

Short communication

Heritability of plasma neopterin levels in the Old Order Amish



Uttam K. Raheja^{a,b}, Dietmar Fuchs^c, Christopher A. Lowry^{d,e,f,g,h}, Sarah H. Stephens^{i,j}, Mary A. Pavlovich^{i,j}, Hira Mohyuddin^a, Hassaan Yousufi^a, Kathleen A. Ryan^{i,j}, Jeff O'Connell^{i,j}, Lisa A. Brenner^{d,e,f}, Cecile Punzalan^k, Andrew J. Hoisington^{f,l}, Gursharon K. Nijjar^a, Maureen Groer^m, Alan R. Shuldiner^{i,j}, Toni I. Pollin^{i,j}, John W. Stiller^{a,n}, Braxton D. Mitchell^{i,j,o}, Teodor T. Postolache^{a,d,f,p,*}

^a Mood and Anxiety Program, University of Maryland School of Medicine, 685 W. Baltimore Street, Suite# 930, Baltimore, MD 21201, USA

^b Child and Adolescent Psychiatry Residency Program, Department of Psychiatry and Behavioral Sciences, Emory University School of Medicine, 12 Executive Park Drive, Atlanta, GA 30329, USA

^c Division of Biological Chemistry, Biocenter, Innsbruck Medical University, Innrain 80, 6020, Innsbruck, Austria

^d Rocky Mountain Mental Illness Research Education and Clinical Center (MIRECC), Veterans Integrated Service Network (VISN) 19, 1055 Clermont St, Denver, CO 80220, USA

^e Department of Physical Medicine and Rehabilitation, University of Colorado Anschutz Medical Campus, 13001 E 17th Pl, Aurora, CO 80045, USA

^f Military and Veteran Microbiome Consortium for Research and Education (MVM-CoRE), 1055 Clermont St, Denver, CO 80220, USA

^g Department of Integrative Physiology and Center for Neuroscience, University of Colorado Boulder, Boulder, CO 80309, USA

^h Center for Neuroscience, University of Colorado Anschutz Medical Campus, 13001 E 17th Pl, Aurora, CO 80045, USA

ⁱ Division of Endocrinology, Diabetes and Nutrition, Department of Medicine, University of Maryland School of Medicine, 685 W. Baltimore Street, Baltimore, MD 21201, USA

^j Program for Personalized and Genomic Medicine, University of Maryland School of Medicine, 685 W. Baltimore Street, Baltimore, MD 21201, USA

^k U.S. Food and Drug Administration, Center for Food Safety and Applied Nutrition Office of Analytics and Outreach, Division of Public Health Informatics and Analytics, 5001 Campus Drive, College Park, MD 20740, USA

^l Department of Civil and Environmental Engineering, US Air Force Academy, Colorado Springs, CO 80840, USA

^m College of Nursing, University of South Florida, 4202 E Fowler Ave, Tampa, FL 33620, USA

ⁿ Department of Behavioral Health, St. Elizabeth's Hospital, 1100 Alabama Ave SE, Washington, DC 20032, USA

^o Geriatrics Research and Education Clinical Center, Baltimore Veterans Administration Medical Center, Baltimore, MD 20201, USA

^p Mental Illness Research, Education and Clinical Center (MIRECC), Veterans Integrated Service Network (VISN) 5, VA Capitol Health Care Network, 209 West Fayette Street, Baltimore, MD 21201, USA

ARTICLE INFO

Article history:

Received 31 October 2016

Received in revised form 7 February 2017

Accepted 21 February 2017

Keywords:

Neopterin

Heritability

Old Order Amish

Biomarkers

Psychiatric disorders

ABSTRACT

Background: We examined the heritability of neopterin, a biomarker for cell-mediated immunity and oxidative stress, and potentially for psychiatric disorders, in the Old Order Amish.

Methods: Plasma neopterin levels were determined in 2015 Old Order Amish adults. Quantitative genetic procedures were used to estimate heritability of neopterin.

Results: Heritability of log-neopterin was estimated at 0.07 after adjusting for age, gender, and household ($p = 0.03$). The shared household effect was 0.06 ($p < 0.02$).

Conclusions: We found a low heritability of neopterin and small household effect, suggesting that non-household environmental factors are more important determinants of variance of neopterin levels in the Amish.

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1. Introduction

Neopterin, a biomarker for cell-mediated immunity and oxidative stress as a result of immune system activation (Berdowska and Zwirska-Korczala, 2001), is produced by interactions among dendritic cells (Sucher et al., 2013; Wirleitner et al., 2002), T helper-1 lymphocytes, macrophages, and granulocytes by the guanosine triphosphate (GTP) pathway through GTP-cyclohydrolase I (GTP-CH-I) (Fig. 1). Activation of GTP-CH-I in macrophages by interferon- γ and, to a lesser extent, interferon- α , tumor necrosis factor, and endotoxins increases

production of neopterin precursors. Neopterin is also produced by microglial cells in the central nervous system (CNS) (Kuehne et al., 2013; Millner et al., 1998). It is detectable in various body fluids, including blood, cerebrospinal fluid (CSF), and urine and is useful clinically as an inflammatory marker (Zuo et al., 2016) in multiple organ systems [e.g., cardiovascular (Fuchs et al., 2009; Grammer et al., 2009; Weiss et al., 1994), respiratory (Fuchs et al., 1984), musculoskeletal (Altindag et al., 1998), nervous (Millner et al., 1998)] and in various neoplasms (Kronberger et al., 1995; Melichar et al., 2014; Murr et al., 1999; Sucher et al., 2010; Yildirim et al., 2008).

Chronic, low-grade inflammation is thought to be a risk factor for several psychiatric disorders (Mondelli et al., 2015). Thus, neopterin could become a potentially useful immune/oxidative-stress biomarker for depression (Maes, 2011; Maes et al., 2012; Taymur et al., 2015),

* Corresponding author at: 685 W. Baltimore Street, Suite #930, Baltimore, MD 21201, USA.

E-mail address: tpostola@som.umaryland.edu (T.T. Postolache).

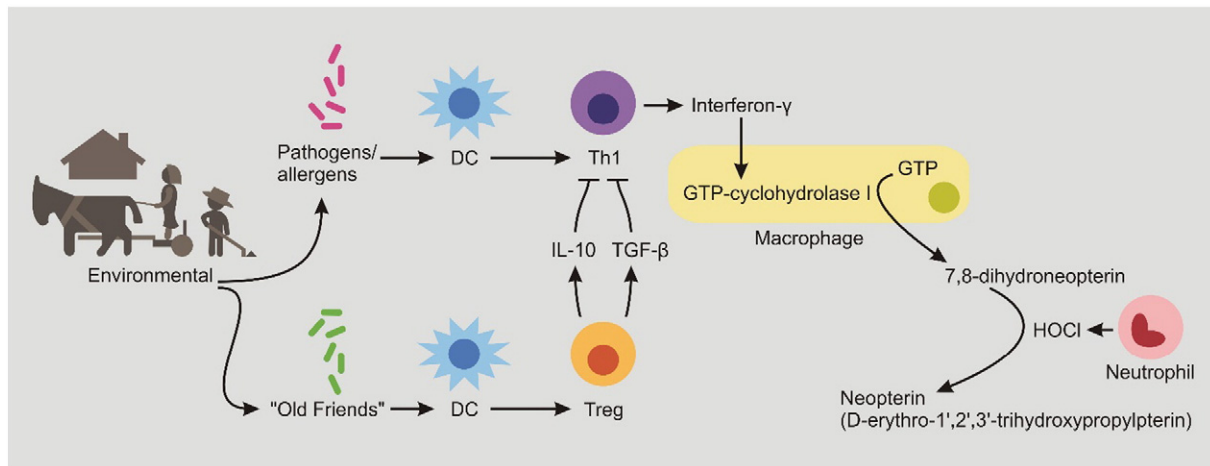


Fig. 1. Neopterin, an aromatic pteridine, is produced as a result of activation of GTP-cyclohydrolase I by interferon- γ from activated T-lymphocytes, and is a marker of cell-mediated immunity and oxidative stress. Household- and, particularly, non-household-related environmental factors influence pathogen and allergen exposures that enhance T helper type 1 (Th1)-specific immune responses, via pathogen/allergen interactions with dendritic cells (DCs), antigen-presenting cells that drive differentiation of naïve T cells to Th1 cells that secrete interferon- γ . Conversely, exposure to "Old Friends", including non-pathogenic, immunoregulatory environmental microorganisms, limit inappropriate inflammation through interactions with DCs that drive differentiation of naïve T cells to regulatory T cells (T_{reg}) that secrete anti-inflammatory cytokines, including interleukin 10 (IL-10) and transforming growth factor beta (TGF- β). Together, these environmental factors control Th1 cell secretion of interferon- γ that in turn activates GTP-cyclohydrolase I in macrophages, leading to enzymatic conversion of GTP to neopterin. Genetic factors, not shown, may act at any level of the host immune response to influence neopterin secretion. Abbreviations: DC, dendritic cell; GTP, guanosine-5'-triphosphate; HOCl, hypochlorite; IL-10, interleukin 10; Th1, T helper type 1 cells; TGF- β , transforming growth factor beta; T_{reg} , regulatory T cells.

postpartum depression (Krause et al., 2014), autism spectrum disorder (Harrison and Pheasant, 1995; Sweeten et al., 2003; Zhao et al., 2015), attention-deficit/hyperactivity disorder (Ceylan et al., 2014), and schizophrenia (Bechter et al., 2010; Chittiprol et al., 2010; Kuehne et al., 2013). Additionally, neopterin has been useful as a biomarker for treatment response and course of multiple sclerosis and HIV/AIDS (Bagnato et al., 2003; Baier-Bitterlich et al., 1996; Fahey et al., 1998; Giovannoni et al., 1997; Hoffmann et al., 2003; Mildvan et al., 2005). The levels of light subunit of neurofilament protein (NF-L) in the CNS, a marker of ongoing axonal injury, correlate with neopterin levels in neuro-asymptomatic HIV patients (Jessen Krut et al., 2014). Neopterin is elevated in acute ischemic stroke (Lin et al., 2012), consistent with its role as biomarker of brain injury. Neopterin production is constitutive to the brain and increases during and is protective against oxidative stress (Ghisoni and Latini, 2015; Ghisoni et al., 2015). Rather than just being a metabolic byproduct with relevance as a biomarker, neopterin may have regulatory roles in inflammation and oxidative stress, enhancing memory and hippocampal long-term potentiation, as shown by intracerebroventricular injection in rodents (Ghisoni et al., 2016).

There are indications of allelic variations that impact the enzymatic steps involved in neopterin synthesis. Segawa disease, a hereditary progressive dystonia, results from a *GCH1* (GTP-CH-I gene) mutation, and is characterized by low CSF neopterin (Fink et al., 1988). Besides additive genetic effects, household and non-household environmental effects can also contribute to neopterin variance. Household effects refer to shared environmental effects by virtue of living in the same household and having similar environmental exposures and built environment, e.g., the household clustering of *Staphylococcus aureus* strains in the Old Order Amish (Rogghmann et al., 2014). Non-household environmental effects are independent of living in the same household. In line with the "hygiene hypothesis", research (Stein et al., 2016) has identified environmental factors likely responsible for lower rates of asthma and allergic sensitization in the Old Order Amish as compared to Hutterites. Community infections, allergies, dietary factors, weight, nutrition rich in antioxidants, and high-fat meals can affect cell-mediated immune responses and neopterin levels (Alipour et al., 2007; Brodin et al., 2015; Cheng et al., 2010; Ledochowski et al., 1999; Myles, 2014; Nappo et al., 2002; Strasser et al., 2016; Tilg and Moschen, 2015).

There are no studies, to our knowledge, of the heritability of neopterin. In this report, we estimate the heritability of plasma

neopterin levels in the Old Order Amish, a rural population ideal for studying heritability because of their relative lifestyle homogeneity and limited alcohol, tobacco, and substance use disorders that reduce the regular major environmental sources of variation.

2. Methods

2.1. Recruitment

The Amish Wellness Study was initiated in 2010 with the purpose of providing wellness screening for cardiometabolic health to members of the Old Order Amish community in Lancaster County, Pennsylvania, USA and performing genetic research related to cardiometabolic health. All participants gave informed consent after a nurse and Amish liaison read the consent to the participant and ascertained understanding. All participants were individuals 18 years of age or older. At the enrollment visit, medical and family histories were obtained and a visit for fasting blood draw was scheduled. Fasting blood draw was obtained by venipuncture either in the mobile clinic, the participant's home, or at the Amish Research Clinic. Whole blood, collected in heparinized tubes, was centrifuged at 5 °C at 3330–3350 rpm for 10 min, and plasma was separated and stored at –80 °C until the time of assay.

2.2. Neopterin

Neopterin concentrations were determined using enzyme-linked immunosorbent assay (ELISA) (BRAHMS GmbH, Hennigsdorf, Germany), following the manufacturer's instructions (Groer et al., 2011). Sensitivity of the assay was 2-nmol/L neopterin.

2.3. Statistical analyses

Heritability of neopterin was estimated with adjustment for age, gender, and household (Raheja et al., 2013). Modeling the phenotypic covariance between any two individuals in the pedigree as a function of their degree of biological association was used to estimate heritability, defined as the proportion of the total trait variance attributable to the additive effect of genes. Heritability was estimated using the maximum likelihood method with the sequential oligogenic linkage analysis routines (SOLAR) software package (Texas Biomedical Research Institute,

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