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Gene-environment interactions linking air pollution and inflammation in Parkinson's disease

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ABSTRACT

Both air pollution exposure and systemic inflammation have been linked to Parkinson's disease (PD). In the PASIDA study, 408 incident cases of PD diagnosed in 2006–2009 and their 495 population controls were interviewed and provided DNA samples. Markers of long term traffic related air pollution measures were derived from geographic information systems (GIS)-based modeling. Furthermore, we genotyped functional polymorphisms in genes encoding proinflammatory cytokines, namely rs1800629 in *TNFα* (tumor necrosis factor alpha) and rs16944 in *IL1B* (interleukin-1β). In logistic regression models, long-term exposure to NO_2 increased PD risk overall (odds ratio (OR)=1.06 per 2.94 μg/m^3 increase, 95% CI=1.00–1.13). The OR for PD in individuals with high NO_2 exposure (≧75th percentile) and the AA genotype of *IL1B* rs16944 was 3.10 (95% CI=1.14–8.38) compared with individuals with lower NO_2 exposure (<75th percentile) and the GG genotype. The interaction term was nominally significant on the multiplicative scale (p=0.01). We did not find significant gene-environment interactions with *TNF* rs1800629. Our finds may provide suggestive evidence that a combination of traffic-related air pollution and genetic variation in the proinflammatory cytokine gene *IL1B* contribute to risk of developing PD. However, as statistical evidence was only modest in this large sample we cannot rule out that these results represent a chance finding, and additional replication efforts are warranted.

1. Introduction

Parkinson's disease (PD) is a chronic and progressive disorder of the nervous system that affects 4.1 million individuals worldwide in 2005. Environmental exposure and genetic factors play a role in the etiology of PD and it is of importance to investigate interactions between these factors to identify the most vulnerable populations. Air pollution is a major contributor to morbidity and mortality responsible for over 3 million premature deaths each year (Mills et al., 2009). More than a decade ago, it has been proposed that the central nervous system (CNS) is a target organ for ultrafine carbon particles that may reach the brain via the olfactory pathway (Oberdorster and Utell, 2002). Recently, some epidemiological studies started to link ambient air pollutants to PD incidence (Palacios et al., 2014a; Ritz et al., 2015). Investigators who assessed traffic-related metal exposures in the Nurses' Health Study cohort, which included 425 incident PD cases, reported no associations with PD (Palacios et al., 2014a). On the other hand, for 1696 PD cases identified from Danish hospital registries and 1800

Abbreviations: PM_{10}, particles of less than 10 μm diameter; $PM_{2.5}$, particles of less than 2.5 μm diameter; O_3, ozone; CO, carbon monoxide; NO_2, nitrogen dioxide; SO_2, sulfur dioxide; IQR, interquartile range; SD, standard deviation; PD, Parkinson's disease; GIS, geographic information systems; *TNFα*, tumor necrosis factor alpha; *IL1B*, interleukin-1β; CNS, central nervous system

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population controls, we recently estimated a positive association between traffic-related NO_2 exposure and PD risk (Ritz et al., 2015).

The first observational study in animal that showed that air pollution may contribute to neurodegenerative disease pathology described enhanced oxidative damage and diffuse amyloid plaques in the olfactory bulb of feral dogs living in high pollution regions of Mexico city (Calderon-Garciduenas et al., 2008a). This finding suggested that the olfactory nervous system linked to the olfactory mucosa may provide the entry route for air pollutants to the brain. Later these same researchers analyzed post-mortem brains of humans exposed to air pollution and described upregulation of pro-inflammatory markers such as cyclooxygenase 2 (COX2), interleukin-1β (IL-1β) and CD-14; disruption of the blood-brain barrier; and α-synuclein accumulation (Calderon-Garciduenas et al., 2008b). Interestingly, both protein aggregation and neuro- or systemic inflammation are considered pathogenetic mechanisms in PD. Air pollution may contribute to PD pathology through the activation of chronic systemic inflammatory processes; for example, experiments suggested that a systemic lipopolysaccharide (LPS) challenge in animal models of PD can induce exaggerated CNS inflammation and induce tumor necrosis factor alpha (TNF-α) and IL-1β production by activated microglia (Cunningham et al., 2009; Genc et al., 2012). Thus, air pollutants may affect the brain either directly via transport of pollutants from the olfactory bulb or through systemic inflammation that contributes to the neurodegenerative process.

We previously reported that the homozygous genotypes of single nucleotide polymorphisms (SNPs) rs1800629 and rs16944 in *TNF* and *IL1B* were associated with PD risk in a highly pesticide exposed population (Wahner et al., 2007), but marginal associations were not observed for either SNP in a recent large meta-analysis of genome-wide association studies (GWAS) (Lill et al., 2012; Nalls et al., 2014). It is highly likely that any effects of these SNPs on PD risk are due to effect measure modification of environmental exposures that cause inflammation such as air pollution. By utilizing one of the largest population-based case-control studies of PD, the Danish PASIDA study, we examine whether *TNF* rs1800629 and *IL1B* rs16944 interact with long-term exposure to traffic related air pollution to increase the risk of PD.

2. Material and methods

2.1. Human subjects

This study was approved by the institutional review board (IRB) of the University of California at Los Angeles, the Danish Data protecting Agency and the Copenhagen Regional Committee on Biomedical Research Ethics. All subjects who participated in the study provided written informed consent.

2.2. Subjects

We identified 3508 patients aged 35 years or more with a first hospital or outpatient clinic contact for PD (ICD-8 code 342 and ICD-10 code G20) between 1996 and mid-2009 from the Danish National Hospital Register. Of these patients, 2762 met the eligibility criteria for participation (i.e., who were alive and available for contact; spoke Danish and English; were well enough to participate in the interview between 2008/1/1 and 2010/12/31). Medically trained research staff supervised by a specialist in movement disorders reviewed medical records rigorously to confirm idiopathic PD (iPD) diagnosis according to standard diagnostic criteria of the United Kingdom Brain Bank (Hughes et al., 1992) and/or Gelb criteria (Gelb et al., 1999) (for details see (Wermuth et al., 2012)). We further revised the date of first PD diagnosis (index date) according to the occurrence of the first cardinal symptom if stated on the medical record. From among 2762 eligible patients, we excluded: (1) 417 patients for whom the diagnosis of iPD could not be confirmed based on the re-review of medical records we received prior or after contact, (2) 20 without medical records to confirm diagnosis, and (3) 497 following their refusal to participate. Thus, 1828 confirmed iPD cases were included in the present study (Fig. 1).

For each case, we randomly sampled 5–10 potential controls matched to cases on sex and year of birth from the Danish Central Population Register. Controls were required to not have a hospital diagnosis of PD before index date (i.e., the date of PD diagnosis of their matched case) and to be available for interview between January 2008 and December 2010. Controls were contacted in random order from each matched set until one consented to participate; out of the 3626 eligible controls we initially contacted, 1909 (53%) completed an interview.

2.3. Assessment of air pollution exposure

We retrieved addresses of each participant from 1 January 1971 until index date from the Central Population Registry by use of the personal identification number. Dates of moving to and from each address are recorded in this database and enabled us to obtain geographic coordinates at the front door of each residence. The precision of the geographical coordinates was within 5 m for most addresses and in our study we successfully geocoded 88% of the addresses. We estimated the yearly concentration of outdoor traffic-related air pollution (NO_2, NO_x, and CO) for each participant at each residential address from January 1971 to the index date by making use of the Danish AirGIS modeling system (http://www.dmu.dk/en/air/models/airgis/). This AirGIS system focuses on estimating traffic-related air pollution and calculates air pollution measures at a location as the sum of: (1) local air pollution from street traffic, calculated from traffic intensity and type, emission factors for the car fleet, street and building geometry, and meteorology information, (2) urban background, calculated from information on urban vehicle emission density, city dimensions, and building height, and (3) regional background, estimated from both trends at rural monitoring stations and national vehicle emissions.

With the coordinate based on an address and a specified year as the starting point, the AirGIS system has been successfully validated (Berkowicz et al., 2008; Ketzel et al., 2011; Raaschou-Nielsen et al., 2000). Measured and modeled ½-year mean NO_2 concentrations at 204 positions in the Copenhagen area correlated with a correlation coefficient (r) of 0.90 and the measured concentrations were on average 11% lower than the modeled (Berkowicz et al., 2008). Measured and modeled one-month mean concentrations of NO_x and NO_2 over a 12-year period (1995–2006) in a street in Copenhagen (Jagtvej, 25,000 vehicles per day, street canyon) correlated with r-values of 0.88 for NO_x and 0.67 for NO_2. The modeled mean concentration over the 12-year period was 6% lower than the measured concentrations for NO_x and 12% lower for NO_2 (Ketzel et al., 2011). Altogether, the model predicted both temporal and geographical variation well. Because traffic-related pollutants, NO_2, NO_x, CO, are correlated ($r=0.81–0.92$), we focused on the concentration of NO_2 which has been shown to capture variation of pollutant mixtures from traffic well (Su et al., 2009). In our analyses, we only included participants for whom the residential address histories allowed us to generate air pollution concentrations for 80% time or more from 1 January 1971 to index date ($n=3496$).

2.4. Genotyping and quality control of TNF rs1800629 and IL1B