Uncovering Eating Disorder Genetics Through Large Scale Sequencing

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INTRODUCTION

Both anorexia (AN) and bulimia (BN) nervosa are marked by a substantial genetic component, with family study heritability estimates of 0.58-0.76 for AN and 0.30-0.83 for BN. Despite such heritability estimates, discovery of genetic risk factors for AN and BN remain limited.

Genome-wide association studies are limited in power and resolution, and discoverability of genetic risk factors is hindered by study-design limitations such as potential confounding by BMI due to current AN nosology.

The **Genetics of Eating Disorders** study at the Broad Institute is currently recruiting participants for deep-phenotyping assessments and DNA sequencing analysis to further elucidate the biopathological mechanisms underpinning eating disorders and associated comorbidities.

METHODS

Our analysis is focusing on existing samples from large biobanks (FinnGen, N=4,616; All of Us, N=2,500; MGB biobank, N=1,000), representing one of the largest collective cohorts in eating disorder genome sequencing so far. We are additionally planning to sequence additional 10,000 AN/BN cases and 10,000 controls over the next 2 years, recruited in the clinics across the United States, Mexico, and Europe, as well as direct-to-participant (DTP) recruitment in the United States.

To facilitate the assessment of DTP participants, we have developed the McLean-Stanford-Washington Eating Disorder (MSWED) questionnaire, a screening tool to identify lifetime diagnosis of eating disorders, which was initially validated in the Mexican clinically-ascertained cohorts (N=350) and is currently undergoing validation against SCID-5 in the United States.

The phenotypic analysis of prospectively recruited individuals in INP Mexico and US DTP is shown in this poster. Analyzed phenotypes include compulsive exercise (CET), disordered eating (EDE-Q), anxiety (GAD-7), depression (PHQ-7), obsessive-compulsive symptoms (OCI-R), and PTSD (PCL-5).

RESULTS

We have identified about 22,000 samples for sequencing, shown in **TABLE 1**, 977 of which have been received for sequencing and 807 of which have been sequenced so far. Extensive phenotypic data collected for Mexico (N=960) and US DTP (N=1,632).

EDE-Q scores (**FIGURE 1**) and CET scores (**FIGURE 2**) show higher eating disorder related and compulsive exercise symptoms among individuals with reported eating or feeding disorder diagnoses compared to those without. Overall EDE-Q and CET scores were equivalent among individuals with a reported eating or feeding disorder diagnosis, regardless of the diagnosis.

OCI-R score (**FIGURE 3**) did not substantially differ with respect to the eating or feeding disorder diagnosis status.

Preliminary validation of MSWED resulted in high specificity (AN=0.93, BN=0.97) and lower sensitivity (AN=0.72, BN=0.51), as intended.

Additional results for the entirety of phenotyping battery are available online via the QR code included at the bottom of this poster.

DISCUSSION

The **Genetics of Eating Disorders** study at the Broad Institute is currently undergoing active recruitment, phenotyping, and DNA sequencing of participants with eating disorders and controls.

Initial analyses of common and rare variants in cohorts where sequencing data are available are underway. We are expanding these cohorts with recruitment and genome sequencing of additional samples from ancestrally diverse clinically recruited and community-based participants.

MSWED validation suggests that it is highly specific, making it a valuable tool for identification of eating disorder cases for genetic research in community-based participants.

TABLE 1

Summaries of DNA sample collections and sequencing, excluding already sequenced samples from large biobanks (e.g., All of Us).

Cohort	$N_{Estimated}$	$N_{Collected}$	$N_{Sequenced}$
Finish Biobank, Finland	4,616	-	-
Instituto Nacional de Psiquiatría, Mexico	6,000	422	422
Careggi University Hospital, Italy	210	60	60
Kings College London, UK	5,000	-	-
Nationwide Children's Hospital, USA	1,000	37	37
MGB Biobank, USA	500	-	-
MGB ED Study, USA	500	-	-
Columbia University Medical Center, USA	64	64	-
University of Florida Health, USA	95	-	-
656-	4,000	394	288

FIGURE 1

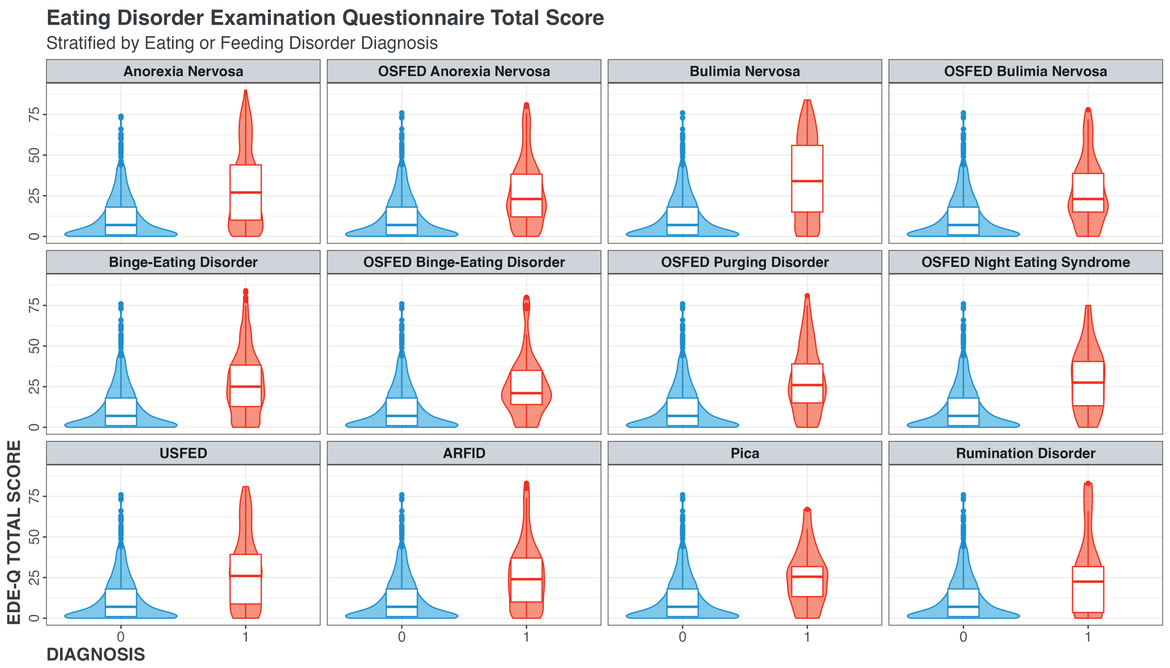


FIGURE 2

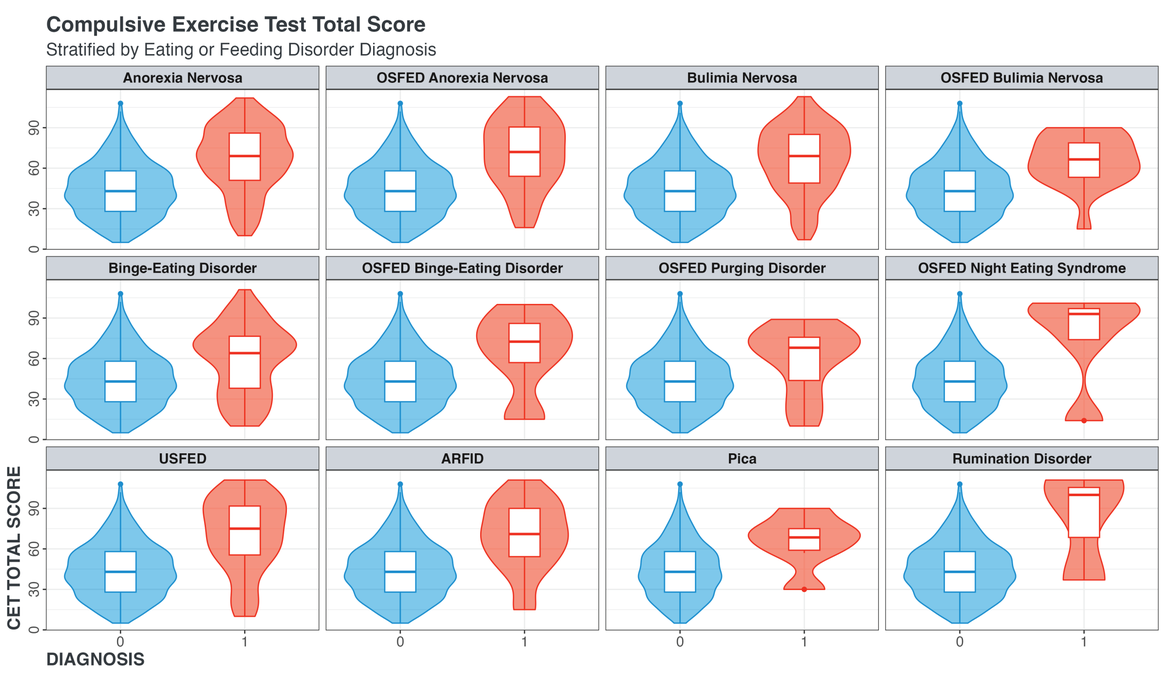
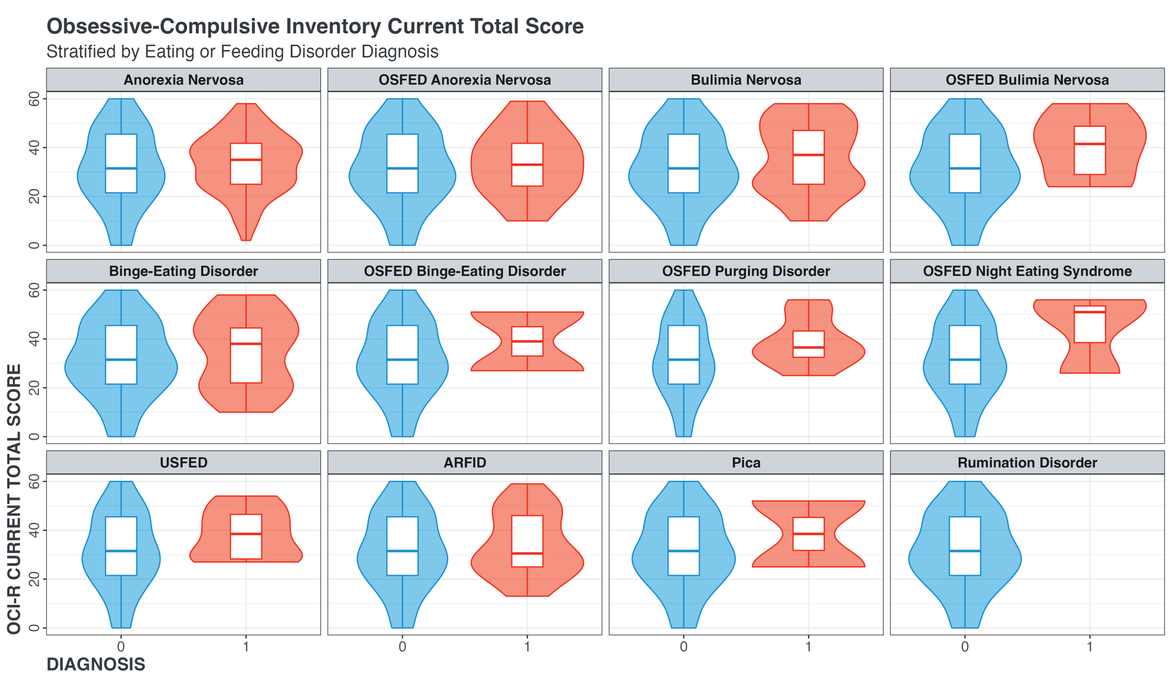


FIGURE 3



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