International Consortium on the Genetics of Electroconvulsive Therapy and Severe Depressive Disorders (Gen-ECT-ic)

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Abstract

Recent genome-wide association studies have demonstrated that the genetic burden associated with depression correlates with depression severity. Therefore, conducting genetic studies of patients at the most severe end of the depressive disorder spectrum, those with treatment-resistant depression and who are prescribed electroconvulsive therapy (ECT), could lead to a better understanding of the genetic underpinnings of depression. Despite ECT being one of the most effective forms of treatment for severe depressive disorders, it is usually placed at the end of treatment algorithms of current guidelines. This is perhaps because ECT has controlled risk and logistical demands including use of general anaesthesia and muscle relaxants and side-effects such as short-term memory impairment. Better understanding of the genetics and biology of ECT response and of cognitive side-effects could lead to more personalized treatment decisions. To enhance the understanding of the genomics of severe depression and ECT response, researchers and ECT providers from around the world and from various depression or ECT networks, but not limited to, such as the Psychiatric Genomics Consortium, the Clinical Alli-ance and Research in ECT, and the National Network of Depression Centers have formed the Genetics of ECT International Consortium (Gen-ECT-ic). Gen-ECT-ic will organize the largest clinical and genetic collection to date to study the genomics of severe depressive disorders and response to ECT, aiming for 30,000 patients worldwide using a GWAS approach. At this stage it will be the largest genomic study on treatment response in depression. Retrospective data abstraction and prospective data collection will be facilitated by a uniform data collection approach that is flexible and will incorporate data from many clinical practices. Gen-ECT-ic invites all ECT providers and researchers to join its efforts.

Keywords Electroconvulsive therapy · GWAS · ECT · Severe depression · Major depressive disorder · Bipolar disorder · Genomic · Cognition

Background

Major Depressive Disorder (MDD) is now recognized by the World Health Organisation (WHO) as the single leading cause of disability worldwide. It is a serious and common mood disorder with an estimated international prevalence of 4.4% [52], accounting by itself for over 40% of the functional

impairment attributed to mental health disorders [71]. MDD is the most common mental disorder associated with suicide, and the second leading cause of death in 15–29 year old peo-ple [61]. Compared to mild depressive disorder, people with severe episodes have double the odds of death from suicide [29]. The heritability of MDD is estimated to range between 40 and 70% [37], lower than for bipolar disorder (BD).

BD is identified as the sixth leading cause of disability worldwide among all diseases as estimated by the World Health Organisation (WHO) [65]. It affects approximately 2% of the population, and has a suicide rate of 20%, which is even higher than in MDD. Heritability estimates for BD typically fall in the range 60–85% [14] and genetic stud-ies indicate that the disorder follows a polygenic mode of transmission.

The Psychiatric Genomic Consortium (PGC) was established circa 2007 (https ://www.med.unc.edu/pgc/), with a goal to build large population samples of genomic and phe-notypic data suitable for genome-wide exploration of the determinants of diagnosis and outcome in mental illness [62]. It has grown to a collaboration of over 800 investiga-tors from over 38 countries, with more than 900,000 samples from individuals in analysis and is the largest consortium and biological experiment in the history of psychiatry [63]. The Major Depressive Disorder working group (PGC-MDD-WG) and the Bipolar Disorder Working Groups were among the first five collaborations to develop. The PGC recently identified 102 genome-wide significant common variant associations for MDD ($P = 8 \times 10^{-10}$) [31, 72] as well as 30 genome-wide significant common variant associations for bipolar disorder (BD) [60]. The subjects in these studies were heterogenous and some were poorly characterized. This limits the interpretability and clinical utility of these findings for clinicians. Based on more recent observations that the severity of MDD is correlated with MDD polygenic risk [72] and BD polygenic risk predicts earlier onset of depression [46], these findings suggest a clear and compelling ration-ale to study the genomics of patients with the most severe forms of mood disorders. The yield of genetic discovery from studying these subjects is expected to be greater than for studies of less severe forms of depressive disorders.

The phenotypic characterization of patients with mood disorders in the numbers required for genome-wide associa-tion studies (GWAS, tens of thousands to millions) is chal-lenging. Earlier genetic studies of mood disorders relied on more comprehensive research assessments to characterize the phenotype in detail. Due to demand for greater statisti-cal power, there is now is a need to rapidly identify, consent, briefly phenotype, biosample, and genotype people with mood disorders to translate genetic findings into clinical and therapeutically actionable findings.

For practical, conceptual, and procedural reasons, recruiting individuals receiving electroconvulsive therapy (ECT) is an obvious choice for identifying those with severe depression and with rich clinical information, often in routine clinical settings. First, ECT is administered to those with the most severe forms of mood disorders [2, 30, 33, 57, 70]. Second, patients considered for ECT have undergone detailed psychiatric and medical evaluation to determine their suitability for ECT. Third, patients' mood and treatment response are assessed periodically over the ECT treatment course, which allows analysis of response to ECT. Such a highly standardized protocol provides a rich clinical characterization that is linked to treatment outcomes. Hence, forming an international consortium to rapidly identify, consent, phenotype, biosample, and genotype people who have a history of receiving ECT with available medical records makes use of a relatively highly standardized procedure around the world. People undergoing ECT will also be approached for consent to provide a blood sample, as well as authorize us to collect pertinent history from their medical records. We have created a data collection protocol that allows us to rapidly extract relevant clinical information (20–30 min), including the patient's psychiatric history, medical history, and response to ECT from available medical records.

The ultimate goal of this study is to contribute to predictive algorithms for treatment response in depression. Approximately 80% of patients respond to ECT, according to a large Swedish study, and a significant proportion of patients discontinue or never initiate ECT due to concern about side-effects [11, 49]. To date, research has met limited success in using clinical features to predict response to ECT or likelihood of experiencing side-effects. A recent meta-analysis identified modest predictive power for several clinical features including psychosis as well as older age and, to a lesser extent, depression severity as predictors of response and/or remission to ECT, while it was not possible to be conclusive about melancholia [69]. There is thus a clinical need to develop better methods to predict response and aid patient selection for specific treatments. In other words, we want to learn whether we can, very early on in treatment or even at first presentation, identify people who will likely respond well to ECT versus people who will likely respond poorly or have adverse effects from ECT, to personalize the recommendations for treatment with ECT for those with depression, at an earlier phase of illness than occurs in current clinical practice. This would also allow ECT to be avoided in those patients for whom the physical or cognitive side-effects of ECT would outweigh the benefits of treatment.

ECT: clinical indications, practice, and mechanism of action

Why are patients receiving ECT?

ECT is one of the most rapid and effective treatments for affective symptoms in both MDD and BD [16, 25, 34, 54].

ECT applies an electrical stimulus to induce a brief generalized seizure under controlled conditions. The procedure is performed under general anaesthesia with the use of a muscle relaxant [19]. ECT is a medically safe procedure with a very low mortality of 2.1 per 100,000 treatments [67]. Because of its good evidence base, international guidelines support the use of ECT in cases where depression or mania is resistant to medication and psychotherapy ("treatment resistant") or where rapid response is desirable such as high suicidality, catatonia, and rapidly deteriorating physical status due to self-neglect [2, 3, 43, 48, 53, 56, 70]. ECT has also been shown to be cost-effective and improve quality of life [23, 58]. It is associated with cognitive side-effects [7] and severe memory-related side-effects in a minority of patients, as well as physiological changes such as hypertension and raised intra-cranial pressure and so requires careful screening and monitoring processes [59, 64, 68]. For these reasons, ECT is usually restricted to the most severe or resistant cases of depression and patients who receive it are well characterized by detailed clinical screening and monitoring practice.

A course of ECT generally requires 6–12 treatments delivered two-to-three times per week. Longitudinal progress, response, and side-effect data are often routinely collected, albeit using different formats and standardized scales, to support treatment decision-making and contribute to the patient's medical record. Furthermore, blood samples can be easily taken following vascular access for anaesthesia. For these reasons, it is possible to study response to ECT in clinical settings with minimal or no additional procedures. To facilitate collaboration between clinicians of varying experience across international boundaries, the Gen-ECT-ic protocol has been specifically designed to allow flexibility in the quantity and complexity of data and type of outcome scales used. We hope that this study will contribute to improving clinical delivery of ECT by encouraging the systematic collection of ECT response and side-effect data. To that end, we have also partnered with the Clinical Alliance and Research in ECT (CARE) Network [41] and the National Network of Depression Centers [24].

Recent research suggests that ECT may mediate its effects via neuroplastic mechanisms within the brain [9] and it has been shown to increase brain region volumes within the hippocampus [22], although hippocampal enlargement might not explain clinical efficacy of ECT [51]. Though altering electrical stimulus dose, stimulus pulse-width and electrode placement can minimize cognitive side-effects [34, 66], it is not yet fully possible to personalize treatment for an individual patient using clinical, biological, and/or procedural variables alone [21, 38, 56]. Latent class analysis suggests up to five trajectories of response including 13% with no improvement and 31% with slow improvement [12]. Despite these response trajectories, treatment recommendations are solely based on clinical assessments and broad clinical guidelines with a high variation in treatment frequency, anaesthetic procedures, electrode placements, and stimulation paradigms internationally [36, 41].

Hence, it has been suggested that multimodal prediction approaches that combine clinical, procedural, and biological as well as emerging genomic markers may improve the accuracy of treatment predictions [69]. In the absence of any previous GWAS for ECT response, only candidate gene studies have been conducted, mostly with small underpowered sample sizes, with mixed associations between response and catechol-O-methyltransferase (COMT), dopamine receptor (D2, D3), serotonin-related (tryptophan hydroxylase, 5-HTTLPR transporter, 2A receptor), brain-derived neurotrophic factor (BDNF), and apolipoprotein E (APOE) genotype [4, 10, 15, 17, 40, 56]. The emerging area of multimodal prediction of treatment response to ECT and the absence of reliable candidate or genomic markers of response stimulates a genomic approach to predicting treatment response to ECT in depression. The formation of the Genomics of ECT international consortium (Gen-ECT-ic) in depression aims to build the platform to meet the gap in ECT research and clinical prediction.

Gen-ECT-ic's scientific goals and objectives

The consortium has been formed to achieve a total sample size of > 30,000 cases over the coming 4–5 years with the following objectives:

The goals and objectives of Gen-ECT-ic are to

1. investigate the genomic underpinnings of severe, treatment-resistant depression;
2. study the genetic contribution of treatment response to ECT;
3. identify genetic markers of patients with increased risk of developing severe cognitive deficits;
4. form the largest clinical study of ECT to date.

The consortium's ambition is to facilitate clinical research in the field of ECT and more broadly in severe depressive disorders by becoming a repository of clinical and genetic data of subjects with a history of ECT or severe depression. Accordingly, we will ask for permission to recontact participants for future studies. To achieve the above objectives, statistical analyses will be performed using the high-quality and well-established bioinformatics pipeline and expertise of the PGC.

Membership in Gen-ECT-ic

We welcome any ECT provider or researchers who wish to study participants with severe depression that have undergone or may undergo ECT to join Gen-ECT-ic. We also welcome providers and research groups with access to patients/subjects/samples derived from persons with a history of clinically documented severe depression. This includes custodians of biobanks with access to DNA samples or samples from which DNA can be derived. Eligibility of the samples for inclusion into the study will be individually verified using the data collection questionnaire, which is described below. We ask that those who join Gen-ECT-ic agree to the PGC's memorandum of understanding (https://www.med.unc.edu/pgc/shared-methods/documents-for-data-access/).

To ensure a constant exchange of ideas between members and allow for rapid realization of Gen-ECT-ic's goals, a monthly conference call is conducted and a listserv has been created which allows for the rapid dissemination of ideas, best practices, as well as a discussion of new developments in ECT and severe depression genomics.

Data and sample collection

The plan for clinical data and DNA sample collection is designed to be as flexible as possible to fit within different clinical workflows of participating ECT centers to capitalize on routine clinical care and minimize the burden of the study on both the patients and provider teams participating in the consortium. Each ECT center will be able to adapt data collection procedures to use the approaches that work best for its clinical operation.

A flexible, modular questionnaire has been developed with this goal in mind. Construction of this questionnaire followed a consensus-based approach with the input of experts in the field of psychiatric genetics, mood disorders, and ECT research, including Members of the NIMH Division of Translational Research, International Society for ECT and Neurostimulation (ISEN), the European Forum for ECT (EFFECT) [8], the Psychiatric Genomics Consortium (PGC) [62], CARE Network [41], NNDC [24] the Consortium for Research in ECT (CORE) [55], the Prolonging Remission in Depressed Elderly (PRIDE) study group [32], and the Global ECT-MRI Research Collaboration (GEMRIC) [50]. This modular approach achieves the balance of maximizing sample collection as well as clinical characterization of each sample included.

The questionnaire can be used for retrospective (from either clinical records or registry-based information) or prospective data collection, and was designed to streamline data collection on the front end to facilitate later data harmonization. It was designed to capture routinely collected clinical data in a flexible way that would minimize exclusion of participants from the study. We have arranged the information into three tiers (basic, minimal, and extended), reflecting the variable level of detail in the existing biobanks and repositories and providing flexibility in the commitment of collaborators collecting new data. The data capture form was designed to extract retrospectively or prospectively collected data present within a medical record for referral to an ECT clinic, routine ECT monitoring, or evaluation of severe/treatment-resistant depression. The entire data collection process can be completed in less than 30 min, with access to the existing notes without a specific participant interview. Collaborators have different options to capture varying depth of available clinical data as detailed below. Both paper-based and online versions have been implemented. The online version utilizes REDCap (https://www.project-redcap.org) [28], a secure web database application for data collection. Access to collaborators can be forwarded via a simple email with hyperlink. The data abstraction form in its paper format is attached as supplement.

Using the three tiers of data, collaborators have different options to capture varying depth of available clinical data.

Tier 1: basic data

Providing samples with basic data (lowest tier) is sufficient for membership in the consortium (sections 1–4). This includes demography, primary and secondary clinical diagnoses, indication for ECT, confirmation that the subject meets study inclusion criteria, and verification of consent. In particular, the diagnosis includes important clinical qualifiers like severity, psychotic features, and treatment resistance.

These data should be available even for samples obtained from pre-existing registries and biobanks with little accompanying clinical information, and it takes less than 5 min to complete.

Tier 2: minimal clinical data

Tier 2 (sections 5–7) captures information on the clinical response to ECT for a selected index acute treatment series. This includes information on the primary indication for ECT and initial ECT administration parameters for the series (section 5). It also includes information on clinical assessments that are routinely captured to document efficacy and safety during the ECT series. The primary efficacy assessment is the Clinical Global Impression-Severity and/or Improvement scales (CGI-S and CGI-I) for before and after the ECT series. The CGI-S and CGI-I scales have been shown to be valid and reliable measures of clinical response that are sensitive to change [5, 26, 44], and have been widely used in numerous clinical trials in psychiatry. In the interest of maximizing flexibility, other efficacy assessments can be provided if the CGI is not available. These include commonly

used measures of depressive symptoms, such as the Montgomery-Åsberg Depression Rating Scale (MADRS) [45], the Hamilton Depression Rating Scale (HAM-D) [27], the Patient Health Questionnaire-9 (PHQ-9) [18, 35, 39], or equivalent. Mania measurements include Young's Mania Rating Scale [73]. For safety assessments, the instrument will capture information on the most commonly used measures of cognitive function in ECT, including the THINC-it tool [42], the Mini-Mental Status Examination (MMSE) [20], the Montreal Cognitive Assessment (MOCA) [47], and any measure of autobiographical memory.

Tier 3: extended clinical data

Tier 3 (sections 8–16) captures a richer set of clinical information that is routinely, but not always, collected during ECT. This includes the following information: extended psychiatric history and psychiatric comorbidities; history of mania; details of past pharmacological treatment trials, psychotherapy and stimulation therapies; medical comorbidities; history of substance use disorders; family history; and history of prior ECT.

Standard operation procedures

Standard operating procedures (SOPs) are provided for the collection of clinical data and the collection and processing of biosamples. The minimal sample requirement is DNA or saliva or peripheral whole blood for DNA extraction. Whole blood can also be processed to extract RNA and serum and plasma for proteomic and other analyses.

Local sites will be responsible for the consent of individual participants, storage of consent forms, as well as storage of linker information to the deidentified data related to this project. Each site will be responsible for applying and obtaining the appropriate ethical permissions required at their site that adheres to the local site's ethics committee, state/province/district, and countries laws and regulations. Each site that consents the participants will also be responsible for the deletion of identifiable data at their local sites should participants decide to withdraw their consent to participate. For data that have already been transmitted to the PGC in deidentified form, the site will then be responsible for informing the data committee the deidentified code number associated with the participant that has withdrawn consent, so that their data may be deleted. Reasonable measures will be taken to delete their data. However, summary statistics obtained from analysis with this individual's data, as well as any published results would likely not be able to be withdrawn.

Non-personal data, that is, deidentified clinical data and deidentified genetic data linked by code will be stored and analyzed in a manner consistent with the practices of the PGC. The PGC has vast experience in these matters. In brief, PGC data are stored in the Dutch LISA/Genetic Cluster Computer hosted by Surfsara ((https://surfsara.nl/systems/lisa) with ISO 27001 certification. Data obtained via PGC are not allowed to be removed from the LISA cluster. Any individual who requests access to the PGC data is required to sign the PGC Memorandum of Understanding (MOU), become approved to become a member of the PGC and submit a proposal to the PGC-MDD workgroup. This workgroup will review the qualifications of the individual PGC member as well as the scientific merit of the project to determine whether this request would be approved. After approval by the workgroup chair, the individual will then apply for data access via the secure PGC data access web portal. The MDD workgroup representative will oversee the approval and access process. The data access committee keeps record of all permissions and approvals and the PGC has the capacity to monitor all data accessed. Data at the individual level require further agreements and documentation. More information can be found https://www.med.unc.edu/pgc/shared-methods/.

Site description

Current consortium members consist of investigators and clinicians from high-volume ECT centers, investigators with access to biorepositories linked to medical records, and researchers in the field of ECT. Table 1 summarizes these sites at the time of submission.

Gen-ECT-ic's current project and long-term mission

Gen-ECT-ic is poised to assess the "pharmacogenomics" of ECT treatment in mood disorders, including both treatment response and emergence of adverse effects. The combined GenECT-ic sample (current sample size of $N = 11{,}400$) is the largest sample set to date to investigate response to ECT on a genome-wide scale and, in addition, we aim to create the largest collection of clinical data on ECT response. As a first project, Gen-ECT-ic intends to conduct a GWAS of response to ECT as compared to non-response to ECT in ECT recipients with a severe depressive episode, regardless of whether the depressive episode is in the context of MDD or Bipolar disorder. As a second major project, Gen-ECT-ic intends to conduct a GWAS of inpatients with severe depression (TDR) (MDD or BD) as compared to mild-to-moderate depression. This comparator group will include participants recruited retrospectively from studies contributing to the PGC with mild-to-moderate MDD (MADRS < 24 or HAMD < 18) and mild-to-moderate BD (MADRS < 24 or HAMD < 18; YMRS < 20) who have not undergone ECT.

Table 1 Overview of sites providing samples in the Gen-ECT-ic Consortium

Institution/network	Country	Existing cases	ECT per year	Biosampling complete
GEMRIC	Multinational	300	–	–
Australia ECT Network CARE	Australia	–	500	–
University of New South Wales	Australia	–	500	–
Northside Group Saint Leonard's Clinic	Australia	–	80	–
Providence Care Hospital, Queen's University	Canada	50	100	–
Sunnybrook Health Sciences Centre	Canada	50	100	–
University of Calgary	Canada	–	50	–
University of British Columbia	Canada	50	30	–
Central Institute Mannheim	Germany	–	100	100
University of Bielefeld	Germany	–	100	–
University of Marburg	Germany	–	100	100
University of Munster	Germany	100	70	100
University of Brescia	Italy	–	100	100
St. Patrick's Mental Health Services, Trinity College Dublin	Ireland	350	130	180
Haukeland University Hospital, Bergen	Norway	200	70	90
Poznan University of Medical Sciences	Poland	40	50	–
University of Barcelona Hospital Clinic	Spain	220	100	–
University Hospital Parc Tauli	Spain	200	60	–
Bellvitge University Hospital-IDIBELL	Spain	120		
Singapore ECT Network CARE	Singapore	–	400	–
Institute of Mental Health	Singapore	30	50	–
PREFECT Study	Sweden	–	–	3200
Bipolar Disorder Research Network	UK	–	–	720
Cardiff University	UK	40	20	–
University of Glasgow	UK	250	80	–
Kaiser Permanente Research Biobank	USA	–	–	760
Biobank at Vanderbilt University	USA	–	–	200
Partners Biobank at Massachusetts General Hospital	USA	–	–	800
National Network of Depression Centers[a]	USA	7350	2785	50
US Affiliate sites[b]	USA	2050	1375	100
Other international ECT networks[c]				
	Total	11,400	6940	68,300

Sites and numbers of cases as of September 2019

Overview of sites in the Gen-ECT-ic Consortium. Each site joining Gen-ECT-ic was asked to provide estimate numbers of possible subjects that they have in their records available to recontact for retrospective collection, as well as subjects that have already completed biosampling with a history of ECT. Each site was also asked to estimate the annual number of individual patients/possible subjects that receive ECT for prospective inclusion into the study. Only the sites that have provided these estimates are represented in this table

[a]National Network of Depression Centers includes Duke University, Emory University, Johns Hopkins University, Lindner Center of HOPE-University of Cincinnati Health, The Mayo Clinic, McLean Hospital/Harvard Medical School, Pine Rest Christian Mental Health Services-Michigan State University College of Human Medicine, Stanford University, the Ohio State University, University of Florida, University of Iowa, and the University of Massachusetts

[b]US Affiliated sites include The Cleveland Clinic, Medical University of South Carolina, University of North Carolina Hospitals, University of Texas-Southwestern, University of Utah, and Zucker Hillside Hospital/School of Medicine at Hostra/Northwell

[c]*GEMRIC* Global ECT-MRI Research Collaboration

The third major analysis planned includes the analysis of clinical predictors of response and non-response to ECT in this largest clinical ECT cohort. Numerous additional secondary analyses are possible using this rich data set in due course (for more information: https://www.ukm.de/index.php?id=gen-ect-ic).

Gen-ECT-ic will continue to invite researchers to join its efforts to increase the available sample size of

participants with severe depression. In collaboration with NNDC centers, the CARE Network, and other ECT researchers, Gen-ECT-ic will be actively engaged in supporting and organizing prospective studies of ECT response as well as in novel analyses of retrospective ECT response data, facilitated by our data collection element. The rich clinical data set alone is likely to yield great insights into the treatment response to ECT, and the genetic findings will further enrich our ability to personalize treatment recommendations.

Conclusions

The purpose of this report was to describe the goals and structure of the Gen-ECT-ic, a novel and ambitious program of international collaboration in the field of mood disorder genomics. The goal of the PGC is to unite investigators around the world to conduct meta- and mega-analyses of genome-wide genomic data for psychiatric disorders, and further connect them to clinical response information to ultimately improve clinical care. The only way that this can be achieved is by large-scale collaboration and an open exchange of information. Gen-ECT-ic aims to be such a platform for ECT clinicians and investigators around the world. Gen-ECT-ic further aims to become the largest repository of ECT response data linked to genomic data in severe depressive disorders. This will allow for examination of genotype–phenotype response association for the most effective treatment for depressive disorders to date.

It is worth noting that projects such as the UK Biobank [6] and NIH's All of Us [1, 13] have also collected phenotypic data in addition to genetic data. However, these have focused on largely clinically heterogenous and healthy populations, and those with severe psychiatric disorders are likely to be underrepresented. By focusing our efforts on those with severe mood disorders and the response to the most acutely powerful treatment as ECT, we aim to accelerate the understanding of these debilitating conditions, thereby allowing us to improve current treatment delivery algorithms and ultimately guide the field to novel treatments.

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Compliance with ethical standards

Conflict of interest None declared.

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