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Targeting aggression in severe mental illness: The predictive role of genetic, epigenetic, and metabolomic markers

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ABSTRACT

Human aggression is a complex and widespread social behavior that is overrepresented in individuals affected by severe mental illness (SMI), such as schizophrenia (SCZ), bipolar disorder (BD), autism spectrum disorder (ASD), and attention-deficit/hyperactivity disorder (ADHD). A substantial proportion of the liability threshold for aggressive behavior is determined by genetic factors, and environmental moderators might precipitate the manifestation of this behavioral phenotype through modification of gene expression via the epigenetic machinery. These specific alterations in the genetic and epigenetic make-up of aggressive individuals might determine distinct biochemical signatures detectable through metabolomics. An additional pathophysiological component playing a role in aggressive behavior might be determined by alterations of gut microbiota. Here, we present a selective review of human data on genetic, epigenetic, and metabolomic markers of aggressive behavior in SMI, discussing also the available evidence on the role of microbiome alterations. Clinical implication of these evidences, as well as future perspectives, will be discussed.

1. Introduction

Human aggression and violence are complex and widespread social behaviors (Siever, 2008). According to the World Health Organization (WHO) violence/aggression is among the leading causes of death worldwide for people aged 15–44 (World Health Organization, 2002), determining a substantial economic burden on the healthcare system (World Health Organization, 2002). In presenting key measures (incidence, prevalence, predicting power of trait-associated clinical, genetic/epigenetic, and metabolomic variables) of behavioral phenotypes such as violence or aggression, definitions matter. Although some authors suggest that violence might be a specific form of aggression (Valzelli, 1982), the vast majority of researchers in the field consider the two terms interchangeable, at least with regard to human behavior (Volavka, 2002). Since we elected to review data collected in human samples, we will henceforth use aggression (or aggressive behavior) to indicate both terms.

One key aspect of human aggression is that tends to be overrepresented in individuals affected by severe mental illness (SMI), particularly schizophrenia (SCZ), bipolar disorder (BD), autism spectrum disorder (ASD), and attention-deficit/hyperactivity disorder (ADHD), compared to unaffected populations (Pulay et al., 2008). Several sets of epidemiological findings support the latter association. Patients affected by SMI commit 1 in 20 violent crimes (Fazel and Grann, 2006). This figure is consistent with the higher risk of homicidal violence found in SMI patients compared to unaffected subjects (Eronen et al., 1996). Furthermore, individuals hospitalized in psychiatric wards have an higher risk of committing a criminal offense compared to subjects with no history of psychiatric admission (Hodgins et al., 1996). And rates of aggression in SMI patients might range from 26% to 84% (Tsiouris et al., 2011).

Undoubtedly, the prevalence of aggressive behavior varies depending on the specific SMI considered. Epidemiological estimates show that the rates of aggressive behaviors might range from 5.7% in ADHD (Gonzalez et al., 2013), 13.9% in male SCZ patients (Fazel et al., 2014), 25% in BD type 1 (Pulay et al., 2008), to reach 68% in ASD (Kanne and Mazurek, 2011). Although impacted by the lack of uniformity in the methodology used for the identification of aggressive behavior (i.e. retrospective self-reported information versus prospective data collection based on structured assessment tools), these figures show unequivocally a substantial raise compared to the rates observed in unaffected populations. Several mediating mechanisms, such as comorbid substance abuse, presence of childhood trauma, poor coping/stress, and behavioral instability, might partly explain the relationship between

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aggression and SMI (Edlinger et al., 2014;Bruce and Laporte, 2015;Coid et al., 2015). Indeed, Edlinger et al. (2014) found that SCZ patients with comorbid psychoactive substance use admitted to acute inpatient units had the highest risk of aggressive behavior compared to patients with affective disorders. Bruce and Laporte (2015) found that SMI patients with history of child trauma had significantly higher odds of engaging in aggressive behaviors compared to those without such history. Finally, Coid et al. (2015) found that violent ideation, behavioral instability, and poor/coping stress were all explanatory variables of the association between aggression and SMI.

1.1. Developmental trajectories of aggression in SMI

The manifestation of aggression in SMI appears to have developmental trajectories specific to each disorder. For instance, SCZ individuals might manifest aggressive behaviors in the context of acute psychopathological dysregulation such as command hallucinations to harm others or paranoid delusions (state-related precipitating factors) (Volavka, 2013; Darrell-Berry et al., 2016). Alternatively, conditions related to personality traits anteceding the onset of psychiatric disorders (particularly BD and ADHD, but also SCZ), such as antisocial conduct disorder, might significantly increase the risk of developing aggressive behavior (Volavka, 2013; Swanson et al., 2008; Gudjonsson et al., 2014; Swann et al., 2011). Both state- and trait- related factors might modulate the liability threshold for the development of aggressive behavior set by the genetic and epigenetic risk components. Indeed, environmental factors can determine modification of the encoded genetic information, by altering gene expression regulatory machinery through epigenetic factors (Fig. 1). State- and trait- related factors are also modulated by these mechanisms, suggesting a constant longitudinal modulation of the liability threshold for the development of aggressive behavior.

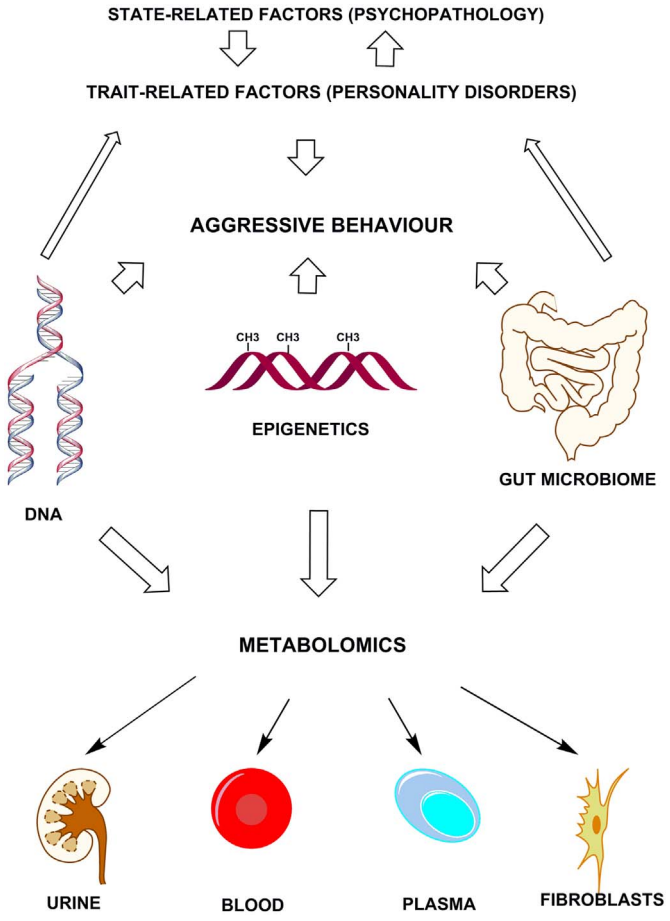

Fig. 1. Representation of the interplay of genetic, epigenetic, and microbiomic factors in aggressive behavior, and role of metabolomics in identifying trait-related biomarkers.

1.2. Genetic and epigenetic of aggressive behavior

A substantial proportion of the liability threshold for aggressive behavior is determined by genetic factors in the general population. Large longitudinal twin studies have shown a heritability of 50% to 80% for this behavioral trait (Porsch et al., 2016). Consistently, molecular genetic data using genome-wide complex trait analyses (GCTA) found that common genetic variation explains 10% to 54% of phenotypic variation in aggressive behavior in children, with the most significant genome-wide association signal on chromosome 2p12 (Pappa et al., 2016). Twin studies have also shown that shared environment might explain up to 20% of the phenotypic variation in aggression (Porsch et al., 2016). As introduced previously, environmental moderators might modulate the liability to aggressive behavior determined by genetic factors during the longitudinal developmental trajectory starting from toddlerhood to adolescence (Nantel-Vivier et al., 2014; Hay et al., 2014;Tremblay et al., 2004; Cote et al., 2006). It is plausible that these environmental moderators, by acting on this considerable genetic liability, might facilitate the manifestation of the behavioral phenotype. Importantly, the exposure to these moderators might happen before birth (Tremblay and Szyf, 2010). In fact, it has been established that having a mother with early onset antisocial behavior is a potent predictor of high levels of physical aggression in children assessed longitudinally from birth to 42 months of age (Tremblay et al., 2004). Similarly, factors such as low income, presence of mothers who smoked during pregnancy, mothers' coercive parenting behavior, and family dysfunction predict the manifestation of aggressive behavior in children (Tremblay et al., 2004). As shown in Fig. 1, this moderation might be exerted through the epigenetic machinery. Of note, specific epigenetic signatures of peripheral white blood cells seem to correlate with the manifestation of physical aggression during childhood (Wang et al., 2012). And recent epigenome-wide analysis in peripheral white blood cells of a large twin sample showed a positive relationship between DNA methylation levels and aggressive behavior near the trichorhinophalangeal synrome I (*TRPS1*) gene on chromosome 8 and between the non-coding RNA PARD6G antisense RNA 1 (*PARD6G-AS1*) and the activity-dependent neuroprotective protein 2 gene (*ADNP2*) on chromosome 18 (van Dongen et al., 2015).

These specific alterations in the genetic and epigenetic make-up of aggressive individuals might determine distinct alterations in the physiological pathways of the Peripheral and Central Nervous System (PNS and CNS) regulating behavioral control.

1.3. Detection of biochemical signals of aggressive behavior

One crucial issue in the study of complex traits such as psychiatric disorders or behavioral phenotypes is the detection of biological signals that might predate the manifestation of symptoms, and consequently help enabling preventive strategies. Biochemical signatures of illness-associated alterations in CNS and PNS might be detected through the analysis of peripheral set of metabolites (metabolome) (Hagenbeek et al., 2016). A recent data synthesis has shown that biochemical markers, such as inflammation markers, neurotransmitters, lipoproteins, and hormones of various classes, are significantly altered in individuals with aggressive behavior (Hagenbeek et al., 2016). It is conceivable that the joint analysis of genetic, epigenetic, and metabolomic data might help refining the prediction of aggressive behavior particularly in at risk populations such as those affected by SMI.

One final introductory remark concerns the hypothesis that an additional pathophysiological component playing a role in aggressive behavior might be determined by distinct alteration of gut microbiota. It is well established that intestinal microbiota and the brain are