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No associations of the mineralocorticoid and glucocorticoid receptor genes with asthma

To the Editors:

Asthma is a multifactorial disease. Although a number of host and environmental risk factors have been identified in the past decades, these cannot fully explain the prevalence of asthma. Previous studies have shown that psychosocial stress confers a risk for the development of asthma [1].

Stress activates the hypothalamus–pituitary–adrenal (HPA) axis, which leads to secretion of cortisol. Cortisol in turn influences the activity of many systems in the human body and shifts, among others, the T-helper type (Th1/Th2) balance of the peripheral blood mononuclear cells towards a predominantly type 2 response. Cortisol binds to the high affinity mineralocorticoid receptor (*NR3C2*) and the low affinity glucocorticoid receptor (*NR3C1*). Single nucleotide polymorphisms (SNPs) in these receptors have been associated with basal cortisol and cortisol responses to stress [2]. So far, two studies have found an association between SNPs in *NR3C1* (*i.e.* rs6195, rs41423247) and asthma development [3, 4]. However, these results have not been replicated in other populations so far. Additionally, it is unknown whether other functional or tagging SNPs in the *NR3C1* are associated with asthma development. In addition, SNPs in the *NR3C2* have not been studied before in relation to asthma development. Also it is yet unclear whether exposure to psychosocial stress modifies the effect of SNPs in *NR3C2* or *NR3C1* on asthma.

We investigated the associations of SNPs in *NR3C2* or *NR3C1* with asthma in adolescents from the general population and attempted to replicate our findings in an asthma case–control study.

In adolescents from the general population, we have previously shown that exposure to perinatal stress more than doubles the risk of asthma development [5]. Therefore, we tested additionally whether exposure to perinatal stress modifies the effect of SNPs in *NR3C2* or *NR3C1* on asthma in adolescents.

We genotyped two functional SNPs in *NR3C2* (rs5522, rs2070951) and 12 functional or tagging SNPs in *NR3C1* (rs4912903, rs6198, rs6196, rs258813, rs33388, rs17100236, rs10482642, rs2963155, rs41423247, rs9324924, rs4244032, rs4607376) in 1,454 adolescents of the prospective TRacking Adolescents' Individual Lives Survey (TRAILS) cohort (48% males; mean $\pm$SD age at survey 1, 11 $\pm$ 0.6 yrs; survey 2, 14 $\pm$ 0.5 yrs; survey 3, 16 $\pm$ 0.7 yrs) [6] and in 998 individuals from the Dutch Asthma GWAS study (44% males; mean $\pm$SD age 42 $\pm$ 12.2 yrs) [7], that acted as replication study. In TRAILS, data on parentally reported asthma was collected at age 11, 14 and 16 yrs *via* self-reported questionnaires [8]. Asthma was defined as a doctor diagnosis of asthma, and/or symptoms of asthma and/or asthma treatment prescribed by a physician in the past 12 months, before or at the age of 16 years (n=141; 10%). Adolescents not meeting these criteria were defined as not having asthma (n=1,293; 89%). Information about asthma was missing in 20 adolescents (1%). The replication study consisted of 529 asthmatics and 469 nonasthmatics; asthma was defined as a doctor's diagnosis of asthma, the presence of asthma symptoms and bronchial hyperresponsiveness [7]. In TRAILS, perinatal stress was defined as *in utero* exposure to the mother's self-reported maternal psychological problems and/or self-reported maternal postnatal depression (n=67 adolescents; 5%) [9].

SNPs were analysed in an additive genetic model for the effect on asthma using logistic regression models. Interactions between genotype and perinatal stress were tested in TRAILS by introduction of perinatal stress and the interaction term of genotype times perinatal stress into the model.

None of the SNPs in *NR3C2* or *NR3C1* were significantly associated with asthma in adolescents. We also found no association between these SNPs in *NR3C2* or *NR3C1* and asthma in the replication study (table 1).

We observed no effect of perinatal stress on the association between SNPs in *NR3C2* or *NR3C1* and asthma in adolescents (*i.e.* no interaction between perinatal stress and SNPs).

Previous studies have shown that SNPs in *NR3C1* (*i.e.* rs6195, rs41423247) were associated with asthma [3, 4]. Our results do not support the findings of these previous studies, specifically not those suggesting that a mutation (G/C) within rs41423247 in *NR3C1* would have a protective effect on asthma development [4]. However, this association was shown in merely one study including only 59 adults with asthma and 70 healthy adults. Since we found neither an association between rs41423247 and asthma in 1,434 adolescents (OR 0.99, 95% CI 0.76–1.28) nor in 998 adult individuals (OR 0.96, 95% CI 0.80–1.15), we feel that the findings from the study of PIETRAS *et al*. [4] may be due to chance.

Although we found no association between SNPs in the glucocorticoid or mineralocorticoid receptor and asthma, this does not exclude a role of glucocorticoid or mineralocorticoid receptor activity in asthma development, since this activity is

TABLE 1 Estimated associations between single nucleotide polymorphisms in *NR3C2* or *NR3C1* and asthma in the TRacking Adolescents' Individual Lives Survey (TRAILS) cohort study[#] and the Dutch Asthma GWAS (DAG) study

	TRAILS cohort[¶]		DAG study[+]	
	MAF (%)	OR (95% CI)	MAF (%)	OR (95% CI)
NR3C2				
(chromosome 4)				
rs5522	G (13)	0.88 (0.60–1.29)	C (14)	1.24 (0.96–1.60)
rs2070951	G (49)	1.27 (0.98–1.63)	G (53)	0.93 (0.78–1.10)
NR3C1				
(chromosome 5)				
rs4912903	A (40)	0.92 (0.71–1.18)	T (43)	0.96 (0.81–1.14)
rs6198[§]	G (16)	0.87 (0.62–1.22)	G (18)	0.84 (0.67–1.06)
rs6196[ƒ]	G (15)	1.12 (0.80–1.56)	C (16)	0.90 (0.70–1.15)
rs258813	A (31)	0.99 (0.76–1.29)	A (33)	0.86 (0.72–1.04)
rs33388	T (47)	1.11 (0.86–1.42)	T (45)	1.15 (0.96–1.36)
rs17100236	G (13)	1.14 (0.81–1.62)	C (11)	1.21 (0.91–1.60)
rs10482642	G (16)	0.87 (0.62–1.22)	C (18)	0.85 (0.68–1.07)
rs2963155	G (23)	1.21 (0.91–1.61)	G (22)	1.10 (0.88–1.37)
rs41423247[##]	C (37)	0.99 (0.76–1.28)	G (37)	0.96 (0.80–1.15)
rs9324924	A (33)	1.03 (0.80–1.33)	T (29)	0.97 (0.77–1.22)
rs4244032	G (20)	1.00 (0.73–1.37)	G (20)	0.87 (0.62–1.23)
rs4607376	G (50)	0.98 (0.77–1.26)	G (50)	0.98 (0.82–1.17)

MAF: minor allele frequency. [#]: information about asthma missing in 20 adolescents. *NR3C2*: mineralocorticoid receptor gene; *NR3C1*: glucocorticoid receptor gene. [¶]: n=1,434, 141 cases and 1,293 controls; [+]: n=998, 529 cases and 469 controls; [§]: in DAG study genotyped with rs11740792 (r^2=1), [ƒ]: in DAG study genotyped with rs9324918 (r^2=1); [##]: in DAG study genotyped with rs853180 (r^2=0.965).

influenced by multiple other mechanisms, such as chaperone proteins that modulate the translocation of these receptors and post-translation changes that modify the conformation of these receptors. In addition, methylation of both receptors can also influence whether cortisol levels are associated with inflammatory processes [10].

In conclusion, we show suggestive evidence that SNPs in *NR3C2* or *NR3C1* are not associated with asthma development. We also find no indications that perinatal stress would affect the role of these genes on asthma development. These results indicate that, while these genes are biologically plausible candidate genes for asthma development in relation to perinatal stress, they cannot be linked to the disease.

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N.M. Vink[*,#], D.S. Postma[#,¶], M.A.E. Nieuwenhuis[#,¶], G.H. Koppelman[#,+], J.G.M. Rosmalen[§] and H.M. Boezen[*,#]

*Dept of Epidemiology, University of Groningen, University Medical Center Groningen, [#]GRIAC research institute, University of Groningen, University Medical Center Groningen, [¶]Dept of Pulmonology, University of Groningen, University Medical Center Groningen, [+]Paediatric Pulmonology and Paediatric Allergology, Beatrix Children's Hospital, University of Groningen, University Medical Center Groningen, and [§]Interdisciplinary Center Psychopathology and Emotion regulation, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands.

Correspondence: H.M. Boezen, Dept of Epidemiology, E3.29, University of Groningen, University Medical Center Groningen, Hanzeplein 1, POBox30001, 9700 RB Groningen, The Netherlands. E-mail: h.m.boezen@umcg.nl

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Nightmares induced by montelukast in children and adults

To the Editors:

Montelukast, a leukotriene receptor antagonist, was approved in Spain in 1998 for the treatment of asthma in both adults and children. Sleep disturbances, including nightmares, related to leukotriene receptor antagonists have not been described in clinical trials. However, several cases of sleep abnormalities, including nightmares, have been reported in post-marketing experience in patients treated with montelukast [1].

Up to December 2011, the Spanish System of Pharmacovigilance had gathered 24 reports of nightmares in patients (17 children, seven adults) treated with montelukast (table 1). Of the 24 patients, 15 were males and nine were females. 14 patients presented with other concomitant psychiatric symptoms: insomnia (n=5), nervousness (n=4), hallucinations (n=3), aggressiveness (n=2), irritability (n=2) and anxiety (n=1). Cases with aggressiveness were rated as serious. In all cases the only suspect medicine was montelukast. Six patients had taken other medicines concomitantly, although on a long-term basis. In 18 patients the nightmares appeared within the first day of exposure (n=11) or within the first week of treatment (n=7). Nightmares rapidly resolved after montelukast discontinuation in 21 cases. Alternative causes other than montelukast were excluded in most reports. Three patients were re-exposed to montelukast after the nightmares resolved, and in all three patients the nightmares reappeared.

In a list of all reported adverse reactions with montelukast in the UK after the first 14 months of marketing, 13 cases of nightmares were included [2].

A total of 44 reports of psychiatric disorders in children during treatment with montelukast as a suspected drug were found in the Swedish Adverse Drug Reaction database (SWEDIS) up to 2007. There were 15 reports of nightmares induced by montelukast, eight (53%) of which occurred in children $\leqslant$5 yrs of age [3]. Details regarding clinical course and causal relationship with montelukast in these cases are similar to those of the paediatric cases in our series.

In the analysis of the psychiatric adverse drug reactions in the paediatric population registered to the SWEDIS database during the period 2001–2010, montelukast was the most frequently suspected drug (excluding vaccines). The most frequently reported psychiatric adverse drug reaction associated with montelukast was nightmares [4].

Nightmares are relatively common parasomnias, defined as an unpleasant or frightening dream usually occurring in rapid eye movement (REM) sleep. A number of different medicines have been involved in cases of nightmares. However, for most of them the eventual pharmacological mechanism is unknown. Various neurotransmitter modulating systems have been implicated in the mechanisms of dreaming and in nightmares. Drugs affecting norepinephrine, serotonin, dopamine, acetylcholine and gamma-aminobutyric acid, such as β-blockers, antidepressants, dopamine agonists, anticholinergic agents and benzodiazepines, have more often been associated with nightmares [5].

The incidence of nightmares is difficult to establish. 80% of the general adult population may suffer from sporadic nightmares [6]. Since children experience more REM sleep than adults, nightmares in childhood tend to be more common and sometimes relapsing [6]. Moreover, among patients with asthma, sleep problems are common complaints. Obstructive pulmonary disease disturbs sleep. Compared with the general population, patients with chronic respiratory conditions have a higher prevalence of sleep disorders, including nightmares [7]. The high proportion of children in our series may also reflect preferential prescribing of montelukast for children.

The higher background incidence of nightmares in patients with asthma adds difficulty to the causality assessment in the cases we present. However, the close time sequence between exposure to montelukast and nightmares, the fact that 18 out of 24 patients were not exposed to any other medicine, the quick recovery after montelukast withdrawal in most cases, and the positive re-challenge in three patients suggest a causal relationship and warrant a more detailed assessment of the risk.

We cannot suggest a mechanism for montelukast-induced nightmares. To our knowledge, nightmares have not been