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# Infectious diseases, *IL6* −174G > C polymorphism, and human development

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ABSTRACT

Interleukin-6 (IL6) is a pro-inflammatory cytokine that is required for resistance against many pathogens. However, sustained IL6 activity can cause tissue damage in the periphery and brain. Previous studies have shown that populations in disease-endemic regions adapt by selecting the high-producing G-allele at the −174G > C (rs1800795) polymorphism, while others have linked increased IL6 to cognitive impairments. The present study sought to determine whether up-regulation of IL6 by the G-allele at rs1800795 polymorphism in disease-endemic regions was associated with increased cognitive deficits and corollary reductions in social, economic, and political development.

We tested these hypotheses in a global sample of 189 nations with World Health Organization ratings for infectious diseases. We also included the Historical Pathogen Prevalence index, a measure of national average intelligence (IQ), and the United Nation Human Development Index (HDI) including per capita income, life expectancy, child mortality, and fertility rate. *IL6* −174G > C allele frequencies were obtained from 171,168 individuals spanning 84 nations.

The high-producing G-allele frequency was positively correlated with infectious disease ranking ($r = 0.745$, $P < 0.001$) and negatively with IQ ($r = -0.524$, $P < 0.001$) and HDI ($r = -0.671$, $P < 0.001$). These robust findings suggest that in regions with a high pathogen burden the need for a strong IL6 response is accompanied by cognitive deficits and reduced HDI ranking.



## 1. Introduction

Interleukin-6 (IL6) is a pleiotropic immune molecule that serves both as a pro-inflammatory cytokine to stimulate the immune response during infection, and as an anti-inflammatory myokine in muscle fibers. In response to contact with pathogens, neutrophils and macrophages secrete pro-inflammatory cytokines like IL6 into the bloodstream. Collectively, these various immune cells initiate tissue inflammation as a protective attempt to remove pathogens and to initiate the healing process. However, this process can even occur in the absence of infection, such as in hay fever or atherosclerosis. Moreover, either intense or sustained inflammation can paradoxically cause damage to the tissue it was intended to heal. Indeed, sustained systemic inflammation contributes not only to peripheral tissue damage but also to several acute and chronic brain pathologies (Amor et al., 2014). Thus, under conditions of chronic exposure, IL6 induces alterations in the level of protein expression in developing CNS cells (Campbell et al., 1993).

Consistent with this evidence, elevated levels of IL6 have been found in Bipolar disorder, Schizophrenia and Intellectual Disability (Brietzke et al., 2011; Potvin et al., 2008; Sasayama et al., 2013; Aureli et al., 2014). Additionally, higher IL6 concentrations have been associated with an increased rate of cognitive decline in both executive function and memory function among the elderly (Mooijaart et al., 2013). With regard to personality development, large-scale studies of Big Five personality traits report that those individuals high in both Conscientiousness and Neuroticism had lower circulating IL6 levels than people with other personality configurations (Turiano et al., 2013). That report supported earlier findings by Chapman et al. (2011), who found that higher Conscientiousness and Openness were associated with lower IL6. Furthermore, low levels of IL6 have been associated with a heightened sense of psychological well-being (Friedman et al., 2007) and positive affect (Steptoe et al., 2008). Dispositional optimism was found to be associated with low IL6 levels in black adolescents (Oreskovic and Goodman, 2013). Conversely, negative

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emotions were found to be associated with increased IL6 levels among individuals in the U.S. but not in Japan (Miyamoto et al., 2013).

The above studies suggest an IL6 continuum of behaviors that range from socially positive traits like conscientiousness, aestheticism and positivism associated with low IL6, to negativism, cognitive impairments and psychopathology associated with high levels of IL6. This raises a host of questions about the evolutionary trade-offs involved in retaining gene variants that up-regulate IL6. The over-arching factor that warrants increases in IL6, of course, is the presence of widespread infectious diseases that characterize much of the world population. What remains to be seen is the degree to which those adaptations also confer liabilities.

Humankind was born in East Africa, and early human development evolved in part by adaptation to a vast array of equatorial diseases. One such adaptation was achieved by the selection of cytokine gene alleles that up-regulate IL6 to better defend against infectious diseases. For example, IL6 has been shown to be required for resistance against many pathogens, such as bacterium *Streptococcus pneumoniae* (van der Poll et al., 1997), suggesting that augmentation of IL6 would be beneficial in regions with a high pathogen burden. Indeed, genetic variability at the *IL6* locus (Chr. 7p15.3) has been shaped by pathogen-driven natural selection through human evolution (Fumagalli et al., 2011). A good example of this adaptation to pathogen burden is seen in the widely studied functional *IL6* −174G > C (rs1800795) single nucleotide polymorphism (SNP), the target of the present study. The G-allele of this SNP is the 'high-producer' allele (Cederholm et al., 2007), causing greater *IL6* expression relative to that of the 'low-producing' C-allele. Thus, across evolutionary time populations exposed to high pathogen burdens, which require a strong IL6 response, adapt by positively selecting the high-producing G-allele, while carriers of the low-producing C-allele are more likely to be removed from the population by greater susceptibility to disease. As a result, studies have shown that populations adapt to pressures from endemic malaria (Upperman et al., 2005) and tuberculosis (Larcombe et al., 2008) by favoring selection of high-producing *IL6* alleles.

By applying an ecological approach, using countries as units of analysis, the present study was thus undertaken (a) to determine whether the extreme global variability in infectious disease burden is reflected in a parallel shift in population selection for either the high- or low-producing *IL6* −174G > C SNP; (b) to determine whether up-regulation of *IL6* by the high-producing −174 G-allele in disease-endemic regions was associated with increased cognitive deficits and corollary reductions in social, economic, and political development, as assessed by the UN Human Development Index (HDI); and (c) to verify whether these changes were reflected in differential rates of child mortality, fertility, and lifespan.

## 2. Materials and methods

### 2.1. IL6 −174G > C rs1800795 allele frequencies search and data extraction

An extensive literature search was carried out on PubMed and Google free search engines using the keywords: "Interleukin 6", "IL6", "polymorphism", "variant", "SNP", "Single Nucleotide Polymorphism" and "genetics" applying the following algorithm: (IL6 OR Interleukin 6) AND (genetics) AND (polymorphism OR variant OR Single Nucleotide Polymorphism OR SNP). The identification of eligible studies was not restricted to English language. Studies references were also analyzed to find any study not available from the electronic databases. All published studies that included genotype frequency information on the samples genotyped for *IL6* −174G > C rs1800795 were included in the data analysis. For case-control studies, only the control group (when reported as "healthy") was considered. *IL6* −174G > C rs1800795 genotypes were also retrieved from 1000 Genome Consortium, Phase 3 variant set (1000 Genomes Project Consortium et al., 2012) and from HapMap Consortium, Release #28 (International HapMap Consortium, 2003). Multiethnic sample populations were not included in the analyses. Hardy–Weinberg Equilibrium was checked for every sample population by Pearson's chi-square, filtering all the collected data using a two-tail *P*-value less than 0.05. Outlier populations were checked for countries where more than 4 populations were available and discarded from the dataset accordingly. Mean allele frequencies were obtained by averaging the allele frequencies obtained from the population belonging to the same country. To guarantee a representative coverage of all ethnic groups for each individual country and to account for the post-colonial movements of human populations, we applied to our raw average-per country *IL6* −174G frequency a matrix transformation based on the "World Migration Matrix," created by Putterman and Weil (2010) which tracks the population movements of 165 countries going as far back as the 1500s.

### 2.2. Cross-national sample of infectious disease burden, Intelligence Quotient (IQ) and mental health disorders

As a measure of total infectious disease burden per country we considered the age-standardized disability-adjusted life years lost (DALY) due to infectious diseases in 2004, obtained from the World Health Organization (WHO) (2004), using the log-transformed data from Eppig et al. (2010). We also used the Historical Pathogen Prevalence index defined by Murray and Schaller (2010). This index is based on disease prevalence data obtained from old epidemiological atlases and is calculated for 230 geopolitical regions (mostly nations) around the world. National average intelligence was taken from Lynn and Vanhanen (2006). We also considered the national IQ scores obtained from Raven's Progressive Matrices Test (2000). Age-standardized DALYs due to Bipolar Disorder and Schizophrenia in 2004 were obtained from the WHO (2004).

### 2.3. Cross-national sample of social and economic development-related variables

As a summary measure of development we used the 2014 Human Development Index (HDI), a composite measure of social, economic and political development defined by the United Nations (http://hdr.undp.org/en/data). We also considered several subcomponents of HDI, namely Gross National Income per capita (GNI), Life Expectancy at Birth, Child Mortality (under 5 years), and Total Fertility rate (Births per woman).

### 2.4. Statistical analyses

Correlations (by Pearson's *r* or Spearman's rho), mediation and multiple regression analyses were used to test our assumptions. Two-tailed *P*-values were reported. Statistical analysis was performed using SPSS v.18.0. Geographical maps were generated using *rworldmap* R package.