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Solving the eating disorders puzzle piece by piece: Commentary on Lutter et al.

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Albeit slowly, we are beginning to piece together the complex biological puzzle of anorexia nervosa (AN), bulimia nervosa (BN), and binge eating disorder (BED). The article by Lutter et al. in this volume, “The eating-disorder associated HDAC4A778T mutation alters feeding behaviors in female mice” (1) brings us one step closer to understanding these illnesses.

To set the stage, heritability estimates for all three eating disorders range from 40–65% with a smaller but still considerable environmental contribution to risk (2). However, the overwhelming predominance of sociocultural explanations and rationalizations has meant there have been comparatively few investigations into the biological underpinnings of these anomalous conditions. AN is a particularly perplexing illness, primarily, but not exclusively, affecting young females, compelling them into prolonged negative energy balance, often to the point of death.

To uncover the biological causes of eating disorders, multiple approaches are required. In genetics, the field is advancing with genome-wide association studies (GWAS) of AN, with the first genome-wide significant locus having recently been identified (3) in a gene previously associated with type 1 diabetes and other autoimmune conditions. This work also suggests a previously overlooked role for metabolic abnormalities in the genesis of the disorder, particular in regard to insulin function and body mass. No GWAS have been conducted for BN or BED.

In their previous work (4), this investigative team advanced the field using familial linkage analysis with whole genome and exome sequencing to identify two missense mutations: one in a genome-wide significant linkage region within the estrogen-related receptor alpha gene (*ESSRA*) and another within a suggestive linkage region, in the histone deacetylase 4 gene (*HDAC4*). Histone acetylation/deacetylation alters chromosome structure and affects transcription factor access to DNA. HDAC4 represses transcription when tethered to a promoter (<https://www.ncbi.nlm.nih.gov/gene?Db=gene&Cmd=ShowDetailView&TermToSearch=9759>). Specifically, a mutation causing

an alanine to threonine substitution at amino acid 786 was found via exome sequencing of a large family with multiple cases of AN and BN as well as subthreshold/unspecified eating disorders. The human HDAC4^{A786T} mutation lies at the junction of two protein domains of HDAC4, is relatively common, at >0.2% in allele frequency, and is predicted by bioinformatic analyses to be either benign or mildly deleterious.

Thus, while the linkage evidence is suggestive and the variant lies on the linkage haplotype, it is unclear if the variant is functionally related to eating disorders. In the current paper (1), the authors address this issue by studies of an equivalent mutation introduced into the mouse HDAK4 protein at amino acid 778 (HDAC4^{A778T}) followed by an array of behavioral tests on heterozygous mice that parallel symptoms characteristic of human eating disorders; namely, anxiety, despair, compulsivity, and fat responsiveness. Several behaviors were affected including weight dysregulation and hyper- rather than hypophagia (more relevant to BN and BED than AN). Critical for the understanding of AN and BN, the authors did conduct sex-specific studies. In addition, they cleverly introduced an environmental stressor into their paradigms by testing mice either singly or group housed. This latter parameter is relevant given the widespread assumption that eating disorders arise from a “perfect storm” of both genetic and environmental risk factors.

Potentially informing the grossly disproportionate sex difference in AN and BN, male heterozygous mice displayed no metabolic or behavioral differences in either the individual or group housed conditions. Why remains a mystery. However, female mice who were individually housed displayed decreased responding for high fat (i.e., rewarding) pellets and increased compulsive grooming. These results parallel fat avoidance in AN (5) as well as increased obsessive compulsive behaviors reflected in clinical comorbidity and twin based correlations between AN and obsessive-compulsive disorder (OCD)(6), and single nucleotide polymorphism (SNP)-based genetic correlations between AN and OCD (7). Observations in group housed female mice diverged in that they displayed increased weight gain on a high fat diet, decreased behavioral despair (took them longer to give up in a force swim test), and increased anxiety. The authors interpret the results of the forced swim test to be associated with “jitteriness/anxiety syndrome” rather than behavioral despair. However, the mouse behavior could also reflect the behavioral symptom of heightened physical activity in AN, where patients continue to engage in high levels of physical activity even when acutely ill (8). One important point to raise is that the behaviors observed in these mice cut across eating disorders presentations, displaying abnormalities that alternately reflect AN or BN/BED. Given the frequency with which diagnostic crossover occurs in eating disorders (9), this is not necessarily a problem; however, future work should take care to disambiguate symptoms associated with specific eating disorder presentations.

The authors also collected tissue and conducted a targeted brain gene expression analysis of HDAC4 target genes in cortex tissues from the HDAC4^{A778T} mice as well as previously stored brain tissue for a similar experiment in *ESRRA*-null mice. Notably, they found gene expression changes in six of seven target genes by task, but only in the group housed mice. Although this is congruent with a potential GxE effect, it is could also represent the effects of a potential environmental confounder caused by the group housing. While the results of

the gene expression analyses are promising, genome-wide RNAseq analyses or an analysis of a broader panel of genes could have addressed possible confounding.

Their previous work on *ESRRA* led them to the hypothesis that disruption of the HDAC-ESRRA activity may function by interrupting mitochondrial function, more specifically mitochondrial biogenesis. Although they did not provide experimental evidence that the HDAC variant exerts its effects via mitochondrial biogenesis, continued investigation of this hypothesis is worthwhile. Nilsson et al. contend that the anorexia and hypothalamic neurodegeneration of the *anx/anx* mouse (an animal model of some facets of anorexia nervosa) may be associated with dysfunction of the mitochondrial complex (10).

The work by Lutter et al. is a valuable contribution to the growing body of literature elucidating the biological etiology of eating disorders. Concerted efforts are required across methodologies to complete the puzzle. It is unconscionable that individuals continue to die from AN. Despite decades of study, our evidence for the treatment of AN remains meagre. Although family based interventions are fairly effective for youth, treatment of adults is unacceptably poor. Moreover, we have no medications that are effective in the treatment of the illness. This comes as no surprise given our incomplete understanding of its biology.

Our recent genome-wide association work demonstrates significant negative genetic correlations between AN and body mass index and other unfavorable metabolic parameters (2), and supports the current findings of Lutter et al. These and other findings encourage an increased focus on metabolic aspects of AN. In a world where the prevalence of obesity continues to rise, and non-surgical treatments for obesity are notoriously ineffective, individuals prone to AN have an unexplained ability to maintain dangerously low body mass indices. Rounding out our understanding of the biology of this extreme end of appetite and weight dysregulation may inform not only the development of effective therapeutics for eating disorders, but also contribute to enhanced understanding of appetite and weight dysregulation in obesity.

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References

1. Lutter M, Kahn M, Satio K, Davis K, Kidder I, McDaniel L, et al. (2017): The eating-disorder associated HDAC4A778T mutation alters feeding behaviors in female mice. *Biol Psychiatry*.

2. Yilmaz Z, Hardaway A, Bulik C (2015): Genetics and epigenetics of eating disorders. *Adv Genom Genet.* 131–150.
3. Duncan L, Yilmaz Z, Walters R, Goldstein J, Anttila V, Bulik-Sullivan B, et al. (2016): Genome-wide association study reveals first locus for anorexia nervosa and metabolic correlations biorxiv. www.biorxiv.org/content/early/2016/11/25/088815.
4. Cui H, Moore J, Ashimi SS, Mason BL, Drawbridge JN, Han S, et al. (2013): Eating disorder predisposition is associated with ESRRA and HDAC4 mutations. *J Clin Invest.* 123:4706–4713. [PubMed: 24216484]
5. Schebendach JE, Klein DA, Mayer LE, Devlin MJ, Attia E, Walsh BT (2014): Assessment of fat taste in individuals with and without anorexia nervosa. *Int J Eat Disord.* 47:215–218. [PubMed: 24282163]
6. Cederlöf M, Thornton L, Lichtenstein P, Larsson H, Boman M, Rück C, et al. (2015): Etiological overlap between obsessive-compulsive disorder and anorexia nervosa: A longitudinal cohort, family and twin study. *World Psychiatry.* 14:333–338. [PubMed: 26407789]
7. Anttila V, Bulik-Sullivan B, Finucane H, Anttila V, Bulik-Sullivan B, Finucane HK, et al. (2016): Analysis of shared heritability in common disorders of the brain. *bioRxiv* 48991 (2016).
8. Gümmer R, Giel KE, Schag K, Resmark G, Junne FP, Becker S, et al. (2015): High levels of physical activity in anorexia nervosa: a systematic review. *Euro Eat Disord Rev.* 23:333–344.
9. Tozzi F, Thornton L, Klump K, Bulik C, Fichter M, Halmi K, et al. (2005): Symptom fluctuation in eating disorders: correlates of diagnostic crossover. *Am J Psychiatry.* 162:732–740. [PubMed: 15800146]
10. Lindfors C, Nilsson IA, Garcia-Roves PM, Zuberi AR, Karimi M, Donahue LR, et al. (2011): Hypothalamic mitochondrial dysfunction associated with anorexia in the anx/anx mouse. *PNAS.* 108:18108–18113. [PubMed: 22025706]