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FROM FAMILY SURROUNDINGS TO INTESTINAL FLORA, A LITERATURE REVIEW CONCERNING EPIGENETIC PROCESSES IN PSYCHIATRIC DISORDERS

Thomas Dubois, Christine Reynaert, Denis Jacques, Brice Lepiece & Nicolas Zdanowicz

Université Catholique de Louvain, Psychosomatic Department, Mont-Godinne University Hospital, Yvoir, Belgium

SUMMARY

Background: *Some behaviors or psychiatric conditions seem to be inherited from parents or explain by family environment. We hypothesized interactions between epigenetic processes, inflammatory response and gut microbiota with family surroundings or environmental characteristics.*

Subjects and methods: *We searched in literature interactions between epigenetic processes and psychiatric disorders with a special interest for environmental factors such as traumatic or stress events, family relationships and also gut microbiota. We searched on Pubmed, PsycINFO, PsycARTICLES and Sciencedirect articles with the keywords psychiatric disorders, epigenome, microbiome and family relationships.*

Results: *Some gene polymorphisms interact with negative environment and lead to psychiatric disorders. Negative environment is correlated with different epigenetic modifications in genes implicated in mental health. Gut microbiota diversity affect host epigenetic. Animal studies showed evidences for a transgenerational transmission of epigenetic characteristics.*

Conclusions: *Our findings support the hypothesis that epigenetic mediate gene-environment interactions and psychiatric disorders. Several environmental characteristics such as traumatic life events, family adversity, psychological stress or internal environment such as gut microbiota diversity and diet showed an impact on epigenetic. These epigenetic modifications are also correlated with neurophysiological, inflammatory or hypothalamic-pituitary-adrenal axis dysregulations.*

Key words: *disorders - epigenome - microbiome - family*

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INTRODUCTION

We often observe in clinical practice that some behaviors or in varying degrees, psychiatric symptoms are inherited from parents or explain by specific environment. But we know how is complex to exactly understand mechanisms behind this transmission. These appear to have multifactorial etiologies and result most of the time in interactions between genetic and environmental factors. All along the precedent decade, researches concerning epigenetic processes in diseases increased in medical literature. Moreover, evidences concerning impact of immune system and gut microbiota in psychiatric disorders pathophysiology became more and more significant. We highlighted these relations in two previous reviews. In this one, we hypothesized interactions between epigenetic characteristics, inflammatory processes and gut microbiota with environmental settings in which someone lives and grew up.

SUBJECTS AND METHODS

We searched in the literature interactions between epigenetic processes and psychiatric disorders with special interest for environmental but also individual factors which could have an impact on this relation. We search on Pubmed, PsycINFO, PsycARTICLES and Sciencedirect articles with the keywords psychiatric disorders, epigenome, microbiome and family relationships. We compared studies with different methodology and probably induce interpretation bias. We have as much as possible promoted recent literature (2015 to early 2020) and large cohort study or meta-analysis. But for a better understanding and to answer the questions asked, we also looked for other more specific and sometimes with a lower statistical significance studies. Animal and human studies are in our scope.

RESULTS

Heritability and gene-environment interactions in psychiatric disorders

Heritability (rate of the variability in a trait in a population due to genetic variation) in psychiatric disorders is well documented in large twins or family studies. For schizophrenia and bipolar disorder, results are similar and around 60 to 80% (Lichtenstein et al. 2009). For major depressive disorder approximately 40% is found (Kendler et al. 2006). In this manner, heritability in most psychiatric disorders is estimated to be moderate to high. However, these results are smaller in molecular genetic studies excluding environmental factors shared within a family in twin-based studies and so attributed to genetic heritability while in molecular studies individuals are unrelated (Smoller 2016). Furthermore, strong contribution of environmental factors to mental disorders is found. Stressful life events in adulthood is well known to contribute to mental health conditions such as major depressive disorder. Prenatal events such as inadequate nutrition, infection or stress

(Van den Bergh et al. 2017) are associated with development of psychiatric disorders in adulthood such as schizophrenia or psychotic disorders. Childhood and adolescence are also a vulnerable period. Maltreatment, psychosocial stressors or drug use are showed to be risk factors for developing psychiatric disorder later in life (Teicher & Samson 2013). Such a combination between high heritability and strong environmental factors suggest a synergy between genetic and environment in psychiatric disorders (Uher, 2014). Molecular genetic studies and genome-wide association studies (GWAS) try to understand which genes are involved in mental disease. First, they found several variants such as single-nucleotide polymorphisms (SNPs) in genome of people with psychiatric disorders. However, these SNPs are scattered all over the genome involving a plethora of genes coding for a wide range of processes involved in neurotransmitters metabolism, neuroendocrine or immune functions. So, it seems that psychiatric disorders are polygenic and depend on several genes' polymorphisms (Smoller 2016). Interestingly, specific gene polymorphisms (SNPs) and environment interactions are found to play a role in mental diseases. For example, there is evidences that specific polymorphisms in the brain-derived neurotrophic factor (BDNF) gene may interact with stressful life events or childhood maltreatment and lead to depression later in life (Zhao et al. 2018). We also found strong evidences of interactions between specific FKBP5 gene polymorphisms (FKBP5 protein decrease the affinity of the glucocorticoid receptor and have a role in hypothalamic-pituitary-adrenal axis regulation) and early-life stress as a significant risk factor for major depressive disorder (MDD) or post-traumatic stress disorder (PTSD) (Wang et al. 2018).

Epigenetic processes mediate gene-environment interactions and psychiatric disorders

Interactions between gene and environment seem to be mediated by epigenetic ("on top of" genetic) processes. They consist of DNA methylations or histone (proteins around which DNA is wrapped) modifications in order to regulate the accessibility of specific DNA regions to transcription factors and allow to adapt genomic expression to the ever-changing environment (Liu et al. 2008). MicroRNA (miRNA), small non-coding RNA molecules have more recently been highlighted in post-transcriptional regulation of gene expression and also seems to be involved in psychiatric disorders (Roy et al. 2020). We found that patients with an history of maltreatment or adversities during childhood have different epigenetic profiles compared to patients without these early life events. For example, Mehta et al. found higher epigenetic modifications in patients with PTSD and childhood maltreatment than in patient with PTSD but no maltreatment during childhood (Mehta et al. 2013). Abdolmaleky et al. highlighted the fact that DNA methylations, histone modifications or miRNAs dysregulations are found in postmortem brain or blood cells of patients with psychotic or autism-spectrum disorders (Abdolmaleky et al. 2015). Several other studies focused on specific gene involved in central nervous system or neuroendocrine physiology. We found several evidences that childhood maltreatment or early life adversities are related to increase DNA methylations within the promoter of NR3C1 gene coding for glucocorticoid receptor (GR) resulting in a lower NR3C1 gene expression. These studies also observed a decrease of GR across several human tissues such as postmortem hippocampal, peripheral blood or saliva and also variabilities in cortisol reactivity (Farell et al. 2018, McGowan et al. 2009, Parent et al. 2017, Perroud et al. 2011). Several studies found that methylation of NR3C1gene is associated with behavior problems during childhood or early life (Parade et al. 2016) and also with psychopathology such as MDD (Farell et al. 2018) or borderline personality disorder (Perroud et al. 2011) in adulthood. Inversely, according some studies, PTSD would be rather associated with hypomethylation and so an higher NR3C1 gene expression (Yehuda et al. 2015). We found only one longitudinal study and this one showed that hypermethylation due to maltreatment decrease at 6-month follow-up (Parent et al. 2017). However, other studies found a positive association between degree of methylation and the repetition or severity of the traumatic event in individuals with MDD or borderline personality disorder (Farell et al. 2018, Perroud et al. 2011, Radtke et al. 2015). Radtke et al. (Radtke et al. 2015) showed an increased vulnerability to develop psychopathology if childhood maltreatment is combined with increased NR3C1 methylation. Tozzi et al. found that depressive patients with specific FKBP5 gene polymorphism and childhood maltreatment or chronic stress early in life have lower methylation of this gene. They demonstrated that lower methylation of FKBP5 is associated with structural and functional changes in brain relevant area in MDD (Tozzi et al. 2018). Other epigenetic studies focused on neurotransmitter physiology and especially the monoaminergic system. It seem that negative life events are associated with DNA hypermethylation within the serotonin transporter (SERT) gene (Ouellet-Morin et al. 2013) and DNA hypomethylation within the monoamine oxidase A (MAOA) gene (Domschke et al. 2012). Unfortunately, as discussed below, there is some limitations impacting interpretations of these studies (Watkeys et al. 2018).

Gut microbiota and epigenetic alterations in psychiatric disorder

We found that gut microbiota diversity can affect host epigenetic and gene expression in various cells such as epithelial or immune cells. It seems that short-chain fatty acid (SCFA) such as butyrate which is commonly produced by bacteria have a role both in DNA methylation and histone modifications (Alam et al.

2017). Impact of diet and gut microbiota on epigenetic alterations have also a broad range of evidences in the physiopathology of obesity, diabetes or chronic bowel diseases (D'Aquilla et al. 2020). But to our knowledge, only one study demonstrated a direct interaction between gut microbiota diversity and epigenetic alterations in psychiatric disorders. Bengesser et al. (Bengesser et al. 2019) showed a correlation between methylation status of the clock gene ARNTL and gut microbiome diversity in bipolar disorder. This gene encodes for a transcription factor interacting with MAOA gene expression, itself coding for the monoamine oxidase A (implies in neurotransmitters degradation). It seems that changes in ARNTL gene expression may influence neurotransmitters such as serotonin, noradrenaline or dopamine levels and mood swings in bipolar disorder (Bengesser et al. 2016).

Transgenerational transmission in psychiatry and epigenetic mechanisms

Studies concerning war veterans or evacuees suggest that effects of traumatic stress can be transmitted to subsequent generation. Even when they are not exposed to traumatic events, significantly higher risk for mental health problems are observed in offspring (Santavirta et al. 2018, Selimbasic et al. 2017). Moreover, parental care seems to be a strong determinant for psychopathology transgenerational inheritance. Infurna et al. found that low maternal care and high paternal stress are associated with borderline personality disorder in daughters (Infurna et al. 2016). Evidences are not sufficient to understand if epigenetic mechanisms are involved in human psychopathology transmission but several evidences are found in animal studies. It seems that germline especially sperm cells are sensitive to environmental factors such as traumatic stress. But also to endocrine or immune factors such as cytokines implicated in stress physiology (Jawaid et al. 2018). It seems that sperm cells epigenetic data are not entirely erased during gametogenesis (Rodriguez et al. 2019). Gapp et al. observed that fertilized oocytes with sperm miRNAs from traumatized males reproduce the same behavioral alterations in the offspring (Gapp et al. 2014). Similar NR3C2 methylations are observed both in mice sperm cells and in the brain of their offspring (Jawaid et al. 2018).

DISCUSSION

Heritability in psychiatric disorders seems to be moderate to high but overestimated in twins or family studies because an impact of environment in transmission. This strong interaction between environment and mental health is well demonstrated in several studies and in general practice. Molecular genetic studies corroborate synergy between genetic characteristics and environmental conditions. Genetic polymorphisms cannot explain, by themselves, psychiatric disorder just like environment conditions alone cannot explain it. It seems that a specific psychiatric disorder could be associated with a plethora of gene polymorphisms in a large variety of genes having a role in immune, endocrine or neurochemical processes. Inversely, it seems that a same polymorphism is represented in several psychiatric disorders. We showed correlations between specific gene polymorphisms and some life events leading to psychiatry disorders such as depressive disorder or post-traumatic stress disorder. This underlines the importance of gene-environment interactions and the fact that psychiatric disorders definitely cannot be only predicted by genes.

How to explain that episodic life events may impact the permanent genetic code (except in rare cases of mutation) and lead to psychiatric conditions with varying evolution over time?

It refers to modifications of the genome that don't change DNA sequences but rather the expression of the genome. Interactions between genetic and environment seem to be mediated by epigenetic ("on top of" genetic) processes. Throughout several evidences we found that early-life events such as adversities or maltreatment could leave marks in epigenetic profile later in life. These epigenetic marks especially DNA methylations are found on several genes known to be involved in psychopathology. They could have an impact on the glucocorticoid receptor but also on serotonin transporter or monoamine oxidase A genes expression. They could be correlate with variabilities in some physiological processes implicated in mental health and stress response such as hypothalamic-pituitary-adrenal (HPA) axis reactivity. Finally, some studies showed that these marks acquired in childhood could be involved in some behavior problems but also in psychopathology later in life. These results are very interesting and seem to confirm the role of epigenetic processes between genetic-environment interactions and psychiatric conditions. Unfortunately, we have to note in studies a lack of consistency. While epigenetic processes are highly tissue and cell-type specific, various cells population are used in these studies. Interpretations greatly depends on the similarity between peripheral cells (saliva, blood cells, etc.) and cells involved in psychiatric disorders physiopathology. Epigenetic is a complex process and genes have several possible targets for epigenetic modifications with different consequences. Given methodology, sample characteristics or laboratory technics variabilities comparisons have to be treated with caution. However, these results open a new field of evidences and should promote to more consistent studies in future.

We showed in a precedent review (Dubois et al. 2019) a large amount of evidences concerning correlations between gut microbiota diversity and psychiatric disorders such as mood disorders, schizophrenia or autism-spectrum disorder. Gut microbiota diversity is

associated with diverse environmental factors such as diet, medication or psychological stress.

We highlighted interactions between gut and brain via various bacterial secretions such as short-chain fatty acid (SCFA) and their abilities to cross the blood-brain barriers (BBB) and having neuroactive properties. Increased gut permeability called "leaky gut" following by chronic inflammatory response and especially cytokines secretion in gut wall are also implicated in mental health (Dubois et al. 2018). Moreover, in this review we pointed out that host epigenetic alterations could be generate by microbiota. Several studies out of our scope demonstrated this fact in obesity or diseases such as diabetes or inflammatory bowel disease. It is interesting to note that SFCA seem to be an important mediator by which bacteria affect host epigenome. These studies showed epigenetic modifications in genes coding for immune or endocrine factors. Indirectly, these observations allow to support the possible role of gut microbiota in epigenetic processes implicated in pathogenesis of mental disorders. Unfortunately, there is a lack of studies demonstrating a direct correlation between gut microbiota, epigenetic and psychiatric disorder.

So, epigenetic could be a mediator between early-life events and psychiatric disorders but psychiatric disorders happened without direct adversities or maltreatment in childhood. We observe in general practice and mainly in systemic or family therapy that the one who has experienced a trauma is not always the one who will develop a psychopathology and next generations are sometimes impacted. Unfortunately we don't found sufficient evidences in human to conclude a role of epigenetic processes in transgenerational transmission of traumatism and stress. It is important to note that this hypothetical transgenerational transmission requires that germ cells epigenome can be affected by life events. But we know that male and female germ cells are sheltered behind complex barriers such as blood-testis barrier or ovarian follicular cells and ovarian stroma. However, it is well known that these cells are sensitive and have receptors for hormones or other factors such as cytokines. We showed that endocrine factors and especially immune factors such as cytokines are involved in stress pathway and are easily transportable through both brain or testis blood barriers.

CONCLUSIONS

Following this review we hypothesize that epigenetic mediates the interactions between genetic and environment in psychiatric disorders (Figure 1).

Epigenetic processes seem to be impacted by several environmental characteristics such as traumatic life events, family adversity, psychological stress or internal environment such as gut microbiota diversity and diet. Several epigenetic modifications are involved in neurophysiological changes, inflammatory response, HPA axis activity and glucocorticoid receptor resistance well known in psychopathology.

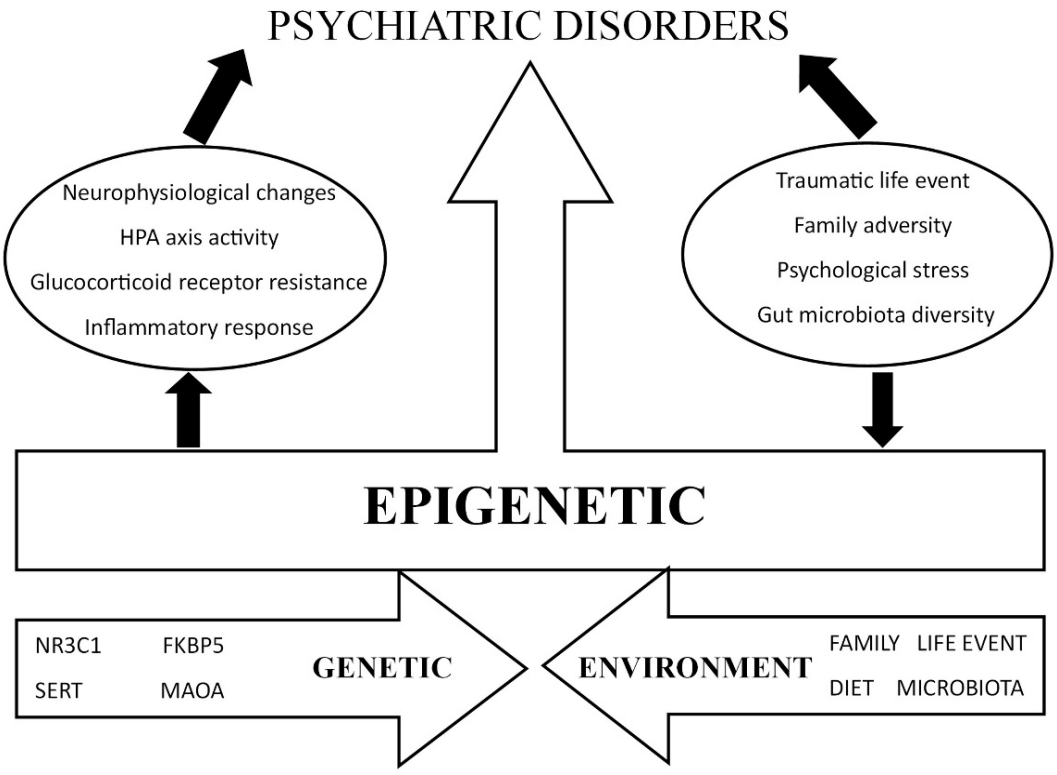

Figure 1. Hypothetical model describing the role of epigenetic as mediator between gene-environment interactions and psychiatric disorder

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Thomas Dubois, Christine Reynaert, Denis Jacques, Brice Lepiece & Nicolas Zdanowicz all made substantial contributions to conception and design and or acquisition of data and/or analysis and/or interpretation of data.

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Correspondence:
Dubois Thomas, MD
Université Catholique de Louvain, Psychosomatic Department,
Mont-Godinne University Hospital
Avenue Dr G. Therasse, 1, B-5530 Yvoir, Belgium
E-mail: thomas.g.dubois@uclouvain.be