Epigenetics of Eating Disorders
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Introduction to Eating Disorders

Eating disorders are a distinct category of mental illness characterized by disturbances in eating behaviors (American Psychiatric Association, 2013). Within the grouping of eating disorders, anorexia nervosa, bulimia nervosa, and binge eating disorder are the most prevalent in the U.S. population (American Psychiatric Association, 2013).

Key diagnostic criteria for anorexia nervosa include: a significantly low body weight based on developmental trajectory, intense fear of gaining weight or consistent behavior to prevent weight gain, and disturbances in the way one's body is perceived (American Psychiatric Association, 2013). For females, the year prevalence rate is 0.4%, meaning that 0.4% of the female population is affected with this disorder in a one-year time period. This disorder is much less common in males, with a 10:1 female to male ratio (American Psychiatric Association, 2013). Anorexia nervosa typically affects individuals during adolescence or young adulthood and more commonly occurs in high-income countries, such as the United States, Australia and Japan.

For bulimia nervosa, diagnostic criteria include: recurrent episodes of binge eating (defined as eating a large amount of food in a period of time while experiencing a sense of a loss of control) and recurrent compensatory behaviors (e.g., laxatives, diuretics or self-induced vomiting). These behaviors must occur at least once a week for three months to fit diagnostic criteria. As well, the individual may have concerns over weight, but their symptoms are not better explained by anorexia nervosa. For females, the year prevalence rate is 1%, meaning that 1% of the female population is affected with this disorder in one-year time period. Bulimia nervosa also, has a 10:1 female to male ratio (American Psychiatric Association, 2013). Typical

onset is adolescence and young adulthood, and typical presentation is in Caucasians (American Psychiatric Association, 2013).

Binge eating disorder is characterized by: recurrent episodes of binge eating (also defined as consuming a large quantity of food and feeling a loss of control), but compensatory behaviors do not occur (American Psychiatric Association, 2013). Individuals with binge eating disorder may eat when not physically hungry, eat alone or in secret, or eat as a coping mechanism for dealing with emotions. Additionally, following a binge episode, they may feel uncomfortably full – more so than normal. These binges occur an average of once per week for three months and are associated with significant distress. The year prevalence rate is 1.6% for females and 0.8% for males, meaning that 1.6% of the female population and 0.8% of the male population is affected with this disorder in one-year time period (American Psychiatric Association, 2013). As well, prevalence rates seem to comparable for Caucasians, Latinos, Asian and African Americans (American Psychiatric Association, 2013). Typical onset of binge eating disorder is adolescence and young adulthood (American Psychiatric Association, 2013).

Across eating disorders, there are many common psychological, social and biological risk factors. For example, the psychological factors of perfectionism and negative emotionality have been linked to eating disorders (Keel & Forney, 2013). Perfectionism is characterized as fear of mistakes and active pursuit of flawlessness, while negative emotionality is defined as persistent negative self-evaluation, low self-esteem and consistent negative emotions (Keel & Forney, 2013). Additionally, impulsivity, defined as a difficulty to controlling one's desires, has been linked to bulimia nervosa and binge eating disorder specifically (Engel et al., 2005; Ivezaj, White, & Grilo, 2016).

Regarding social factors, family, peers and the media play into risk of eating disorders (Lyke & Matsen, 2013; Cruwys, Leverington, & Sheldon, 2016; Culbert, Racine, & Klump, 2015). Aspects of a family's dynamic, such as the level of affective responsiveness, defined as the ability of family members to display appropriate emotions, and self-reported general functioning, have been associated with risk for eating disorders, so that low levels of affective responsiveness and general functioning increase risk. As well, families that have parents with a past history of psychopathology, for example depression, anxiety, bipolar disorder and personality disorders, are more likely to have an offspring with an eating disorder (Bould et al., 2015). Related to peers, fat talk, defined as a form of self-degrading communication focused on the thin ideal, within a peer group increases risk for eating disorders (Cruwys et al., 2016). Along with peers, the media is another social component in eating disorder risk. An increased level of media exposure, such as reading a fashion magazine, has been linked to eating disorders in adolescents and young adults (Culbert et al., 2015). This increased risk from media exposure can be partially explained by the amount of thin ideal images commonly seen in media that associate thinness with beauty (Culbert et al., 2015).

In addition to social risk factors, some biological factors, such as hormone or neurotransmitter levels, also play a role. For example, appetitive hormones, such as leptin and ghrelin, and stress hormones that regulate the hypothalamus-pituitary-adrenal (HPA) axis have been studied in relation to developing eating disorders (Culbert et al., 2015; Lo Sauro, Ravaldi, Cabras, Faravelli, & Ricca, 2008). Along with hormones, abnormalities in neurotransmitters, such as serotonin and dopamine, have been linked eating disorders (Frank, 2014). Dopamine and the reward pathway have also been linked to eating disorder behaviors (Heal et al., 2017).

Although there are many different environmental risk factors for eating disorders, genetics underpins all of these. For psychological factors, perfectionist tendencies may indeed have a genetic component (Iranzo-Tatay et al., 2015). For social factors, such as one's family dynamic, the similarities in family attitudes or behaviors may also be related to genetics similarities. As well, biological factors, such as hormones and neurotransmitters, are linked to genetics, in the way that that a particular gene may be to regulate hormone or neurotransmitter levels. In this way, environmental factors involved in eating disorders link back to genome, showing the complex interplay between the genetics and the environment in this form of psychopathology.

Research shows that relatives of those affected by eating disorders are five times more likely to develop an eating disorder than the general population (Durand, Barlow, & Hofman, 2017). To assess how much of this relationship is related to genes or a shared environment, twin studies have been conducted. These studies are performed with the rationale that higher prevalence of eating disorders in identical twins, who have all the same genes, versus fraternal twins, who do not share identical genes, would indicate how much of a role genetics play. For example, one study looked at 2,163 twin pairs comparing prevalence rates for bulimia (Durand et al., 2017). It found a 23% prevalence rate for identical twins versus a 9% prevalence rate for fraternal twins, indicating a strong role of genetics for eating disorders, such as bulimia (Durand et al., 2017).

In addition to twin studies, adoption studies are used to look the genetic component of eating disorders. In adoption studies, biological siblings who are raised apart are studied to indicate the effect of genetics on certain outcomes, since they did not have a shared environment growing up (Klump, Suisman, Burt, McGue, & Iacono, 2009). Klump et al. (2009) conducted the

first adoption study on eating disorders and found significant genetic influences (59%-82%) on all forms of disordered eating by comparing biological and adopted twins on responses to the Minnesota Eating Behaviors Survey (von Ranson, Klump, Iacono, & McGue, 2005).

In the field of genetic research, the study of epigenetics in relation to diseases and disorders represents the latest methods in the field (Yilmaz, Hardaway, & Bulik, 2015). Epigenetics looks into changes in gene expression, without changes to the actual sequence, that can accumulate over one's life in response to the environment (Campbell, Mill, Uher, & Schmidt, 2011). In this way, epigenetic changes can be used to understand different levels of psychopathology in relatives with identical or almost identical genomes, showing how life experiences have a differential effect on each individual.

Looking at mental illnesses, which are classified as a distinct set of psychological, behavioral and physiological aspects, through an epigenetic lens represents a novel way of conceptualizing the gene-environment interaction by directly looking at physical changes caused by the environment. In turn, these environmental changes can be conceptualized as the interplay of psychological, social and biological aspects which exert effects on the epigenome (Guintivano & Kaminsky, 2016). These changes can be viewed as a mechanism from which experiences translates into changes in behavior and physiology, resulting in a mental illness, such as an eating disorder (Campbell et al., 2011). In this paper, the field of epigenetics will be described and suggestions for using epigenetics to study eating disorders will be outlined, representing an approach with nascent implications for eating disorder research. Specifically, this paper will discuss the effects of maternal nutrition on the epigenome, early life stress on the epigenome and potential biological and psychological genes of interest in epigenetic research for eating disorders.

Epigenetics

Epigenetics assesses differences in gene expression not caused by changes in the DNA sequence and in many cases these changes are reversible, changing through one's life (Campbell et al., 2011; Dulac, 2010). The structure of DNA and the associated binding proteins are involved in changing expression without changing the actual DNA sequence. The DNA sequence is made up a coding region that codes for a particular gene and several noncoding regions such as the promoter, that initiates transcription of a gene and a termination region, that ends transcription (Kellis et al., 2014). Within the DNA sequence itself, some noncoding regions are associated with proteins called histones which help to compact and coil DNA for storage (Kellis et al., 2014). The structure of these histone proteins, with large globular heads and charged N-terminus (amino acid) tails, allows for the chemical modifications to be made that results in epigenetic changes seen in altered expression of a gene (Jenuwein & Allis, 2001).

The two most common types of epigenetic modifications are DNA methylation and histone modifications (Szyf, 2009). Methylation occurs by adding a methyl group (CH_4) to the specialized noncoding regions of the DNA molecule, which can, in turn, serve as a site for other proteins to bind or modify histones (Szyf, 2009). Regions of hypermethylation have many bulky methyl groups attached which interfere with transcription, the process of transferring the DNA code to RNA (Szyf, 2009). As a result, there is decreased gene expression at these sites (Szyf, 2009). On the other hand, regions of hypomethylation have less methyl groups attached and easier access to the DNA sequence for transcription to occur, resulting in increased expression (Szyf, 2009). For histone modifications, there are several types, such as histone acetylation and histone methylation (Strahl & Allis, 2000). Histone acetylation adds an acetyl group (CH_3CO) to the histone tail, which causes the loosening of DNA-histone structure, allowing for increased

expression of genes (Strahl & Allis, 2000). For histone methylation, less is known about this form of epigenetic modification, but it is known that methyl groups are added and that either increased or decreased expression can occur (Hayakawa & Nakayama, 2011). Histone modification differs from DNA methylation by acting on the DNA-protein complex instead of directly on the DNA molecule by attaching to noncoding regions (Strahl & Allis, 2000).

Epigenetic research, examining types of modifications on specific genes, has been used to look into the association between particular epigenetic modifications and specific diseases or disorders. In short, the epigenome contains all epigenetic modifications that have accumulated throughout an individuals' life in response to changes in the environment, seen in factors such as nutrition and stress (Moosavi & Ardekani, 2016). As far as the methods in epigenetic research, particular genes associated with biological processes or behaviors associated with a disease can be assessed to see changes at the epigenetic level, such as increased methylation. For example, epigenetic research has targeted cancer, looking for hypermethylation, which would lead to decreased expression, of tumor suppressor genes since an increase in tumor production is a hallmark feature of cancer (Moosavi & Ardekani, 2016). This same form of methodology can be proposed to be used to look at epigenetic factors related to psychological disorders such as eating disorders, looking for epigenetic changes on genes related physiological or psychological processes of the disorder. This paper will focus on how prenatal nutrition and early life stress results in epigenetic modifications and how the reciprocal relationship of epigenetic modifications to genes for reward, appetite, and psychological components, can affect one's behavior in relation to eating disorders.

Maternal Nutrition and the Epigenome

Women with eating disorders have been shown to have poorer outcomes during pregnancy, seen in low birth weight children and preterm delivery (Pasternak et al., 2012). As well, women with eating disorders are more likely to undergo fertility treatments, which could show that these women are trying to conceive at very low weights or are experiencing hormonal issues caused by their eating disorders (Pasternak et al., 2012). In addition, women who have recovered or are in the process of recovering from an eating disorder may find pregnancy to be a challenging time in which they fear weight gain during pregnancy, causing the reemergence of symptoms and eating disorder cognitions (Mitchell & Bulik, 2006). In this way, women with an active eating disorder or a history of one may be prone to under-eating resulting in improper nutrition during pregnancy (Mitchell & Bulik, 2006).

Undereating for mothers during pregnancy, like what may occur in mothers with a history of an eating disorder, has been linked to epigenetic changes in children (Heijmans et al., 2008). The most prominent epidemiological study of maternal undereating is the Dutch Famine Study, which looked at nutrition in the Netherlands in 1944 during World War II (Lumey et al., 2007). During this period of time, caloric intake in the Netherlands dropped to as low as 500 calories a day, representing severe caloric restriction, as is commonly seen in eating disorders, particularly anorexia (Lumey et al., 2007). Epigenetic analysis indicated hypomethylation of IGF2 DMR gene in offspring of mothers who were pregnant during the Dutch Famine, which is a gene related to insulin-like growth factor which has an important role in human growth and development (Heijmans et al., 2008). This study shows that maternal nutritional deprivation has an epigenetic effect on nutritional and metabolic factors in offspring, demonstrating that epigenetic effects can develop during as early as in utero. Although in the Dutch Famine study

specific genes of offspring were not analyzed for eating disorders specifically, it was found that mothers who were pregnant during the famine period gave birth to children who were more likely to have psychological disorders, such as schizophrenia and schizophrenia spectrum personality disorders (Hoek, Brown, & Susser, 1998).

The Dutch Famine study shows the effects of nutrition deprivation during pregnancy on metabolism and growth, and psychological problems in offspring. Although no studies so far have looked at maternal under-eating and the specific link to eating disorders in offspring, the IGF2 gene, shown to have hypomethylation in the Dutch Famine study, has been documented as a candidate gene for eating disorders (Heijmans et al., 2008; Bachner-Melman, Zohar, Nemanov, Heresco-Levy, & al, 2005). Eating disorders also have a high rate of comorbidity with other psychological conditions, such as bipolar, depressive and anxiety disorders (American Psychiatric Association, 2013). Although schizophrenia, which occurred in the offspring of the mothers who experienced the Dutch Famine, is not the most common comorbid condition with eating disorders, brain scans have revealed a reduction of gray matter in both samples, possibly a characteristic of abnormal brain activity that may lead to other psychological conditions more generally (Hoek et al., 1998; Mainz, Schulte-Rüther, Fink, Herpertz-Dahlmann, & Konrad, 2012; Takayanagi et al., 2013). These alterations in structure of an individual's brain may be caused by epigenetic changes during pregnancy. In relation to maternal nutrition, epigenetics can serve as a mechanism where mothers with an eating disorder, or history of one, pass on changes in the epigenome to their offspring in utero. These changes, in turn, predispose their offspring to eating disorders, through the mother's diet during pregnancy.

Early Life Stress and the Epigenome

Along with maternal nutrition, stress during pregnancy and early in life has also been linked to negative outcomes for children, such as cognitive impairments, behavioral issues and adult psychopathology (Talge, Neal, & Glover, 2007). In general, pregnant women with a history or a current eating disorder have increased stress related to fear of gaining gestational weight (Mitchell & Bulik, 2006). Further, individuals with eating disorders often have comorbid anxiety or anxiety-related disorders, which could make dealing with pregnancy and the transition to motherhood particularly stressful (Lavender et al., 2013).

Although studies have not been conducted on stressful environments and epigenetic effects in humans, studies on rodents have indicated epigenetic modifications due to stress, conceptualized as low maternal care (McGowan et al., 2011). Rats raised in an environment with low maternal care, a high-stress environment, had regions that were hypermethylated within the gene NR3C1, indicating lower expression of that gene (McGowan et al., 2011). The NR3C1 gene is a glucocorticoid receptor gene that plays a role in activating the hypothalamus pituitary adrenal (HPA) axis or the fight-or-flight stress response (Weaver et al., 2004). This methylation pattern would indicate malfunctioning of the stress response system so that rats raised in stressful environments would be stressed more easily and be more anxious (Weaver et al., 2004). However, it is interesting to note with this study that epigenetic modifications linked to increased methylation could be reversed by administering drugs that decreased methylation, showing the possibility of reversing epigenetic modifications in humans related to psychological disorders as well (Weaver et al., 2004).

As stated previously, individuals with eating disorders have high levels of anxiety, which could result in creating an environment that is stressful and low in maternal care (Lavender et al., 2013). This type of environment, even though only in rats, has been shown to cause epigenetic

modifications in genes related to the stress response resulting in more anxious offspring. In this way, mothers with eating disorders can be seen to facilitate more stressful environments and produce more anxious children, who will possibly have a higher risk for eating disorders, through this proposed epigenetic mechanism. Since eating disorders are often comorbid for anxiety disorders, it would seem evident that highly anxious children may be more at risk for an eating disorder through this process of being raised in a stressful environment (American Psychiatric Association, 2013). As well, research has shown that developmental anxiety disorders often turn into eating disorders later in life, further supporting this link (Bulik, Sullivan, Fear, & Joyce, 1997).

Biological and Psychological Genes for Eating Disorders in Epigenetic Research

Life experiences, such as changes in nutrition and level of stress, have been shown to cause to epigenetics changes (Heijmans et al., 2008; Weaver et al., 2004). On the other hand, epigenetic modifications can occur which can translate into physiological and psychological functioning. Genes related to physiological functions like the reward circuit and appetite regulation, both functions involved in eating disorders, would be of interest to epigenetics studies. Additionally, looking into epigenetic modifications in genes related to psychological components, like perfectionism and negativity emotionality, would also be a method of applying epigenetics to eating disorder research.

Researchers have looked into finding epigenetic changes associated with dopamine genes within the reward circuitry of the brain given the links between dopamine, reward responses and eating disorders (Frieling et al., 2010). For example in binge-eating disorder, genetic analysis has shown the presence of variations in genes that regulate dopamine, suggesting that individuals with binge-eating disorder are hypersensitive to rewards (Davis et al., 2012). Similar variations

in dopamine genes have been documented for bulimia nervosa and anorexia nervosa even when controlling for body weight, indicating that genetic differences in dopamine genes are related to underlying eating disorder pathology, not weight status (Groleau et al., 2012; Nisoli et al., 2007). For epigenetic research, hypermethylation of a dopaminergic gene, DAT, which is involved in transporting dopamine, was found in patients with anorexia and bulimia (Frieling et al., 2010). This epigenetic modification may be related to certain behaviors exhibited in eating disorders, such as binge eating that is present in bulimia and binge eating disorder (Davis et al., 2012). This research suggests that there are not just genetic variations, but also changes at the epigenetic level for dopaminergic genes in eating disorder populations (Davis et al., 2012; Frieling et al., 2010).

In addition to reward circuit, epigenetic research in eating disorders has examined appetite-regulating genes connected to the hormone leptin that functions to suppress appetite and control fat storage (Campbell et al., 2011). Leptin-regulating genes, such as LEP-R, have been linked to increased body weight (Heber & Carpenter, 2011). For eating disorders such as binge eating disorder or bulimia, individuals are often overweight or obese currently, while for the restrictive subtype of anorexia, individuals often have a history of being overweight (Mathisen et al., 2018; Lebow, Sim, & Kransdorf, 2015). As well, leptin is linked to development of metabolic diseases associated with obesity, such as diabetes mellitus, that have been shown to occur in binge-eating disorder and bulimia nervosa (Heber & Carpenter, 2011; Raevuori et al., 2015). For epigenetic research on leptin, a study found epigenetic modifications to a leptin-regulating gene in rodents that caused upregulation of leptin, which has been linked to obesity (Lecoutre et al., 2017). Although this study was not done in humans, rodents provide an effective model in epigenetic research for candidate genes (Rosenfeld, 2010).

Additionally, epigenetic modifications may result in psychological aspects of eating disorders such as perfectionism and negative emotionality. Although traits, like perfectionism, have been shown to have a strong genetic component, studies have not identified a specific perfectionism gene (Iranzo-Tatay et al., 2015). One study proposed one gene, the COMT gene, involved in regulating catecholamine such as dopamine, epinephrine and norepinephrine, for linking the psychological trait of perfectionism to eating disorders, although many genes are thought to be related to this psychological trait (Mikołajczyk, Grzywacz, & Samochowiec, 2010). In the study, individuals with the low COMT specific genotype scored higher in scales for perfectionism (Mikołajczyk et al., 2010). This would make the COMT gene a potential gene for epigenetic research in psychological components of eating disorders since it is linked to perfectionism, a prominent psychological feature in eating disorders (Keel & Forney, 2013). Although a specific gene has not attributed to negative emotionality, polymorphisms of genes, such as monoamine oxidase A and B (MAOA and MAOB) and the serotonin transporter polymorphism (5-HTTLPR), have been associated with it (Dlugos, Palmer, & Wit, 2009; Pauli-Pott, Friedel, Hinney, & Hebebrand, 2009). Therefore, epigenetic research could explore the genetic of negative emotionality related to eating disorders. However, it is more challenging to identify genes for epigenetic studies related to eating disorders for psychological traits than physiological traits.

Conclusions and Future Directions

Conceptualizing eating disorder development through the lens of epigenetics represents a nascent view of psychological conditions focused on looking at the interplay between genetic predispositions and environmental agents. For maternal nutrition and stress, these factors can be conceptualized as a mechanism through which an environmental factor leads to epigenetic

modifications that play a role in the development of an eating disorder later in life. In addition, as an adult, epigenetic modifications of one's genes can be seen to translate into changed behavior, related to reward response, eating, or psychological functioning that may contribute to one's eating disorder. In this way, epigenetic modifications can be associated with behaviors related to eating disorders, such as intense dieting or preoccupation with food.

Although these two mechanisms of epigenetic effect represent novel ways of thinking of this form of psychopathology, there are some limitations. Many of these epigenetic studies have been on animal models, such as rats, raising questions of generalizability for humans. However, some animal studies (e.g. raising rats in an environment with low maternal care) would not be ethically possible for humans, so this may be the only way to look at causal associations of epigenetic modifications. Another limitation is seen in applying epigenetics to psychological disorders. As opposed to more biologically-based diseases, such as cancer, psychological disorders are more complex with an interplay of biological, social and psychological elements that may need to addressed in treatment, making finding genes to target for epigenetic interventions difficult. Although this is true, eating disorders are a form of psychological disorder with strong physiological components related to nutrition and physiological mechanisms for appetite regulation making it a good candidate form of psychopathology to study within an epigenetic context.

From this model of eating disorders, epigenetics can be used to look to treatment options for the future. Many epigenetics changes have been shown to be reversible with drugs that can alter methylation or acetylation patterns (Weaver et al., 2004). This idea could be used in future treatment interventions to reverse epigenetic changes that occurred early in life that could contribute to the maintenance of an eating disorder. Even though current research has only

looked at pharmacological agents' for reversing epigenetic changes, talk therapy could represent a future direction in reversing epigenetic changes possibly in the context of eating disorder treatment (Stefanska & MacEwan, 2015). Viewing eating disorders, and psychological disorders, from an epigenetic lens would completely restructure the types of pharmacological interventions used to target psychological disorders, targeting the cause at the genome level, instead of altering brain chemicals (Kular & Kular, 2018). Additionally, studies have shown that psychotherapy can change neurotransmitters levels and overall brain functioning, which could, in turn, reverse epigenetic changes related to production of neurotransmitters in these regions (Yoshimura et al., 2014; Cervenka et al., 2012). In this way, talk therapy could be targeted at the epigenome level as well. All in all, pharmacological treatment and talk therapy targeted to reversing epigenetic modifications in genes linked to psychological disorders, such as eating disorders, represents novel future treatment approaches.

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