



Polygenic risk score of *SERPINA6/SERPINA1* associates with diurnal and stress-induced HPA axis activity in children

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ABSTRACT

Purpose: Corticosteroid-binding globulin (CBG) transports glucocorticoids in blood. Variation in genes *SERPINA6* encoding for CBG, *SERPINA2* and *SERPINA1* (serpin family A member 6, 2, and 1) have been shown to influence morning plasma cortisol and CBG in adults. However, association of this genetic variation with diurnal and stress-induced salivary cortisol remain unknown. This study aims to investigate the effect of genetic variation in *SERPINA6/2/1* loci on diurnal and stress-induced salivary cortisol in children.

Methods: We studied 186, 8-year-old children with genome-wide genotyping. We generated weighted polygenic risk score (PRS) based on 6 genome-wide significant SNPs (rs11621961, rs11629171, rs7161521, rs2749527, rs3762132, rs4900229) derived from the CORNET meta-analyses. Salivary cortisol was measured across one day and in response to the Trier Social Stress Test for Children (TSST-C).

Results: Mixed models, adjusted for covariates, showed that the PRS x sampling time interactions associated with diurnal ($P < 0.001$) and stress-induced ($P = 0.009$) salivary cortisol. In the high PRS group (dichotomized at median) the diurnal salivary cortisol pattern decreased less from awakening to bedtime than in the low PRS group (standardized estimates of sampling time -0.64 vs. -0.73 , $P < 0.0001$ for both estimates). In response to stress, salivary cortisol increased in the high PRS group while it remained unchanged in the low PRS group (standardized estimates of sampling time 0.12 , $P = 0.015$ vs. -0.06 , $P = 0.16$). These results were mainly driven by minor alleles of rs7161521 (*SERPINA6*) and rs4900229 (*SERPINA1*).

Conclusions: Genetic variation in *SERPINA6/2/1* loci may underpin higher hypothalamic-pituitary-adrenocortical axis activity in children.

1. Introduction

Studies on the candidate genes have indicated several single nucleotide polymorphisms (SNPs) e.g. in glucocorticoid receptor (*NR3C1*) (van West et al., 2010), FK506 binding protein 5 (*FKBP5*) (Velders et al., 2011), serotonin transporter (*5HTT*) (Wust et al., 2009), beta-2-adrenergic receptor gene (*ADRB2*) (He et al., 2015), corticotrophin-releasing hormone (CRH) system (*CRHR1* and *CRHBP*) (Sheikh et al., 2013), and mineralocorticoid receptor (*MR*) (DeRijk et al., 2006)

influencing levels of cortisol in plasma and saliva under resting condition and in response to stress. However, none of these findings were replicated in the only genome-wide association meta-analyses (GWAMA) of morning plasma cortisol levels published thus far (Bolton et al., 2014). Instead, common variants in the serpin family A member 6, 2, and 1 (*SERPINA6*, *SERPINA2*, and *SERPINA1*) loci influenced morning plasma cortisol in adults of 14 cohorts participating the CORTisol NETwork (CORNET) consortium (Bolton et al., 2014). *SERPINA6* encodes for cortisol binding globulin (CBG) and resides within a

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cluster of serine proteinase inhibitor (*SERPIN*) genes on chromosome 14q32.1 in close proximity to several other *SERPIN* genes such as *SERPINA2* and *SERPINA1* (Billingsley et al., 1993). Previous studies have reported that various non-synonymous *SERPINA6* mutations are associated with reduced level of CBG binding activity (Hammond, 2016). CBG is an alpha-globulin protein with corticosteroid-binding properties and it serves as a major transport protein for glucocorticoids (Hammond, 2016). Cortisol bound to CBG in plasma is considered to be more biologically inactive compared to free cortisol. Salivary cortisol is commonly considered to reflect plasma free cortisol (Kirschbaum and Hellhammer, 1994). The proportion of free cortisol is typically higher in saliva than in plasma, since around 90% of cortisol in blood and 14% in saliva is bound to CBG (Hellhammer et al., 2009; Kirschbaum and Hellhammer, 1989). Consequently, variation in *SERPINA6* gene may have different effects on plasma versus salivary cortisol levels. However, it is not currently known whether and to what extent common genetic variation in *SERPINA6*, *SERPINA2*, and *SERPINA1* genes influences salivary cortisol levels.

Cortisol levels show both basal circadian and ultradian fluctuations that are under endogenous circadian control (Kirschbaum and Hellhammer, 1994). Humans have a prominent daily fluctuation of cortisol levels with high levels during early morning around the habitual time of awakening, a maximal peak some 30 min later, and then a decrease across the day to an evening nadir (Pruessner et al., 1997). Superimposed on this rhythm, stimulus-induced cortisol is secreted by stress and other stimuli (Hellhammer et al., 2009). To our best knowledge, it is currently not known whether variants at these *SERPIN* family genes associate with diurnal or stress-induced cortisol levels. Furthermore, participants of the Bolton et al. (2014) study of plasma cortisol comprised adolescents to elderly (Bolton et al., 2014). Since ageing is related to higher evening cortisol levels (Van Cauter et al., 2000) and increased cortisol responses to a challenge (Otte et al., 2005), and puberty may alter CBG and hypothalamic-pituitary-adrenocortical axis activity (HPAA) regulation (Angeli et al., 1977), *SERPINA6*, *SERPINA2*, *SERPINA1* genes may show different effects on cortisol levels in adults and in children. We are not aware of studies examining the extent to which genetic variation in *SERPINA6*, *SERPINA2*, and *SERPINA1* loci influences cortisol levels in prepubertal children.

Therefore, we set out to study if genetic variation in *SERPINA6*, *SERPINA2*, and *SERPINA1* loci is associated with diurnal salivary cortisol patterns and salivary cortisol in response to the Trier Social Stress Test for Children (TSST-C) in a sample of 186, 8-year-old Finnish children. In order to analyze whether SNPs of these *SERPIN* genes together influence cortisol values, we first used a recently established polygenic risk score (PRS) method that aggregates multiple genetic markers into a single predictive score (Bulik-Sullivan et al., 2015; Maier et al., 2015). Polygenic analyses have larger cumulative effect sizes and greater predictive power than single-variant predictors (Bulik-Sullivan et al., 2015; Maier et al., 2015) and previous studies have shown that PRS may associate with phenotypes even in the absence of single SNP associations (Traylor et al., 2016). In the PRS method, we weighted alleles in the target cohort with effect estimates derived from the CORNET GWAMA study (Bolton et al., 2014). These product terms were then summed across a set of independent SNPs that showed significant association with morning plasma cortisol (Bolton et al., 2014). This approach has recently been labelled as hypothesis based “top-hits” approach (Belsky and Israel, 2014). If combined effects were detected, we continued analyzing associations with single SNPs to see whether certain SNPs were driving these findings.

2. Materials and methods

2.1. Participants

The study participants were included from an urban community-

based birth cohort Glycyrrhizin in Licorice Study (GLAKU) (Strandberg et al., 2001). This is a prospective study cohort of 1049 infants born between March and November of 1998 at the Helsinki University Hospital and Helsinki City Maternity Hospital, Finland.

922 (87.9%) mothers and children agreed to follow-up and were contacted in 2006 (Raikonen et al., 2010b). Of these mothers, a subgroup of 413 children was invited; as the primary study objective in this cohort was to examine the effects of maternal licorice consumption during pregnancy on their offspring's developmental outcomes, participants whose mothers had consumed high levels of licorice during pregnancy were preferentially recruited to the follow-up. Of the invited, 321 (77.7%) participated in a follow-up examination at the mean age of 8.1 years (standard deviation (SD) = 0.3, range 7.4–8.9 years) (Raikonen et al., 2010a). When inviting the children, we also preferred those still living in or close to the greater Helsinki area to manage travel costs. Children who could not complete the study protocol due to sickness, noncompliance and refusal were excluded (Raikonen et al., 2010b). Thus, salivary cortisol measurements during one day were obtained from 302 children, and in response to TSST-C stress from 294 children. Of them 186 provided both diurnal and TSST-C stress-induced salivary cortisol measurements and genotype data, and hence comprised the analytic sample of the current study. Table 1 shows the sample characteristics according to child's gender. The study sample ($n = 186$) did not differ from those without genotype data ($n = 116$ with diurnal salivary cortisol; $n = 108$ with salivary cortisol during TSST-C) in child's gender, weight or height at birth or age at follow-up testing or in maternal age, weight, height or occupation at delivery or consumption of licorice, tobacco or alcohol during pregnancy (p -values > 0.05). However, those with no genotype data had higher cortisol levels at 0 min ($P = 0.046$), 20 min ($P = 0.026$), and 30 min ($P = 0.029$) during the TSST-C.

The Ethical Committees of the City of Helsinki Health Department, and the Ethical Committee of the Helsinki University Hospital of Children and Adolescents at Helsinki and the Uusimaa Hospital District approved the project. All participant's parents provided written informed consent for the collection of samples and subsequent analysis.

2.2. Measures

The protocols for diurnal salivary cortisol and salivary cortisol sampling during the TSST-C were conducted on separate days. Cortisol was measured in saliva using a competitive solid-phase, time-resolved fluorescence immunoassay with fluorometric end point detection (DELFI; Wallace, Turku, Finland) as previously described (Pesonen et al., 2012; Raikonen et al., 2010b). Diurnal and TSST-C sampling variables are summarized in Table 1.

2.2.1. Diurnal salivary cortisol

Salivary samples were obtained from the study participants using cotton swabs (Salivette, Salimetrics, Inc.). Saliva on a weekend or school holiday was collected at seven time points: at awakening ($M = 07:48$ h (h), $SD = 47$ min (min)), 15 min after, 30 min after, 10:30 h, 12:00 h, 17:00 h, and at bedtime ($M = 21:14$ h, $SD = 73$ min).

2.2.2. Stress-induced salivary cortisol

TSST-C is commonly used to study stress in children and it elicits reliable HPAA and autonomic responses (Buske-Kirschbaum et al., 1997; Jones et al., 2006). The participants were carefully instructed and asked to abstain from eating for 2 h before the TSST-C to avoid postprandial variations in cortisol secretion. They were told to arrive at the clinic at 12:00 h or 14:00 h. After the child and parent/guardian had signed an informed consent, a saliva sample, termed arrival hereafter, was obtained, and weight and height of the child were measured. After this, they spent relaxed time with their family and watched a calming video for 5 min before baseline recordings. The stress test was performed without the parent(s)/guardian(s) and with the child as

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