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Modification of the association between antipsychotic treatment response and childhood adversity by *MMP9* gene variants in a first-episode schizophrenia cohort

Nathaniel McGregor[a,*], Nicole Thompson[a], Kevin Sean O'Connell[a], Robin Emsley[b], Lize van der Merwe[a,c], Louise Warnich[a]

[a] Systems Genetics Working Group, Department of Genetics, Faculty of AgriSciences, Stellenbosch University, Stellenbosch 7600, South Africa
[b] Department of Psychiatry, Faculty of Medicine and Health Sciences; Tygerberg Medical Campus, Stellenbosch University, Tygerberg 7505, South Africa
[c] Department of Genetics, Faculty of AgriSciences, Stellenbosch University, Stellenbosch 7600, South Africa

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ABSTRACT

Antipsychotics remain the most effective, and wide used option for ameliorating the symptoms of schizophrenia. However, inter-individual differences in treatment outcome are vast and suggest a role for genetic and environmental factors in affording favourable outcomes. A notable epigenetic relationship which has gained considerable traction in recent literature is the way in which the severity of childhood trauma can modify associations seen between genetic variation and antipsychotic treatment response. A potential mechanism of action which may facilitate this relationship is synaptic plasticity. This study investigated the role of variants in *matrix metallopeptidase 9* (*MMP9*), a gene involved in synaptic plasticity, with treatment outcome considering the severity of childhood trauma as an interacting variable. The cohort comprised South African first episode schizophrenia patients treated with a single injectable antipsychotic, flupenthixol decanoate, monitored over 12 months. Relationships between novel and previously described variants, and haplotypes, with antipsychotic treatment response were found to be modified when considering childhood trauma as an interacting variable. This study provides the first evidence for the involvement of polymorphisms within *MMP9* and the severity of childhood trauma in antipsychotic treatment response, and warrants further investigation into the role gene-environment interactions may play in the betterment of antipsychotic treatment strategies.

1. Introduction

Schizophrenia is a chronic, multifactorial and debilitating psychiatric disorder with an approximate prevalence of 1% worldwide (Bakhshi and Chance, 2015; Escudero and Johnstone, 2014; Wyatt et al., 1988). Antipsychotics remain the most effective, and widely used, option for ameliorating the symptoms of schizophrenia but only prove to be effective in approximately 50% of cases (McIlwain et al., 2011; Owen et al., 2016). Recently, traction has been gained for the role factors other than genetic variation play in treatment response, *viz* the environment (Albus, 2012; Drögemöller et al., 2013; Foster et al., 2010; Li et al., 2015; Owen et al., 2016). The most notable of these is the ability of childhood adversity to modify the associations seen between genetic variation and antipsychotic treatment response (Hassan and De Luca, 2015).

Individuals with a history of childhood trauma have been reported to be at three times greater risk for developing psychosis (Davis et al., 2016; Sahin et al., 2013; Varese et al., 2012), and childhood adversity has previously been implicated in the variability of treatment response (Hassan and De Luca, 2015; Hovens et al., 2012; Lochner et al., 2002; Rajkumar, 2015). Generally, the higher the severity of childhood trauma reported, the more severe the symptoms of schizophrenia observed (Braehler et al., 2013; Davis et al., 2016; Sahin et al., 2013). Specifically, sexual abuse has been positively correlated with positive symptom domains in schizophrenia (Chae et al., 2015). When focusing specifically on treatment outcome, studies have reported higher severities of childhood trauma in treatment refractory schizophrenia cases (Hassan and De Luca, 2015) and a history of childhood trauma has been reported to be more frequent in non-responders (Misiak and Frydecka, 2016).

The precise mechanisms of action whereby early adversity may influence treatment response remains incompletely understood, however, one hypothesis is that synaptic plasticity may be involved (Hassan and De Luca, 2015; Koga et al., 2017; McGregor, 2013; Misiak and

* Correspondence to: Department of Genetics, Faculty AgriSciences, Stellenbosch University, Stellenbosch 7600, South Africa.
E-mail address: nwm@sun.ac.za (N. McGregor).

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Frydecka, 2016). Plasticity refers to the ability of the neural activity generated by an experience to modify neural circuit functioning, ultimately leading to the modification of thoughts, feelings and behaviour (Citri and Malenka, 2008). Subsequently, synaptic plasticity is the ability of the brain to incorporate experiences as persistent memory traces by activity-dependent modification, and is extensively involved in early neural circuitry development (Citri and Malenka, 2008; McGregor, 2013). It has been reported that major life events, such as early childhood adversity, can alter the regular plasticity mechanisms thereby contributing to both the development and progression of neuropsychiatric disorders. This may also explain the variability observed in antipsychotic treatment outcomes (Bartolomeis et al., 2015; Citri and Malenka, 2008; Hall et al., 2015; Hassan and De Luca, 2015; Koga et al., 2017; Lepeta and Kaczmarek, 2015; McGregor, 2013; Misiak and Frydecka, 2016; Waltereit et al., 2014).

The MMP9 protein represents a core element involved in synaptic plasticity, learning and memory. MMP9 is part of the matrix metalloproteases (MMPs), a large family of zinc-dependent extracellularly acting endopeptidases (Rybakowski, 2009), which play a role in the degradation of extracellular matrix constituents, domains and growth factors (Lepeta and Kaczmarek, 2015). By doing so, they allow for synaptic and circuit level reorganization (Reinhard et al., 2015). Growing evidence suggests that *MMP9*, and polymorphisms therein, may play a role in the pathogenesis of schizophrenia and antipsychotic treatment response (Yamamori et al., 2013)).

Due to the proposed involvement of *MMP9* in synaptic plasticity, the implication of synaptic plasticity in modulating schizophrenia treatment outcome, and the potential modification of this by the severity of childhood adversity, it may be beneficial to investigate the possible role of variants in *MMP9* in antipsychotic treatment response considering the severity of childhood trauma as an interacting variable. Therefore, this study aimed to investigate the association of previously described and novel variants in *MMP9* with antipsychotic treatment response in a cohort of 103 South African first episode schizophrenia (FES) patients for which a history of trauma is known.

2. Methods

2.1. Patient samples

A cohort of 103 unrelated, previously drug naïve, South African first-episode schizophrenia (FES) patients were used in this study. The cohort comprised 82 South African Mixed Ancestry (MA), 13 Xhosa and eight Caucasian individuals all of whom were recruited from Stikland Hospital, in the Western Cape (Drögemöller et al., 2014). Patients were administered with a single injectable first generation antipsychotic (FGA), flupenthixol decanoate, every two weeks for 12 months. During this time, individuals were clinically assessed at nine time intervals, fortnightly, for six weeks and every three months thereafter. Clinical data and demographic information (gender, age and ethnicity) was obtained for all of the patients (Chiliza et al., 2015a; Chiliza et al., 2015b; Drögemöller et al., 2014). To correct for population stratification, 100 ancestry informative markers (AIMs), designed specifically for the South African Mixed-Ancestry (MA) population, were available for the study (Drögemöller et al., 2016). Written and informed consent was obtained from patients or their caregivers. Ethical approval was obtained from the Human Research and Ethics Committee (HREC), Faculty of Health Sciences, University of Stellenbosch (Clinical: N06/08/148; Genetics: 1907/005).

2.2. Clinical instruments

2.2.1. PANSS

The Positive and Negative Syndrome Scale (PANSS) is commonly used to measure the diverse psychopathology of schizophrenia, including positive, negative and general symptom domains (Kay et al., 1987). The scale comprises 30-items using ratings 1 (absent) to 7 (extreme) providing an indication of symptom severity, which is highly variable between individuals (Albus, 2012; Joyce and Roiser, 2007; Owen et al., 2016; van Os and Kapur, 2009). Observing the change in PANSS scores over time was used to assess antipsychotic treatment response and drug efficacy (Chiliza et al., 2015a; Chiliza et al., 2015b).

2.2.2. Childhood Trauma Questionnaire

The Childhood Trauma Questionnaire (CTQ) (Bernstein et al., 1997) was used to assess the severity and type of childhood trauma. CTQ scores were obtained for a subset of the FES patients (n = 75). Five subscales *viz* emotional abuse, emotional neglect, physical abuse, physical neglect and sexual abuse were considered during assessments. Each subscale total score was subsequently totalled to represent the overall perceived trauma (CTQ overall score). Additionally, a minimization/denial scale is incorporated which is indicative of underreporting or misrepresentation of maltreatment.

2.3. DNA extraction

DNA samples for all FES patients were available for this study (Drögemöller et al., 2014).

2.4. Polymorphism selection

The Human Gene Mutation Database (HGMD) (http://www.hgmd.cf.ac.uk/ac/index.php, PharmacoGenomic Mutation Database (PGMD) (https://www.qiagenbioinformatics.com/products/pgmd/), PharmGKB (https://www.pharmgkb.org), SNPedia (https://www.snpedia.com) and a literature search were used to identify functionally relevant variants in *MMP9*. For the latter, a search was conducted using the key words “schizophrenia”, “susceptibility”, “treatment response”, “refractory”, “pharmacogenetics/genomics”, “adverse drug reactions” and “*MMP9*” in PubMed (https://www.ncbi.nlm.nih.gov/pubmed) and Elsevier Science Direct (https://www.elsevier.com/solutions/sciencedirect).

2.5. Data mining and prioritization

A TagSNP approach (LD TAG SNP Selection, National Institute of Environmental Health Sciences, http://snpinfo.niehs.nih.gov/snpinfo/snptag.php, (Xu and Taylor, 2009) was used to prioritize variants spanning *MMP9* with the HapMap and dbSNP (https://www.ncbi.nlm.nih.gov/snp, (Sherry et al., 2001) databases considering African, European, Asian, Nigerian and Kenyan populations. Considering haplotype analyses, R^2 values were calculated using a linkage disequilibrium (LD) threshold of 0.8, a maximum distance between single nucleotide polymorphisms (SNPs) of 250 000 base pairs (bp) and a minor allele frequency (MAF) range of 0.05–0.5. Subsequent to identifying variants, the allele and genotype frequencies in the African, Asian and European populations were obtained from Ensembl (http://www.ensembl.org/, (Aken et al., 2016) and dbSNP (https://www.ncbi.nlm.nih.gov/snp, Sherry et al., 2001) and prioritized with a preference for common variants (MAF $\geq$ 0.1). Whole-exome sequence (WES) data for 11 South African mixed-ancestry (MA) patients was available and served as representative of the FES cohort (Drögemöller et al., 2014). Genome wide association study (GWAS) data was available for all 103 FES patients obtained and was generated using the Illumina HumanOmniExpressExome BeadChip (Illumina, California, USA) and analysed using PLINK v1.07 (http://pngu.mgh.harvard.edu/purcell/plink/, (Purcell et al., 2007). Quality control thresholds for GWAS were as follows: Call rate > 98%; MAF > 5%; and HWE, p > 0.001.

2.6. Genotyping

Genotyping was performed using restriction fragment length