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The Anorexia Nervosa Genetics Initiative (ANGI): Overview and methods

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Abbreviations: AN, anorexia nervosa; ANGI, Anorexia Nervosa Genetics Initiative; ANGI-ANZ(AUS), Study recruitment for Australia/New Zealand from Australia; ANGI-ANZ(NZ), Study recruitment for Australia/New Zealand from New Zealand; ANGI-DK, Study recruitment for Denmark from the national register and biobank system; ANGI-DK(clinic), Study recruitment for Denmark from the Danish Psychiatric Biobank; ANGI-SE(Community), Study recruitment for Sweden from the community; ANGI-SE(LifeGene), Study recruitment for Sweden from the LifeGene study; ANGI-SE(Riksät), Study recruitment for Sweden from the Riksät-National Quality Register for Eating Disorders Treatment; ANGI-SE(SCÄ), Study recruitment for Sweden from the Stockholm Centre for Eating Disorders; ANGI-US, Study recruitment for the United States; ANGI-US(PFCG), Study recruitment for the United States from The Price Foundation AN Trios Study; ANZ, Australia/New Zealand; CHDS, Christchurch Health and Development Study; DK, Denmark; DNSB, The Danish Neonatal Screening Biobank; DSM-5, Diagnostic and Statistical Manual of Mental Disorders, 5th edition; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, 4th edition; GSA, Global Screening Array; GWAS, genome-wide association studies; iPsych, The Lundbeck Initiative for Integrative Psychiatric Research; PGC, Psychiatric Genomics Consortium; PGC-ED, Eating Disorders Working Group of the Psychiatric Genomics Consortium; PKU, phenylketonuria; RUCDR, Rutgers University Cell and DNA Repository; SCID, Structured Clinical Interview for DSM-IV; SE, Sweden; UNC, University of North Carolina at Chapel Hill; US, United States

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ABSTRACT

Background: Genetic factors contribute to anorexia nervosa (AN); and the first genome-wide significant locus has been identified. We describe methods and procedures for the Anorexia Nervosa Genetics Initiative (ANGI), an international collaboration designed to rapidly recruit 13,000 individuals with AN and ancestrally matched controls. We present sample characteristics and the utility of an online eating disorder diagnostic questionnaire suitable for large-scale genetic and population research.

Methods: ANGI recruited from the United States (US), Australia/New Zealand (ANZ), Sweden (SE), and Denmark (DK). Recruitment was via national registers (SE, DK); treatment centers (US, ANZ, SE, DK); and social and traditional media (US, ANZ, SE). All cases had a lifetime AN diagnosis based on DSM-IV or ICD-10 criteria (excluding amenorrhea). Recruited controls had no lifetime history of disordered eating behaviors. To assess the positive and negative predictive validity of the online eating disorder questionnaire (ED100K-v1), 109 women also completed the Structured Clinical Interview for DSM-IV (SCID), Module H.

Results: Blood samples and clinical information were collected from 13,363 individuals with lifetime AN and from controls. Online diagnostic phenotyping was effective and efficient; the validity of the questionnaire was acceptable.

Conclusions: Our multi-pronged recruitment approach was highly effective for rapid recruitment and can be used as a model for efforts by other groups. High online presence of individuals with AN rendered the Internet/social media a remarkably effective recruitment tool in some countries. ANGI has substantially augmented Psychiatric Genomics Consortium AN sample collection. ANGI is a registered clinical trial: clinicaltrials.govNCT01916538; https://clinicaltrials.gov/ct2/show/NCT01916538?cond=Anorexia+Nervosa&draw=1&rank=3.

1. Introduction

Genetic factors play a substantial role in liability to anorexia nervosa (AN). Relative risk is ~11 in female first-degree relatives of those who have AN [1], and twin studies estimate heritability at 48%–74% [2–5]. The Eating Disorders Working Group of the Psychiatric Genomics Consortium (PGC-ED) reported the first genome-wide significant locus on chromosome 12 in a region previously implicated in type 1 diabetes and autoimmune illnesses [6]. The goal of the Anorexia Nervosa Genetics Initiative (ANGI) was to rapidly expand available samples for genome-wide association studies (GWAS) of AN. Given the complex genetic architecture of psychiatric disorders, large sample sizes, perhaps hundreds of thousands, are necessary to identify variants associated with these disabling conditions [7,8]. We provide an overview of recruitment procedures and methods used in ANGI, which collected the largest sample of AN cases and controls in the world, considerably augmenting existing samples in the PGC-ED [9].

A secondary goal of ANGI was to provide efficient phenotyping for future investigations. In the absence of biomarkers for psychiatric disorders, the large sample sizes required for GWAS encourage the development of valid assessments with minimal investment of time and effort. Structured clinical interviews, regarded by some as the preferred method for assessing eating disorders [10], are not economically feasible for such studies. Well-validated and easily accessible self-report assessments provide an alternative and may encourage greater openness about disordered eating behaviors than face-to-face interviews [11,12]. To this end, we report the validity of an online eating disorder questionnaire (ED100K-v1) designed to capture AN cases and controls for inclusion in ANGI. Data generated from ANGI will provide pertinent information about the etiology of AN and contribute to the development of biologically informed therapeutics.

2. Materials and methods

2.1. Collaborative arrangements

ANGI is an international collaboration sponsored by the Klarman Family Foundation and the National Institute of Mental Health. Four primary hubs for data collection, selected because of experience in collecting large genetic samples and access to individuals with a lifetime history of AN, included the University of North Carolina at Chapel Hill [(UNC), United States (US)]; QIMR Berghofer Medical Research Institute [Brisbane, Australia with assistance from the University of Otago in Christchurch, New Zealand (ANZ)]; Karolinska Institutet [Stockholm, Sweden (SE)]; and Aarhus University [Aarhus, Denmark (DK)]. The organizational structure consists of a lead principal investigator (Bulik); site principal investigators (Bulik, Martin, Landén, Mortensen); deputy director (Thornton); steering committee (chair: Bulik); biological sample committee (chair: Sullivan); analysis group (chair: Sullivan); phenotype group (chair: Thornton); and publication and editorial committee (chair: Bulik). A scientific advisory council provided external oversight of study procedures; monitored progress of sample collection, genotyping, and data analysis; and ensured adherence to ethical standards and data sharing procedures. The appropriate ethics or institutional review boards at each location approved study protocols.

2.2. General study procedures

In the US, ANZ, and SE, inclusion criteria for cases were based on the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) AN Criteria A, B, and C. Amenorrhea (Criterion D) was not required since it is not applicable to males and was removed from the DSM-5. In DK, cases were defined as any individual present in the national patient register or who presented in the clinic with an ICD-10 diagnosis of F50.0 (AN) or F50.1 (atypical AN).

Recruitment and study procedures varied across sites (see Fig. 1) due to local ethical requirements or the manner in which cases were identified and are discussed below.

2.3. United States and Australia/New Zealand

2.3.1. Recruitment approach

A primary focus of our recruitment strategy was to include individuals who: 1) may not live close to recruitment centers, but who desired to participate; 2) may have suffered from AN and never