. Next, we will discuss studies in which investigators have tried to determine whether specific genes or genetic profiles correlate with these markers of severity.

Molecular studies. Many early molecular studies of depression, performed in the 1970s and 80s, focused on single markers or single genes, chosen because of the availability of markers, or because particular genes had a plausible biological relationship to MDD. These studies yielded no robust results, likely because they were underpowered to detect small effects, and were limited by our meager understanding of the myriad contributing factors to MDD etiology [52]. Focus shifted in the 1990s and early 2000s to a genome-wide approach, free of prior biological hypotheses, using the family-based linkage method to detect chromosomal regions harboring MDD risk loci. Studies such as the Genetics of Recurrent, Early-Onset Depression (GenRED) project focused on the phenotypic features that the genetic epidemiology studies referred to above, suggesting these should yield the most highly heritable forms of illness and thus the greatest power to detect genetic loci [53]. However, these studies failed to yield robust and replicable findings, likely again because of insufficient power to detect small effects, along with heterogeneity both within and across families [54]. The focus shifted to GWAS studies in the late 2000s because of their greater power to detect common loci of small effect and improvements in the technology and cost of this platform [55].

Genome-wide association studies. As discussed, the heritability of MDD has been found to be 30–40% and, as a result, sample sizes in the vicinity of 100,000 cases or more have been required to identify genome-wide significant loci [4, 6]. To obtain such large sample sizes, studies have relied on pre-existing datasets, which often do not provide a robust evaluation of past psychiatric history, and rely on individual self-reporting [7, 9, 56]. In this section we will first review how GWAS have been used to examine the SNP-based heritability of aspects of MDD severity. Then we will examine efforts to use the more severe forms of MDD to search genome-wide for specific risk loci.

Several studies have been conducted using large-scale datasets for which phenotypic information relies on self-report. These have the advantage of the power of the sizable UK biobank and 23andMe databases, though their phenotypic methods are less robust than those employing direct assessment or hospital records. Some have looked at the impact of severity-related features of MDD on estimates of SNP-heritability. Harder et al.

Table 1. Family and twin studies of clinical severity features in MDD.

MDD severity features	Genetic epidemiology
Earlier AAO	• MDD risk higher in first-degree relatives of probands with AAO of <20 years than when proband age ≥40 [38]** • First-degree relatives of probands with AAO < 51 years had higher RR when compared to those age >51 [42]* • AAO < 30 years had higher heritability than AAO > 30 [45]* • Every 10-year increase in AAO of co-twin resulted in decline in HR for MDD in index twin [46]* • Every 10-year increase in AAO in index twin resulted in reduction in HR for MDD in the co-twin [47]** • 1-year decrease in age at diagnosis of proband significantly increased MDD in twins and siblings [49]** • First age of registration for MDD age <25 associated with higher MDD FGRS [51]** • No significant difference [32, 43]
Recurrence	• First-degree relatives of probands with >1 episode of depression had higher RR compared to relatives of those with single episode [42]** • More episodes in index twin resulted in increase in HR for MDD in the co-twin [47]* • MDD risk highest in co-twins of index twins with 7–9 episodes of MDD [48]** • MDD recurrence significantly associated with increased MDD risk in twins and full-siblings. In monozygotic twins risk highest with ≥5 episodes [49]** • Increasing number of episodes associated with higher MDD FGRS [51]**
Hospitalization	• Index monozygotic twin requiring hospitalization significantly associated with increased MDD risk in co-twin; association not significant in full-siblings [49]** • No significant difference [35, 44]
Impaired functioning	• Increased degree of impairment in proband's worst episode significantly increased risk of MDD in co-twin [48]* • Incapacitation in index twin predicted increase in depression risk in co-twins compared to no or mild impairment [32] **
Treatment resistance	• No data
Treatment with ECT	• Proband having received ECT not significantly associated with increased MDD risk in twins and full/half-siblings [49]
Psychosis	• Higher frequency of MDD in monozygotic co-twins of index twins with psychotic symptoms vs those without (no *p*-value) [33] • No difference in MDD FGRS. MDD with psychotic features associated with higher schizophrenia and bipolar disorder FGRS [51]** • No significant difference [50]

AAO age at onset, *RR* relative risk, *HR* hazard ratio, *FGRS* family genetic risk score, *ECT* electroconvulsive therapy, *MDD* major depressive disorder.
*$p = <0.05$, **$p = <0.005$.

studied 94,154 individuals who met broad criteria for MDD in the UK Biobank database to assess the impact of AAO of MDD on SNP-heritability with AAO being defined by individual self-report of age of diagnosis or symptom onset. They found overall SNP-heritability in broad MDD was relatively low at ~6% and there was a sharp decrease in MDD polygenic risk score (PRS) in those with symptom onset after the age of ~32. Conversely, with each standard deviation increase in MDD PRS, the average age of symptom onset decreased by ~6 months. As the PRS indicates strength of genetic effect, this is consistent with a higher level of heritability for earlier onset illness [57].

Nguyen et al. also used the UK Biobank database to examine the heritability of MDD phenotypes. In this study, the vast majority of MDD diagnoses were based on self-report or questionnaires with only 2.7% of individuals in the 459,590 person sample having ICD-coded MDD based on hospital records. When looking at phenotypic markers of MDD severity, early-onset MDD (defined as ≤30 years of age) had a SNP-heritability of 13%, as compared to 4.3% for the late-onset subtype. They also found higher SNP-heritability in individuals with recurrent vs. single-episode MDD: 10.7% compared to 8.2%, respectively. Finally, SNP-heritability increased with the degree of impairment (defined as "impact of MDD on normal roles") in a dose-dependent manner, with mild impairment at 6%, moderate at 9.1% and severe at 11.3% [58].

Hyde et al. used the 23andMe database to analyze the effect of age of self-reported MDD diagnosis in 94,891 individuals. They found earlier AAO of MDD was significantly associated with increased genetic risk score [7]. Mitchell et al. combined an Australian sample with the 23andMe sample and reported on a number of MDD subtype analyses, including finding MDD-PRS increased with number of reported episodes. They also observed that those with earlier AAO of MDD had higher PRS for schizophrenia, attention deficit hyperactivity disorder, and Townsend Deprivation Index, the latter suggesting a role for gene-environment interaction [59]. Als et al. performed a meta-analysis of six datasets, including the UK Biobank and 23andMe, comprising >1.3 million individuals, 371,184 with a depression diagnosis. They found a higher depression PRS predicted a significantly greater risk for recurrent depression as compared to having only a single episode [60].

These findings from very large-scale datasets support increased MDD heritability in individuals with earlier AAO and in those with recurrent episodes. Another study used a narrower phenotype to ask similar questions, and provided comparable evidence for the increased heritability of recurrent MDD. Musliner et al. analyzed the iPSYCH2012 sample comprising 16,180 individuals in Denmark, including MDD cases ascertained from a hospital-based setting, indicating a more severe MDD sample. They observed that those with a higher MDD PRS were at increased risk of developing recurrent MDD (adjusted hazard ratio per 1-SD increase, 1.07) [61].

Of note, one large-scale analysis, from the China, Oxford and Virginia Commonwealth University Experimental Research on Genetic Epidemiology (CONVERGE) study, a case-control sample of Chinese women with recurrent MDD, did not detect increased heritability for the early onset form of the illness. When the investigators divided their sample into those with AAO < 34 years (2767 cases) and those with AAO ≥ 34 years (2578 cases), they observed SNP-based heritability of MDD estimated at 19% for the former and 22% for the latter [62].

Table 2 summarizes the SNP-heritability and PRS results associated with MDD severity features. We now shift to the question of what loci have been identified in association with severe MDD. These results, including common SNPs and rare variants, are summarized in Table 3, which, for ease of interpretation, are presented in the form of the genes they implicate.

Table 2. Aggregate SNP-based genetic risk associated with MDD severity features.

MDD severity features	Study population	SNP-heritability	PRS or GRS
Earlier AAO	94,154 individuals diagnosed by self-report [57]		AAO decreased by ~6 months with each SD increase in MDD PRS†
	459,590 individuals, 87% diagnosed with self-report or questionnaire [58]	AAO ≤ 30 years old 13%, vs. 4% if ≥44 years old***	
	94,891 individuals diagnosed by self-report [7]		Earlier AAO associated with higher genetic risk score**
	5345 women recruited from Chinese psychiatric centers [62]	AAO < 34 years old 19% vs. ≥34 years old 22% (not statistically significant)	
Recurrence	459,590 individuals, 87% diagnosed with self-report or questionnaire [58]	11% in recurrent MDD vs 8% with single episode‡	
	Metanalysis of >1.3 million individuals, 371,184 with MDD [60]		Higher MDD PRS predicted significantly greater risk for recurrent MDD vs. a single episode**
	5278 individuals with recurrent MDD under community or hospital based psychiatric care [64]	20–29% of the variance in MDD risk explained by common SNPs in individuals with recurrent MDD***	
	16,180 individuals with a single MDD episode seen in both inpatient and outpatient psychiatric hospital settings [61]		Higher PRS-MDD significantly increased hazard of recurrence*
Hospitalization	No data		
Impaired functioning	459,590 individuals, 87% diagnosed with self-report or questionnaire [58]	Mild impairment 6%, moderate 9%, severe 11% (severe/moderate CI do not overlap with mild)	
Treatment resistance	2146 TRD and 14,097 non-TRD cases, along with 130,252 controls [80]	TRD 25% vs. non-TRD 19% (not statistically significant)	
Treatment with ECT	1796 individuals receiving ECT for MDD and 4035 controls [81]	SNP-based heritability 29–34%	Those treated with ECT had higher GRS for MDD*, bipolar disorder** and schizophrenia*

AAO age at onset, *PRS* polygenic risk score, *GRS* genetic risk score, *ECT* electroconvulsive therapy, *MDD* major depressive disorder, *SNP* single nucleotide polymorphism, *SD* standard deviation.
*$p = <0.05$; **$p = <5e^{-4}$; ***$p = <5e^{-10}$; †statistical significance not determined; ‡non-overlapping confidence intervals (CI).

Table 3. Common and rare loci associated with MDD severity subtypes.

MDD severity features	Genes implicated by GWAS loci	Genes with implicated rare variants
Earlier AAO	*NEGR1*‡, *AC012593.1*†, *CADM2:CADM2-AS2*‡, *ZNF184*†, *GABBR1*†, *MPP6*†, *BNC2*†, *CTBP2*†, *OLFM4*†, *PSMA3P*†, *U95743.1*†, *IL12RB1*†, *CDH4*‡ [58]	*CCL14***, *FYB***, *GPRASP1**, *CTNND2** [73]
Recurrence	*SIRT1*‡, *LHPP*‡ [65] *NBAS*†, *CACNB4**, *ERBB4**, *CTC-340A15.2*†, *GABBR1*‡, *AP001482.1*†, *AC007796.1*† [58]	
Hospitalization	No data	
Impaired functioning	*NEGR1*†,*CTC-340A15.2*†, *ZNF184*†, *RPSAP2*†, *OLFM4*‡ [58]	*BHLHE22** [77]
Treatment resistance	*ENSG00000226113** [86], *FTO*‡, *MCHR1*† [79]	*ZNF248****, *PRKRA****, *PYHIN1****, *SLC7A8****, *STK19**** [75]
Treatment with ECT	*HLA-B*† [81]	

AAO age at onset, *ECT* electroconvulsive therapy, *MDD* major depressive disorder, *GWAS* genome-wide association study.
*$p = <0.05$; **$p = <0.005$; ***$p = <5e^{-5}$; †$p = <5e^{-8}$; ‡$p = <5e^{-10}$.

The first GWAS to focus on a severe depression phenotype was conducted by Shi et al. using the GenRED sample, which included 1020 cases with recurrent (≥2 episodes), early-onset MDD (onset before age 31) and 1636 controls. This sample, that was in retrospect quite small by GWAS standards, found no genome-wide significant evidence for association. The strongest signal was observed on chromosome 18q22.1 (rs17077540, $p = 1.83 \times 10^{-7}$) within an mRNA detected in human brain tissue (BC053410) and approximately 75 kb upstream of *DSEL*, which is involved in tumor rejection and D-glucuronic acid metabolism [63].

In 2015, the CONVERGE study first published on its sample of Chinese women with the aim of identifying genetic risk factors for recurrent MDD [64–66]. This sample included ~5300 cases, in which "recurrent" meant ≥2 lifetime episode of MDD as defined by DSM-IV criteria, and a similar number of controls [65]. GWAS was performed using low pass sequencing, and common SNPs were found to

explain 20–29% of the variance in risk in this cohort [64]. Two loci were associated with an MDD phenotype at a genome-wide level of significance, one on chromosome 10 near *SIRT1*, thought to be involved in the regulation of aging and chronic inflammation, and another in an intron of *LHPP*, associated with regulating stress-related depression in mouse models [65, 67, 68]. Interestingly, when further selecting for increased MDD severity by excluding individuals who did not meet the DSM-IV criteria for melancholic depression, CONVERGE found increased significance for the association near *SIRT1*, consistent with the hypothesis that a more severe MDD phenotype can yield larger effect sizes for risk variants in GWAS investigations [65].

Nguyen et al. used their UK Biobank sample to define 16 depression subtypes and to perform subtype-specific GWAS with them. The subtypes included early-onset, recurrence, and severe impairment. For the latter subtype, they identified five genome-wide significant loci, though all had previously been reported in large-scale broad phenotype analyses of MDD. With regard to recurrence, they identified seven genome-wide significant SNPs, including one in *ERBB4* that had not stood out in prior studies of broad MDD, and was not nominally significant in their analyses of single episode MDD. However, this result, at $p = 2.87 \times 10^{-8}$, did not hold up to Bonferroni correction for testing 16 phenotypes ($p < 3.12 \times 10^{-9}$). Several prior studies have implicated *ERBB4* in MDD pathophysiology [69, 70]. With regard to early-onset, they observed 13 genome-wide significant SNPs, including two that had not previously been seen in analyses of the broad phenotype, were not nominally significant in the late-onset group, *and* surpassed the Bonferroni-corrected significance level. One of these was in *CAMD2*, which has been examined more extensively for its relationship in the UK Biobank dataset to psycho-behavioral traits, and was found to correlate with "nervous feelings" at the significance level of 2.6×10^{-22} [71]. The other implicated early-onset SNP in this category was in *IL12RB1*, which encodes a subunit of the receptor for IL-12, a cytokine shown to be neuroprotective in mouse models [58, 72].

Whole exome sequencing studies. While GWAS interrogates common loci of small effect, exome-wide sequencing studies are aimed at detecting rare variants conferring larger effects on risk of illness. Only a few studies to date have been reported on severe MDD. Kang et al. performed an exome-wide analysis on 1000 Korean individuals to identify rare genetic markers associated with earlier AAO MDD, where AAO was based on patient self-report. They found four variants in *CCL14*, *FYB*, *GPRASP1*, and *CTNND2* associated with earlier AAO of depression [73]. Both *CCL14* and *FYB* are involved in inflammatory pathways potentially related to depressive disorders [73]. *CTNND2* is involved in neural maintenance and plasticity, and the gene encoding it was associated with MDD in a separate GWAS [74]. No individual variant was associated with recurrent depression or depression with psychotic features [73]. Shah et al. performed an exome-wide analysis on 149 TRD cases, 24 of whom had been referred for ECT, along with 1976 controls. They used three different data sources where TRD was variably defined as: failing to respond to >2 antidepressants, referral to ECT, and non-response to ≥3 consecutive treatments with good adherence reported. The length of each medication trial was not specified. Several variants reached exome-wide significance, including two in genes coding for immune response proteins (*PHYIN1* and *PRKRA*) and one in a gene regulating synaptic clustering of GABA and glutamate receptors (*ZDHHC3*) [75]. GABA receptors were also found to be associated with TRD in an exome-wide analysis done by McClain et al. TRD was defined as non-response to three maximum dose medications for ≥6 weeks each. They found enrichment of damaging alleles in the GABA receptor activation pathway in a cohort of 124 individuals with TRD [76].

Whole-genome sequencing studies. Exome-wide studies rely on the sequencing of rare variants in the part of the genome where variation is most likely to be consequential—the coding regions, which are the exons. Whole genome sequencing is predicated on the hypothesis that non-coding regions can influence disease risk through their regulatory effects on gene expression. Only one whole-genome study to date has reported on patients with severe MDD. Hupalo et al. performed a whole-genome study of male-male Veteran twins. In this study, severe depression was defined as an "interference with occupational or social functioning". There were 47 severely depressed individuals, an exceedingly small number by contemporary standards, who were compared to 1007 non-severely depressed. Though it belies the special value of the whole genome approach, to increase power the investigators focused their analyses on the exomic variants, and found one rare coding variant, in *BHLHE22*, significantly associated with severe depression when compared to non-severely depressed individuals (OR 8.45) [77]. BHLHE22 drives a neocortical developmental process and was also implicated in a small family study of early-onset MDD [77, 78].

Treatment-resistant depression and ECT treatment

As discussed, the population of patients receiving ECT generally have a severe MDD profile and will often have not responded adequately to several antidepressant trials. Thus, TRD status and having had ECT can be utilized as approximations of severity in MDD. This is supported by a GWAS done by Kang et al., who used ECT as a proxy for TRD. To validate ECT as a TRD subset, they extracted data from the EHRs of two study sites and found TRD rates, defined as receiving at least two antidepressants, of 92% and 72% [79]. We referred earlier to one twin study reporting that MDD proband treatment with ECT did not significantly affect relative MDD risk [49]. We identified one study that looked at estimated SNP-based heritability in TRD vs. non-TRD MDD. There are, to date, three other GWAS studies in this arena, and one exome-wide study.

Fabbri et al. examined SNP-based heritability of TRD and non-TRD MDD cases in the UK Biobank. TRD was defined as ≥2 switches of antidepressant, with each drug being trialed for ≥6 consecutive weeks and the time interval between the two drug prescriptions <12 weeks. They included 2146 TRD and 14,097 non-TRD cases in their analyses, and noted those with TRD had a greater rate of certain features and comorbidities than those with non-TRD, e.g., anxiety disorders, anxiety with their depression, eating disorders, and self-harm/suicidal behaviors. TRD was found to have an estimated SNP-based heritability greater than that of non-TRD (0.25 vs. 0.19), suggestive of a stronger genetic basis for illness in the TRD group, though the difference was not statistically significant [80].

When studying 1796 individuals receiving ECT for MDD and 4035 controls, Clements et al. found SNP-based heritability to be 29–34% in patients receiving ECT, far higher than the 6–9% seen in studies looking at those with less severe forms of depression [8, 57, 58, 81]. This supports the idea that large-scale studies based on self-report and/or electronic medical record coding result in findings of lower SNP-based heritability than those selecting for more rigorously defined severity. They also found individuals receiving ECT for MDD had a higher genetic risk score for MDD, but also higher PRS for other major mental illnesses, including bipolar disorder and schizophrenia, when compared to individuals with mild-moderate depression [81]. Previous studies have similarly found that earlier age of self-reported onset MDD, as well as recurrent MDD, showed higher genetic correlation with schizophrenia, anorexia nervosa and bipolar disorder [58, 61, 82].

As mentioned, using ECT as a proxy for TRD, Kang et al studied 185,409 individuals with a diagnostic code of MDD or depressive disorder, 467 of whom had received ECT, to establish predicted probabilities of receiving ECT using machine learning. They then

used this model to generate two quantitative TRD phenotypes, applying this to 154,433 individuals across four biobanks. They identified two novel loci associated with TRD. One was located in the intronic region of *FTO* on chromosome 16, associated with the pathogenesis of obesity and some forms of cancer [83]. The other, *MCHR1*, was located on an intergenic region on chromosome 22. In addition to being associated with feeding behavior, it has been linked with bipolar disorder [84, 85]. They found significant genetic overlap with smoking and alcohol traits, attention deficit hyperactivity disorder, cognition, and body mass index [79].

Two other GWAS have found genome-wide significant loci in association with TRD and ECT treatment. Li et al. performed a GWAS on >50,000 individuals in the 23andMe database who self-reported treatment resistance to different antidepressant classes. TRD was defined as failing ≥2 antidepressants taken for ≥5–6 weeks. In a meta-analysis of their TRD phenotype, the investigators found evidence for a genome-wide significant SNP on chromosome 10p11.1 that spans multiple genes and harbors expression quantitative trait locus variants [86]. Clements et al., in their study mentioned above of patients receiving ECT for MDD, found one robust genome-wide significant locus in their GWAS. It was located in an intron of *HLA-B* in the major histocompatibility locus on chromosome 6. They noted that region contains the greatest number of GWAS associations in the genome, and has been previously associated with multiple psychiatric disorders, including MDD, schizophrenia, and PTSD [81].

Using the phenotype of TRD, Fabbri et al. performed an exome-wide analysis on 1209 individuals with a diagnosis of MDD based on DSM-IV-TR criteria. TRD was defined as no response to ≥2 antidepressants, each taken for >4 weeks, dosed at the minimum therapeutic dose or higher. They found no overall difference in the distribution of functional and deleterious variants between individuals with TRD and treatment responders. They then constructed a pathway-based polygenic predictor of TRD which did show significant prediction of this phenotype. The pathways associated with TRD included those involved in neurodegeneration, modulating cell survival and proliferation and immune response [87].

DISCUSSION

Family and twin studies have shown increased heritability of aspects of a more severe MDD phenotype, in particular recurrence and early AAO. GWAS have similarly found increased SNP-heritability for these two phenotypic features, as compared to that seen for broad MDD. Several GWAS have focused on samples ascertained based on these features, with the CONVERGE consortium focusing on recurrent cases and the GenRED dataset consisting of cases with both recurrence and early AAO. Most GWAS results pertaining to severe MDD, however, have come from secondary analyses of much larger MDD samples, mostly using self-report, though some have used hospital records. Cai et al. have shown that minimal phenotyping approaches typical of very large sample collections often identify loci that are not specific to MDD [88].

Some genome-wide significant results have been generated by studies of the severe MDD phenotype, though none have yet been robustly replicated. These include the CONVERGE results for variants in *SIRT1* and *LHPP*. They also include loci identified in UK Biobank analyses, including those in *ERBB4*, *CAMD2*, and *IL12RB1*. One approach to making sense of the large number of loci that emerge from GWAS analyses is to determine whether they coalesce into a pathway that is associated with the phenotype. This approach has implications for potential new target development by investigators aiming to develop novel treatments. The CONVERGE investigators asked this question with regard to their recurrent MDD sample and found evidence implicating the GO:0017144 drug metabolism pathway [66]. Notably, genes in the GO:0017144 pathway metabolize several common antidepressants (*CYP2C19*) and play a role in protecting against apoptosis, neurodegeneration and oxidative stress (*CBR1*) [66, 89–91].

Samples undergoing ECT treatment generally consist of cases of TRD who also have a more severe form of MDD. Clements et al. showed higher SNP-heritability in their ECT sample than in broad MDD, along with higher MDD PRS and also higher PRS for the arguably more severe disorders of BP and schizophrenia. They also implicated one genome-wide significant locus, in *HLA-B* in the major histocompatibility locus. A GWAS of TRD found evidence for a genome-wide significant SNP on chromosome 10p11.1 that spans multiple genes [81].

There are a number of important caveats to the strategy of studying ECT and TRD cases as a means of focusing on the genetics of severe MDD, and to focusing on severe MDD at all. First, there are several indications for the use of ECT that may not be markers of disease severity, namely when there are medical contraindications for typical antidepressants, and in MDD with catatonic features. Second, we recognize that, though ECT is available to many patients, the use of and access to ECT for depression is quite variable across the US and internationally. Third, it is possible that dysphoria and severe MDD are simply alternative manifestations of an overlapping genetic architecture, with a study by Jermy et al finding no significant differences in genetic correlations between Psychiatric Genomics Consortium-defined depression, 23andMe self-reported depression and broad depression when enriched for varying components of the MDD phenotype [92]. Fourth, obtaining high SNP heritabilities and PRS prediction R^2s are not the only or sufficient evidence that we have found phenotypes enriched for genetics of MDD rather than, for example general dysphoria. While validation of genetic results through the use of biomarkers would add to the evidence base, we are limited by the absence of definitive biomarkers specific to MDD. Fifth, it is also possible that, by studying only those individuals with severe MDD phenotypes we will capture genetic markers that specifically lead to these measures of severity, indexing different aspects of MDD pathology that may not be equivalent to each other. There are not studies directly comparing all the clinical markers of severity examined in this review, so we do not know which may be most powerful in identifying factors significantly influencing heritability of illness. Nevertheless, determining specific genetic markers for aspects of disease severity will still provide clinically useful information given the impact severity has on function and quality of life. These concerns will be further investigated in the future by the GenECT Study (see below) where results will be brought together with other more broadly phenotyped samples from around the world effectively creating a control set of less severe phenotypes. Sixth, a related consideration is that genetic markers for treatment resistance and those for MDD severity could be distinct from each other rather being on the same continuum.

The results to date implicating particular loci in association with the severe MDD phenotype remain to be replicated and validated. However, the elevated heritability and especially SNP-heritability seen in work on severe MDD suggest the value of pursuing additional genome-wide interrogation of samples from this population. The challenge now is generating a cohort of adequate size with consistent phenotyping to confidently establish the clinical severity of the sample. We are currently pursuing such a strategy with the GenECT Study, involving over 20 centers across the U.S. in collaboration with a consortium of close to 30 centers around the world [14, 93].

The GenECT Study, an initiative of the Psychiatric Genomics Consortium, aims to ascertain and assess 25,000 patients with severe MDD appropriate for ECT and related interventions. These patients will come from ECT centers globally, with data collection protocols harmonized across sites to obtain consistent

phenotypes on the different aspects of clinical severity and treatment-resistance that are common indications for ECT [94]. This should allow for large-scale GWAS of severe MDD generally, as well as careful delineation of the most heritable facets of the severity subtype. Our hope is to identify genetic factors of high clinical relevance in MDD.

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AUTHOR CONTRIBUTIONS

CEF and JBP drafted the manuscript. CEF drafted the tables. PPZ conceptualized the project and was lead editor. EA, MA, KB, MTB, BRC, SKC, MMH, KAK, TL, WMM, BJM, JM, SN, TN, SN, KR, IMR, SS, GS, NTT, BV, JHW and PS contributed further to the tables and manuscript and approved the final version.

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COMPETING INTERESTS

PFS is a consultant and shareholder for Neumora Therapeutics. In the past 2 years GS has served as consultant to Abbvie, Ancora/Embark, Aptinyx, Atai, Axsome Therapeutics, Biogen, Biohaven Pharmaceuticals, Boehringer Ingelheim International GmbH, Bristol-Myers Squibb, Clexio, Cowen, Denovo Biopharma, Daiichi Sankyo, ECR1, EMA Wellness, Freedom Biosciences, Gilgamesh, Intra-Cellular Therapies,

Janssen, KOA Health, Levo therapeutics, Lundbeck, Merck, MiCure, Navitor Pharmaceuticals, Neurocrine, Novartis, Noven Pharmaceuticals, Perception Neuroscience, Praxis Therapeutics, Relmada Therapeutics, Sage Pharmaceuticals, Seelos Pharmaceuticals, Taisho Pharmaceuticals, Usona Insititute, Valeant, Vistagen Therapeutics, and XW Labs; and received research contracts from Johnson & Johnson/Janssen, Merck, and the Usona Institute over the past 36 months. Dr. Sanacora holds equity in Biohaven Pharmaceuticals, Freedom Biosciences, Gilead Relmada, and Tetricus and is a co-inventor on a US patent (#8,778,979) held by Yale University and a co-inventor on US Provisional Patent Application No. 047162-7177P1 (00754) filed on August 20, 2018, by Yale University Office of Cooperative Research. Yale University has a financial relationship with Janssen Pharmaceuticals and may receive financial benefits from this relationship. Dr. Sanacora does not receive any direct payments through this relationship and the University has put multiple measures in place to mitigate this institutional conflict of interest. Questions about the details of these measures should be directed to Yale University's Conflict of Interest office. All other authors have no conflicting interests to declare.

ADDITIONAL INFORMATION

Correspondence and requests for materials should be addressed to Peter P. Zandi or James B. Potash.