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A gene variant of AKR1C3 contributes to interindividual susceptibilities to atopic dermatitis triggered by particulate air pollution

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To the Editor,

The pathogenesis of atopic dermatitis (AD) involves an impairment of the skin barrier by an interplay of genetic and environmental factors. The resulting inappropriate defense against allergens, microbes, and pollutants results in a chronic, mainly T-helper (Th) 2 cell-driven skin inflammation.[1] Environmental factors that may increase the risk for AD are airborne particulate matter (PM) and commonly associated polycyclic aromatic hydrocarbons (PAHs).[1,2] However, the available epidemiological data provide a heterogeneous picture. While some studies found a significant association between PM exposure and AD symptoms, in particular in children, other studies reported null associations.[1,2] This data

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CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

inconsistency in airborne PM exposure-related AD may depend on interindividual genetic susceptibilities.[3]

A gene that is highly expressed in lesional AD skin[4] and upregulated in PAH-exposed keratinocytes in an aryl hydrocarbon receptor-dependent manner[5] encodes aldo-keto reductase (AKR)1C3. AKR1C3 reduces prostaglandin (PG)D_2 to 9α,11β-PGF_2, a metabolically stable stimulator of Th2 cells that serves as a systemic biomarker for allergen-induced mast cell activation.[6] Herein, we demonstrate the functional and clinical relevance of the *AKR1C3* gene variant rs12529 for the PM exposure-associated development of AD.

Study individuals enrolled in the GINIplus/LISA birth cohort were restricted to 457 participants (49.5% male; age: mean = 15.1 years, sd = 0.2; BMI: mean = 21.2, sd = 3.3) with available AD diagnosis at the 15-year follow-up examination, air pollution, and genetic data. AD, defined as ever diagnosed by a physician, was present in 174 individuals. Median chronic exposures to PMs with interquartile ranges were for $PM_{2.5}$ 17.3 μg/m^3 (0.9), for PM_{10} 25.2 μg/m^3 (1.5), for $PM_{2.5\ absorbance}$ 1.16 10^{-5}/m (0.2), and for PM_{coarse} 8.4 μg/m^3 (0.6). The single nucleotide polymorphism (SNP) rs12529 was genotyped with sufficient quality (estimated R^2 = 0.997), and the minor/effect allele frequency (EAF) was G: 0.400. We found consistent effects for all PM exposures showing a higher chance for adolescent carriers of the rs12529 effect allele (G) to develop AD as compared to rs12529 major allele (C) carriers under constant airborne PM exposure (Figure 1). With the increase per one effect allele, the odds ratio for developing AD significantly increases by 38% (PM_{10}, $PM_{2.5}$, $PM_{2.5\ absorbance}$) and 37% (PM_{coarse}), respectively.

Next, we investigated whether the rs12529 effect allele, causing an amino acid exchange in codon 5 from His to Gln, affects the catalytic activity of AKR1C3. In comparison with the major allele variant, the overexpression of an effect allele-resembling *AKR1C3* variant in CRISPR/Cas9-generated *AKR1C3*-knockout (HaCaT-AKR1C3-KO) keratinocytes (Figure S1A-C) resulted in an enhanced 11-ketoreduction of PGD_2 to 9α,11β-PGF_2 (Figure 2A). However, after normalization of the LC–MS data to the protein level, this effect was diminished (Figure 2B,C), indicating that the rs12529 effect allele affects AKR1C3 enzyme activity indirectly by enhancing its protein stability. Accordingly, treatment of transfected HaCaT-AKR1C3-KO cells with the translation blocker cycloheximide revealed a delayed degradation of the effect allele-resembling AKR1C3 enzyme over time (Figure 2D), indicating that the SNP-related amino acid exchange indeed enhances protein stability.

Importantly, *AKR1C3* expression is not only inducible by PAHs, such as benzo[a]pyrene, but also by PAH-rich PM. In fact, treatment of HaCaT keratinocytes with an organic extract of $PM_{2.5}$ collected from traffic-related air pollution and a repetitive topical exposure of human ex vivo skin with diesel exhaust particles increased the expression of *AKR1C3* (Figure 2E, Figure S2A) and the prototypic aryl hydrocarbon receptor target gene cytochrome P450 (CYP)1A1 (Figure S2).

Taken together, our data show that under constant chronic PM exposure, the increase per one AKR1C3 SNP rs12529 effect allele increases the chance to develop AD significantly by approx. 37%–38%. PM exposure induces *AKR1C3* expression in human skin; therefore,

this observation might be due to an enhanced protein level and corresponding catalytic activity of AKR1C3. The allele frequency of rs12529 varies markedly across continental populations.[7] Hence, we speculate that due to a higher rs12529 EAF, some populations (e.g., Asians, EAF = 0.861) might be more susceptible to PM/PAH exposure-induced or -exacerbated AD than others (e.g., Europeans, EAF = 0.405).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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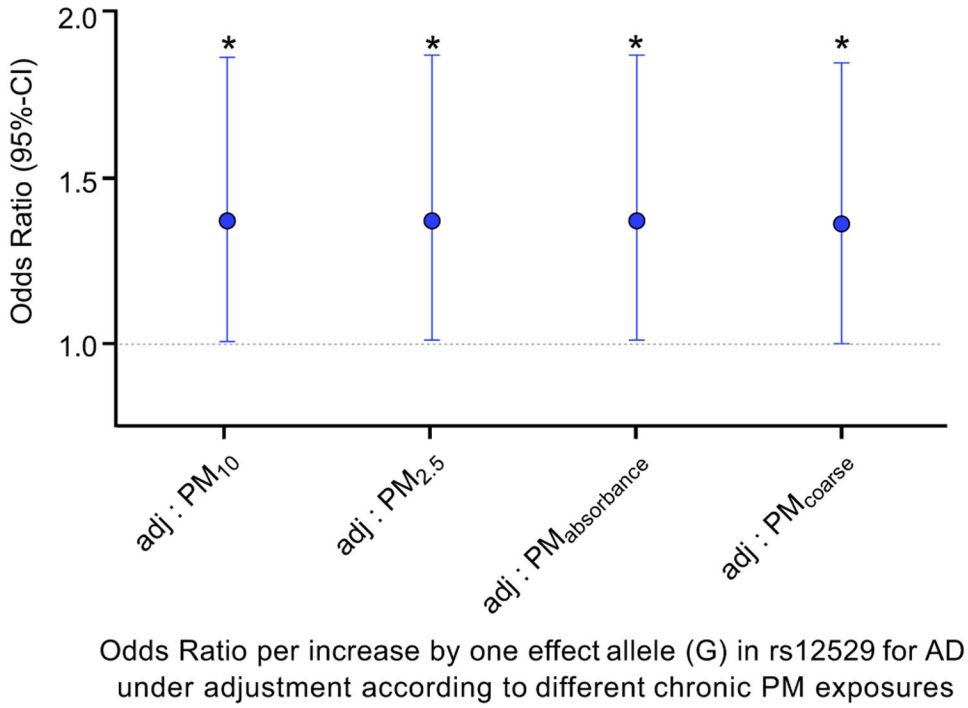

FIGURE 1.

Carriers of the effect allele (G) in rs12529 have a higher chance to develop AD when adjusting to different chronic PM exposures. Individual chronic exposure to particulate matter with a median aerodynamic diameter of ≤2.5/ ≤10 μm ($PM_{2.5}$/PM_{10}), diameters of 2.5–10 μm (PM_{coarse}), and the reflectance of $PM_{2.5}$ filters ($PM_{2.5\ absorbance}$/ in figure: $PM_{absorbance}$) was considered. 417 (for $PM_{2.5}$, PM_{10}, $PM_{2.5\ absorbance}$) and 420 (for PM_{coarse}) participants were included in the regression model. With the increase per one effect allele G, the odds ratio (OR) for developing AD significantly increases by a factor of 1.38, hence per 38% ($p = 0.043$, 95% confidence intervals (CI) = 1.011;1.879) under constant chronic exposure to PM_{10} ($PM_{2.5}$: OR = 1.38, 95% CI = 1.015;1.885, $p = 0.040$; $PM_{2.5\ absorbance}$: OR = 1.38, 95% CI = 1.015;1.886, $p = 0.040$; PM_{coarse}: OR = 1.37, 95% CI = 1.005;1.861, $p = 0.046$). * = $p < 0.05$.

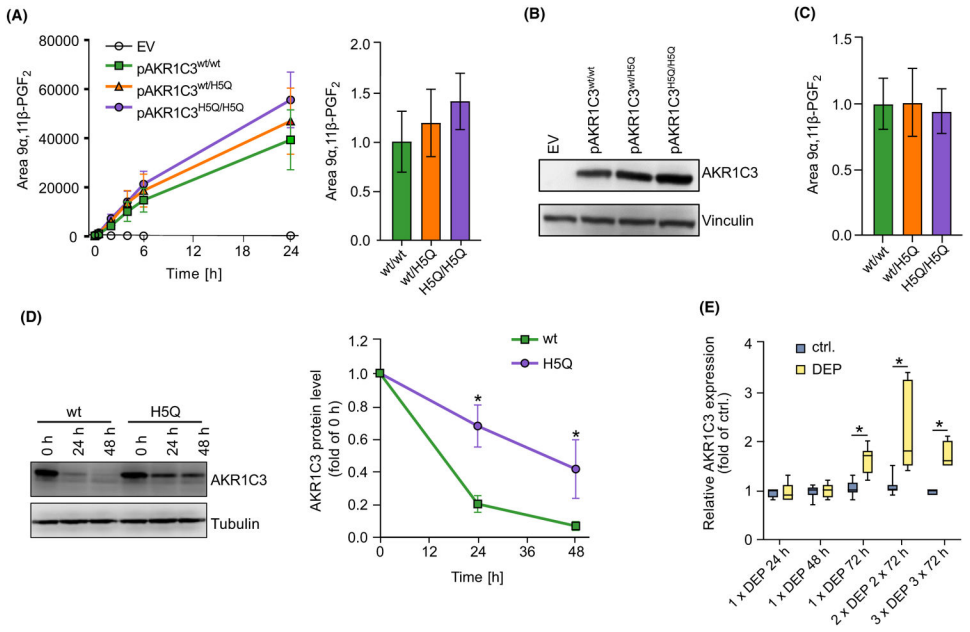

FIGURE 2.

The SNP rs12529 increases AKR1C3 protein stability and airborne PM upregulates AKR1C3 in human skin explants. A) LC–MS analyses of supernatants from HaCaT-AKR1C3-KO keratinocytes transfected with pAKR1C3wt, pAKR1C3H5Q, pAKR1C3wt/pAKR1C3H5Q (50:50), or empty vector. After 24 h, cells were treated with PGD_2 (1 μM) for up to 24 h. Shown as mean ± SEM of n = 3 (left) and normalized to pAKR1C3wt/wt at 24 h (right). (B) AKR1C3 protein level of 24 h samples shown in (A). Representative blot of n = 3. (C) LC–MS quantification of 9α,11β-PGF_2 after 24 h depicted in (A) normalized to AKR1C3 protein level shown in B). Shown as mean ± SEM of n = 3. (D) Keratinocytes were either transfected with pAKR1C3wt or pAKR1C3H5Q. After 24 h, cells were treated with 10 μM cycloheximide for up to 48 h. Representative blot (left) and mean quantification ± SEM of n = 4 (right). (E) Six μg/cm^2 diesel exhaust particles (DEP) were topically applied to cultured human skin explants at days 1, 4, and 7. Skin samples were harvested after single, double, or triple DEP application for 3 days. Gene expression of *AKR1C3* was analyzed by qPCR and normalized to 18 S rRNA level. *$p \leq 0.05$.