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Haptoglobin in ultra-high risk of psychosis – Findings from the longitudinal youth at risk study (LYRIKS)

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1. Introduction

The role of immune dysregulation in mental disorders is not new and has been investigated in acute psychosis, schizophrenia, depression, bipolar disorder, and post-traumatic stress disorder (Çakici et al., 2020; Debnath et al., 2021; Karanikas et al., 2021). Smith and Maes (1995) proposed the monocyte and T-lymphocyte theory of schizophrenia, which hypothesised activation of macrophages and T-lymphocytes in psychosis (Smith and Maes, 1995). Early findings focused on measurements of protein levels of commonly studied immune markers in individuals with schizophrenia (Müller et al., 1999; Neelamekam et al., 2014). These are supported by recent reports on immune inflammatory processes in peripheral blood and brain on a larger network of immune markers, and association studies on various stages of psychosis (Maes et al., 1994, 1997; Goldsmith et al., 2016; van Kesteren et al., 2017).

While there is evidence for dysregulation of immune markers in first-episode psychosis, chronic schizophrenia, and treatment-resistance schizophrenia, only two studies reported higher plasma IL-6 levels in individuals at ultra-high risk of psychosis (UHR) and in those who converted to psychosis (Stojanovic et al., 2014; Zeni-Graiff et al., 2016). Much of the focus has been on the various cytokines with scant work done on acute phase proteins (APP) in mental disorders. Studied APP in schizophrenia include haptoglobin (Hp), fibrinogen, complement component 3, C4, alpha-1 antitrypsin, alpha-2 macroglobulin, alpha 1-acid-glycoprotein, hemopexin, and C-reactive protein (Wong et al., 1996; Maes et al., 1997; Morera et al., 2007; Wan et al., 2007; Yee et al., 2017). From the available but limited literature, these APP were understood to have anti-inflammatory properties through different mechanisms such as regulating production of cytokines and promoting DNA repair mechanisms (Gruys et al., 2005).

Hp, a positive APP member, rises in serum levels in presence of inflammation. It prevents iron loss and renal damage by binding strongly to free haemoglobin. Hp also has anti-bacterial properties and can bind to receptors on cell membranes of leukocytes (Wassell, 2000). Hp has been reported to be elevated in first-episode psychosis and schizophrenia and was associated with depression and excitement symptoms on the Positive and Negative Syndrome Scale (PANSS) (Seal and Eist, 1966; Bock et al., 1971; Maes et al., 1997; Yang et al., 2006; Wan et al., 2007; Yee et al., 2017). To date, there has been no published study on Hp in individuals at UHR, which will provide insights into the role inflammation-immune processes have on the etiopathogenesis of psychosis. The present study seeks to (1) extend findings from a previous report on elevated Hp gene expression level in first-episode psychosis into individuals at UHR (Yee et al., 2017), (2) examine the association of Hp gene expression level with symptom severity and transition to psychosis, and (3) explore Hp gene polymorphisms in UHR.

2. Materials and method

2.1. Study settings and subjects

LYRIKS was a prospective, observational study conducted in Singapore on youths aged 14 to 29 to assess risk factors for psychosis. Details of the study have been previously reported (Lee et al., 2013; Mitter et al., 2014; Lim et al., 2015). In brief, participants were recruited from psychiatric clinics, various community agencies including educational institutes and social services, or were self-referred. Participants were excluded if they (i) had a past or current history of psychosis or

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intellectual disability, (ii) were currently using illicit substances, (iii) were taking mood stabilizers, (iv) had previous antipsychotic exposure of more than 5 mg haloperidol per day for 3 weeks (or equivalent) or were on an antipsychotic at the point of recruitment, or (iv) had medical causes associated with their attenuated psychotic symptoms. Data collected at baseline and 24-month/final study visit was used for this study.

Ethics approval for this study was provided by the National Healthcare Group's Domain Specific Review Board. After complete description of the study to the participants, written informed consent was obtained.

2.2. Assessments

The Comprehensive Assessment of At-Risk Mental State (CAARMS) is a semi structured interview used to evaluate if an individual meets the UHR criteria (Yung et al., 2005). The positive symptom subscale was used, which assesses four symptom domains: Unusual Thought Content (UTC), Non-bizarre Ideas (NBI), Perceptual Abnormalities (PA), and Disorganized Speech (DS). Each symptom was rated for the maximum intensity, frequency and duration, pattern, and related distress over the last one year.

UHR positive individuals fall into one or more of the following groups: Vulnerability group (at risk of psychosis due to the combination of a trait risk factor and a significant deterioration in mental state and/or function), Attenuated Psychotic Symptoms group (APS, at risk of psychosis due to sub-threshold psychotic syndrome) and Brief Limited Intermittent Psychotic Symptoms group (BLIPS, at risk of psychosis due to a recent history of frank psychotic symptoms that resolved spontaneously within a week). CAARMS total score refers to the sum of multiples of intensity and frequency of CAARMS subscales - Unusual Thought Content (UTC), Non-Bizarre Ideas (NBI), Perceptual Abnormalities (PA), and Disorganized Speech (DS). The CAARMS interview was repeated at 6-montly intervals up to 24 months after enrolment.

Conversion to psychosis was determined if the participant fulfils CAARMS psychotic threshold criteria of at least one psychotic symptom lasting more than one week and occurring at least three times a week. Remission status was defined if an individual who met UHR criteria at baseline no longer fulfils UHR criteria at 24 months. Individuals who met UHR criteria at 24 months or had converted to psychosis were categorised as non-remitters. Therefore, individuals at UHR were categorised as remitters or non-remitters, and converters or non-converters.

The Structured Clinical Interview for DSM IV Axis I Disorders (SCID-I) was used to assess for the presence of any psychiatric disorders. This interview was performed at recruitment, and again at the end of the follow-up period or when a participant developed psychosis.

UHR participants were further assessed at recruitment and at 6-monthly intervals on the Calgary Depression Scale for Schizophrenia (CDSS) and Positive and Negative Syndrome Scale (PANSS). Global Assessment of Functioning (GAF) was assessed at recruitment.

2.3. Haptoglobin gene expression levels and genotyping

Participants who provided a blood sample were included into the present study. A sample of venous whole blood was collected from all subjects at recruitment and a follow-up visit into Tempus™ Blood RNA Tube (Thermo Fisher Scientific), and stored at −80 °C. The Tempus™ Blood RNA Tube contains stabilizing reagent, which lyses blood cells, inactivates cellular RNases and selectively precipitates RNA. Total RNA was then extracted with the Tempus™ Spin RNA Isolation Kit (Thermo Fisher Scientific) according to manufacturer's protocol. Quality and concentration of extracted RNA was measured with 2100 Bioanalyzer System (Agilent). Only samples with RNA integrity number above 9 were included in the study.

Gene expression levels were measured by quantitative PCR using Applied Biosystems' ViiA™ 7 system (Foster City, CA, USA). Pre-designed TaqMan Gene Expression Assay, Haptoglobin (Hs00978377_m1) (Applied Biosystems, Foster City, CA, USA) were used to quantify expression of Haptoglobin gene. Each sample was assayed in triplicates and was normalised to the average expression of three reference genes: Peptidylprolyl isomerase A (Hs99999904_m1), TATA box binding protein (Hs00427620_m1), and ubiquitin C (Hs00824723_m1). A second normalization against inter-run calibrator was performed to remove run-to-run difference. Relative quantitation using the $2^{\Delta\Delta}$-Ct formula which derives fold change corresponding to gene expression was performed to analyse the results obtained from all the real-time PCR runs.

Genomic DNA was extracted from whole blood. The samples were genotyped on the Illumina Infinium OmniZhongHua-8 BeadChip. Standard quality control procedures were performed in PLINK 1.9 to exclude single nucleotide polymorphisms (SNPs) with minor allele frequency <0.01, call rate <0.98, Hardy-Weinberg equilibrium p-value < 1e-06; and exclude individuals with mismatch between recorded and genotyped sex, and related individuals. Imputation was performed against the full 1000 genomes phase 3 reference panel and has been elaborated in an earlier study by Keane at al (Lim et al., 2020).

2.4. Data analysis

Data was analysed on SPSS Statistics version 23 (IBM Co., Armonk, NY, USA). Descriptive statistics were tabulated for control and UHR positive groups. Statistical significance was set at $p < 0.05$. Categorical and continuous data were analysed using chi-squared test and Mann-Whitney *U* test or Kruskal Wallis H test to compare characteristics between groups. Linear regression model was used to investigate the association between Hp gene expression level and symptom severity namely, a PANSS 5-factor model that was previously validated in our local dataset and CDSS (Lim et al., 2021). The final linear regression model included age, sex, body mass index (BMI), smoking status and use of anti-depressants, which were studied to be associated with changes in APP levels (Maes et al., 1997; Lakoski et al., 2006; Dietrich et al., 2007; Johnsen et al., 2016).

3. Results

3.1. Clinical characteristics

A total of 87 individuals at UHR and 90 healthy controls were included in this study. Characteristics of both groups are summarized in Table 1. There were no significant differences in age, sex, ethnicity, smoking status and BMI between groups. 52% of UHR individuals were on antidepressants at the time of recruitment. Seven UHR individuals converted to psychosis by the end of study period. There were no differences in clinical characteristics at baseline between these seven converters and those who did not.

3.2. Hp gene expression and genotype profiles

The UHR group was observed to have significantly higher Hp gene expression level than healthy controls at baseline (2.31 vs 1.38; $U = 2236.5$, $p = 0.002$). A comparison of baseline Hp levels between converters and individuals with UHR did not find a significant difference (2.36 vs. 1.61; $U = 152.0$, $p = 0.675$). Both remitter and non-remitter UHR groups had comparable Hp levels (2.3 vs. 2.1), which were higher than controls, but this difference did not reach statistical significance ($\chi2(3) = 3.239$, $p = 0.356$). For individuals who converted to psychosis, there was no significant change in Hp level from baseline (1.61 vs 1.44; $Z = -0.674$, $p = 0.500$).

A total of four SNPs were imputed and there was no significant difference in allele frequencies between groups (Table 2). One of the SNPs, rs3852780, was observed to be significantly associated with baseline Hp gene expression level before and after controlling for age, sex, BMI,

Table 1
- Characteristics of study samples at recruitment.

	Control (n = 90)	UHR (n = 87)	P-value
Age (years)	21.81 (4.01)	21.44 (3.52)	0.202
Sex (M, %)	34 (37.8)	21 (35.6)	0.876
Ethnicity (n, %)			0.611
Chinese	60 (66.7)	63 (72.4)	
Malay	17 (18.9)	15 (17.2)	
Indian	11 (12.2)	6 (6.9)	
Others	2 (2.2)	3 (3.4)	
Smoking (Y, %)	17 (18.9)	27 (31.0)	0.082
BMI (kg/m^2)	22.05 (3.54)	22.59 (5.22)	0.885
Antidepressants (Y, %)	0 (0)	49 (52.1)	<0.001
CAARMS total	0.98 (2.83)	24.91 (15.43)	<0.001
PANSS			
Positive	–	8.74 (2.73)	–
Negative	–	12.20 (4.67)	–
Cognitive	–	10.07 (2.78)	–
Depression		10.40 (4.25)	
Hostility		4.86 (1.54)	
CDSS	–	6.01 (5.32)	–
GAF	–	55.70 (12.20)	–
SCID-I Dx (Lifetime Prevalence and Current)			
Depressive Disorders[a]	1 (1.1)	31 (35.6)	<0.001
Anxiety Disorders[b]	2 (2.2)	30 (33.1)	<0.001
Others[c]	0 (0)	8 (9.0)	<0.001
Hp	1.38 (1.16)	2.31 (1.98)	0.002

Abbreviations: Body Mass Index (BMI); Comprehensive Assessment of At Risk Mental States (CAARMS); Global Assessment of Functioning (GAF); Structured Clinical Interview for the DSM-IV Axis I Disorders (SCID-I); Haptoglobin (Hp).

[a] Major Depressive Disorder, Dysthymic Disorder.

[b] Panic Disorder, Agoraphobia w/o History of Panic Disorder, Social Phobia, Specific Phobia, Obsessive Compulsive Disorder, Post-Traumatic Stress Disorder, Generalised Anxiety Disorder.

[c] Alcohol Dependence, Undifferentiated Somatoform Disorder, Anorexia Nervosa, Adjustment Disorder.

Table 2
- The distribution of genotypes for four polymorphisms of the Hp gene.

HP Genotypes/Group	Genotype Distribution			P-value
rs2070937	AA	AG	GG	0.362
Control	40 (54.8%)	24 (32.9%)	9 (12.3%)	
UHR	31 (44.3%)	31 (44.3%)	8 (11.4%)	
rs5473	**AA**	**AG**	**GG**	0.490
Control	73 (100%)	0	0	
UHR	69 (98.6%)	1 (1.4%)	0	
rs3852780	**AA**	**AC**	**CC**	0.534
Control	65 (89.0%)	9 (11.0%)	0	
UHR	63 (90.0%)	6 (8.6%)	1 (1.4%)	
rs470428	**AA**	**AG**	**GG**	–
Control	73 (100)	0	0	
UHR	70 (100)	0	0	

smoking status and subject group (Table 4).

3.3. Association between Hp and symptom severity

Linear regression models were performed to examine the associations between Hp gene expression and PANSS 5-factors. Each model was adjusted for age, sex, BMI, smoking status and use of antidepressants. Hp gene expression level was associated with PANSS cognitive symptom factor (p = 0.032) (Table 3). There were no significant associations between Hp gene expression levels and CDSS or GAF.

4. Discussion

To our knowledge, this is the first study to examine Hp gene expression levels in individuals at UHR for psychosis. Individuals at UHR had higher Hp gene expression levels compared to controls. Hp gene expression levels at baseline did not predict UHR remission, non-remission, or conversion to psychosis. Hp gene expression levels are associated with PANSS cognitive symptom factor. There is no difference in allele frequency of commonly studied Hp SNPs.

Although Hp is not extensively studied, reports on its elevated levels in various stages of psychosis or schizophrenia (first-episode psychosis, acute episodes, chronic and treatment-resistant) have been consistent from as far back as 1965 (Gammack and Hector, 1965; Seal and Eist, 1966; Bock et al., 1971; Wong et al., 1996; Maes et al., 1997; Yang et al., 2006; Wan et al., 2007; Yee et al., 2017). Taken together with the findings from the present study, it suggests that inflammatory processes in psychosis commenced before the first psychotic episode. Though elevated, we did not see a large magnitude increase in Hp expression. This is consistent with findings from other immune biomarker studies in psychosis and might indicate a low-grade inflammatory process or immune dysregulation, rather than an acute inflammatory process (Müller, 2018; Osimo et al., 2018; Fond et al., 2019).

While activation of immune-inflammatory response system (increased production of pro-inflammatory cytokines, chemokines, and soluble receptors) is observed in schizophrenia, an increase in immune markers with immunoregulatory effects (anti-inflammatory) was observed as well (Noto et al., 2014; Gadelha et al., 2015; Li et al., 2016; Maes and Carvalho, 2018). Therefore, Roomuangwong et al. proposed a compensatory immune-regulatory reflex system (CIRS) to be applied to schizophrenia and its phenotypes, namely first-episode psychosis, acute episodes, chronic and treatment-resistant schizophrenia, comorbid depression, and deficit schizophrenia (Roomruangwong et al., 2020). Hp, with its anti-inflammatory properties such as stimulation of Th-2 phenotype, inhibiting cyclooxygenase 2 and effector cells is proposed to function as part of the CIRS in schizophrenia, and may act as a protective factor (Roomruangwong et al., 2020).

Work on the impact of Hp or other acute phase proteins on symptom severity in psychosis is limited with only two reporting significant associations between CRP and Hp with symptom severity (Fan et al., 2007; Yee et al., 2017). In line with these reports, the present study too observed significant associations between Hp gene expression and symptom severity. However, underlying mechanisms behind

Table 3
- Association between Hp gene expression and symptom severity.

	Unadjusted				Adjusted for age, gender, BMI, smoking and use of anti-depressants			
	R^2	B	95% CI	P-value	R^2	B	95% CI	P-value
PANSS								
Positive	0.002	−0.047	−0.201 to 0.134	0.689	−0.051	0.010	−0.175 to 0.190	0.936
Negative	0.002	0.042	−0.086 to 0.124	0.724	−0.040	0.111	−0.069 to 0.169	0.404
Cognitive	0.045	0.213	−0.012 to 0.316	0.068	0.021	0.268	0.017 to 0.367	**0.032**
Depression	0.001	−0.024	−0.120 to 0.098	0.838	−0.051	0.019	−0.115 to 0.133	0.885
Hostility	0.009	0.097	−0.192 to 0.466	0.410	−0.045	0.078	−0.256 to 0.483	0.542
CDSS	−0.014	0.002	−0.084 to 0.085	0.984	−0.049	−0.097	−0.076 to 0.115	0.690
GAF	−0.012	−0.041	−0.046 to 0.032	0.726	−0.038	−0.119	−0.063 to 0.023	0.362

Table 4
Association between Hp gene expression and Hp SNP.

	Unadjusted				Adjusted for age, gender, subject group[a]			
	R2	B	95%CI	P-value	R2	B	95% CI	P-value
rs2070937	0.004	0.065	−0.266 to 0.573	0.471	0.078	0.025	−0.348 to 0.467	0.774
rs5473	0.003	−0.054	−4.298 to 2.280	0.545	0.085	−0.085	−4.738 to 1.586	0.326
rs3852780	0.130	0.360	0.899 to 2.431	<0.001	0.204	0.360	0.911 to 2.414	< **0.001**

[a] UHR or Healthy Control.

inflammation and psychosis is work in progress. Possible mechanisms postulated to lead to development of psychosis includes deficient blood flow in frontal and temporal lobes and prolonged inflammation damaging microvascular system in the brain resulting in breached homeostasis within the brain (Fan et al., 2007).

We explored the distributions of four Hp genotypes in the current study. These genotypes were previously studied in individuals with schizophrenia (Wan et al., 2007). Although we did not detect differences in Hp genetic polymorphism frequencies between groups, rs3852780 is observed to be a significant predictor of Hp gene expression. With the limited studies around Hp genes, it would be unclear to hypothesise the mechanism or regulatory roles the SNP has.

The present study has some limitations. We were unable to control for participants' prior use of psychotropic medication which has been studied to influence acute phase protein levels due to the naturalistic setting of this study (Bouwens et al., 2014). Nevertheless, there is no significant difference in Hp gene expression levels between groups taking and not taking anti-depressants (2.1 vs 2.4; U = 711.0, p = 0.499). The current study lacks protein information of Hp, thus we are unable to further evaluate its function in UHR. Further, the current study did not obtain detailed immune profiles from the participants, which might provide a more comprehensive understanding of immune-inflammatory processes involved in psychosis pathogenesis. Lastly, the small sample size for converters would have limited the statistical power to detect a difference in Hp gene expression level between UHR groups.

The current study is the first to explore Hp gene expression levels in an UHR group and if it contributes to prognostic accuracy in predicting clinical outcomes. We noted a higher level of Hp gene expression in individuals at UHR, which may be attributed to its compensatory immune-regulatory mechanism. Findings from the present study adds to available evidence indicating that inflammation or immune dysregulation precedes psychosis and might be involved in the aetiopathogenesis of psychosis. Future studies might examine engagement of various components or pathways of the immune-inflammatory response system to study possible mechanisms underpinning immune system in psychosis.

Conflict of interest

All authors declare no conflict of interest.

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