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Association of filaggrin gene mutations and childhood eczema and wheeze with phthalates and phosphorus flame retardants in house dust: The Hokkaido study on Environment and Children's Health

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ABSTRACT

Background and aim: Exposure to phthalates and phosphorus flame retardants (PFRs) is considered to be a risk factor for asthma and allergies. However, little is known about the contribution of loss-of-function mutations in the gene encoding filaggrin (*FLG*) gene, which are considered to be predisposing factors for eczema and asthma, to these associations. We investigated the associations between exposure to phthalates and PFRs in dust and eczema/wheeze among Japanese children, taking into consideration loss-of-function mutations in *FLG*.

Methods: This study was part of the Hokkaido study on Environment and Children's Health. Seven phthalates and 11 PFRs in household dust were measured by gas chromatography–mass spectrometry. Eczema and wheeze were assessed in children aged 7 years using the International Study of Asthma and Allergies in Childhood questionnaire. Eight *FLG* mutations previously identified in the Japanese population were extracted from cord blood samples. Children with one or more *FLG* mutations were considered to be positive for *FLG* mutations. The study included 296 children who had complete data (birth records, *FLG* mutations, first trimester and 7 years questionnaires, and phthalate/PFR levels). Odds ratios (ORs) and 95% confidential intervals (CIs) of eczema and wheeze were calculated for log-transformed phthalate/PFR levels by logistic regression. We also performed stratified analyses based on *FLG* mutations.

Results: The prevalence rates of eczema and wheeze were 20.6% and 13.9%, respectively. Among children without any *FLG* mutations, tris (1, 3-dichloro-2-propyl) phosphate (TDCIPP) increased the OR of wheeze, (OR: 1.22, CI: 1.00–1.48). Significant *p* values for trends were found between tris (2-butoxyethyl) phosphate (TBOEP) and eczema and di-iso-nonyl phthalate (DiNP) and eczema among children without any *FLG* mutations, respectively.

Conclusions: Despite our limited sample size and cross-sectional study design, the effects of indoor environmental factors on childhood eczema and wheeze were clearer in children without loss-of-function mutations in *FLG* than in children with mutations. Children with *FLG* mutations might already be cared for differently in terms of medication or parental lifestyle. Further studies in larger populations are warranted so that severity of symptoms and combinations of *FLG* mutations can be investigated.

Abbreviations: BBzP, butyl benzyl phthalate; DEHP, di-(2-ethylhexyl) phthalate; DEP, diethyl phthalate; Der p1, *Dermatophagoides pteronyssinus*; Der f1, *Dermatophagoides farinae*; DiBP, di-iso-butyl phthalate; DiNP, di-iso-nonyl phthalate; DMP, dimethyl phthalate; DnBP, di-n-butyl phthalate; *FLG*, filaggrin gene; GC–MS, gas chromatography–mass spectrometry; Ig, immunoglobulin; IL, interleukin; ISAAC, International Study of Asthma and Allergies in Childhood; LOQ, limit of quantification; MHCII, major histocompatibility complex class II; PFR, phosphorus flame retardant; SVOC, semi-volatile organic compound; TBOEP, tris (2-butoxyethyl) phosphate; TCEP, tris (2-chloroethyl) phosphate; TCiPP, tris (2-chloro-iso-propyl) phosphate; TDCiPP, tris (1, 3-dichloro-2-propyl) phosphate; TEP, triethyl phosphate; TEHP, tris (2-ethylhexyl) phosphate; TMP, trimethyl phosphate; TCP, tricresyl phosphate; TNBP, tri-(n-butyl) phosphate; TPhP, triphenyl phosphate

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1. Introduction

Phthalates and phosphorus flame retardants (PFRs) are types of semi-volatile organic compounds (SVOC); phthalates are mainly used as plasticizers, personal care products, fragrances and PFRs are used as flame retardants and plasticizers, respectively. Because they are semi-volatile, phthalates and PFRs do not chemically bond when applied to a matrix; therefore, they accumulate in dust and air particles. It is believed that food intake is the main exposure route for phthalates (Kishi et al., 2017). However, house dust and dermal contact should also be considered when assessing exposure to phthalates and PFRs in the indoor environment. Recent experimental studies have demonstrated cutaneous exposure to indoor SVOCs (Cao et al., 2016; Cao et al., 2018; Pelletier et al., 2017). In particular, children are more highly exposed than adults from indoor environments because of their hand-to-mouth behavior, longer time spent in the home, a higher ratio of body surface area to volume than adults, and high level of dust ingestion (Ait Bamai et al., 2015; U.S. EPA, 2002).

We previously reported that high levels of di-isobutyl phthalate (DiBP) and butyl benzyl phthalate (BBzP) in dust increased the odds ratio (OR) of parental-reported eczema in Japanese children (Ait Bamai et al., 2014); we also found that tris (2-chloro-isopropyl) phosphate (TCiPP) and tris (1, 3-dichloro-2-propyl) phosphate (TDCiPP) in dust increased the OR of self-reported eczema, and that tri-(n-butyl) phosphate (TNBP) in dust increased the OR of self-reported asthma in Japanese inhabitants living in newly built detached houses (Araki et al., 2014a). Previous studies in Swedish, Bulgarian, and Danish children reported that high levels of di-(2-ethylhexyl) phthalate (DEHP) and BBzP in dust were associated with asthma and eczema, respectively (Bornehag et al., 2004; Callesen et al., 2014; Kolarik et al., 2008). A recent meta-analysis suggested that postnatal exposure to DEHP and BBzP from dust had strong positive associations with childhood asthma (Li et al., 2017). Animal and in vitro studies suggest that phthalates and PFRs may have immunocytotoxic effects in mice (Canbaz et al., 2017; Koike et al., 2010; Tanaka et al., 2013). Mice sensitized to DEHP and ovalbumin had increased levels of immunoglobulin E (IgE), IgG1, interleukin-21 (IL-21) and IL-4, suggesting that DEHP acts as an allergy adjuvant (Tanaka et al., 2013). Mice injected with di-iso-nonyl phthalate (DiNP) had increased expression of histamine and eotaxin (Koike et al., 2010). Suppressive or repressive effects on major histocompatibility complex class II (MHCII) and cytokines such as CD80, CD86, CD40, IL-6, and IL-10 were observed in bone marrow-derived dendritic cells exposed to triphenyl phosphate (TPhP) and TDCiPP (Canbaz et al., 2017).

Previous findings are unclear and inconsistent regarding the effects of each specific phthalate or PFR on asthma and allergies. Some observed differences might be due to differences in genetic factors among study populations. Therefore, not only environmental chemical exposure, but also genetic factors should be considered in relation to allergic diseases. Filaggrin (filament aggregating protein) is a key molecule in skin barrier function, preventing transepidermal water loss and minimizing entry of allergens, toxic chemicals, and infectious microorganisms (Candi et al., 2005). Loss-of-function mutations in the gene encoding *FLG* impair skin barrier function and hydration. Therefore, *FLG* null variants are considered to be risk factors for allergic disease development. Several studies have reported that loss-of-function mutations in *FLG* are the major predisposing factors for not only eczema (Palmer et al., 2006), but also allergic sensitization, asthma, and rhinitis (Chan et al., 2018; Debinska et al., 2017). Furthermore, parameters of barrier dysfunction such as stratum corneum dehydration and transepidermal water loss were significantly increased in *FLG*-related eczema patients (Nemoto-Hasebe et al., 2009a). To date, > 50 *FLG* null mutations have been reported in the European, American, Asian, and African populations. In the Japanese population, six recurrent *FLG* mutations—*3321delA*, *Q1701X*, *S2554X*, *S2889X*, *S3296X*, and *K4022X*—have been identified, which are carried by > 20% of Japanese atopic dermatitis patients (Nemoto-Hasebe et al., 2009b; Nomura et al., 2008; Nomura et al., 2009). Recent epidemiological studies have reported that *FLG* mutation carriers have significantly higher levels of environmental chemicals in urine such as mono-n-butyl phthalate, mono-iso-butyl phthalate, and methyl paraben compared to non-carriers and suggested that *FLG* loss-of-function mutation carriers may have higher internal exposure to phthalates because of increased trans epidermal absorption and/or higher exposure to topical medication (Joensen et al., 2014; Joensen et al., 2017). On the other hand, Overgaard et al. (2017) have reported that there is no association between *FLG* mutations and urinary phthalate metabolite levels in Danish children. However, children with eczema had significantly higher mono-n-butyl phthalate levels than children without eczema due to frequent use of emollients (Overgaard et al., 2017). Moreover, two birth cohort studies have indicated that cat exposure enhances the effect of *FLG* mutations on the development of eczema and allergic sensitization (Bisgaard et al., 2008); (Schuttelaar et al., 2009). Cat ownership in early life substantially increases the risk of developing eczema and sensitization within the first year of life in children with *FLG* mutations (Bisgaard et al., 2008; Schuttelaar et al., 2009). However, no other epidemiological studies have assessed the contribution of *FLG* mutations to the effects of environmental chemicals on asthma and allergies. To help fill in the knowledge gaps regarding associations between exposure to phthalates and/or PFRs and allergies, we investigated whether children with *FLG* mutations are more vulnerable to cutaneous exposure to phthalates and PFRs in dust, and thus have higher risk of eczema and wheeze than those without such mutations.

2. Methods

2.1. Study population

Recruitment of children for the Hokkaido study on Environment and Children's Health (Hokkaido cohort) has been reported elsewhere (Kishi et al., 2017; Kishi et al., 2013; Kishi et al., 2011). For the present study, among 20,926 children who were enrolled from February 2003 to March 2012, 7350 children who reached the age of 7 years by March 2013 were selected; mothers of these children received the follow-up questionnaire for 7-year-olds and 2697 were returned. At the same time, mothers were asked to collect house dust samples, of which 2087 mothers agreed, and finally, 888 house dust samples were obtained. *FLG* mutation carriers were screened from 1066 cord blood samples of the participants who had complete data sample at birth, birth record, maternal first-trimester questionnaire, and follow-up questionnaires for 7-year-olds. Among these, 2 participants were excluded due to missing data in the eczema category of the ISAAC questionnaire. Finally, we selected 296 children who had both dust samples and cord blood *FLG* mutation assessments, in order of dust arrival for measurement of phthalates, PFRs, and mite allergens.

2.2. Assessment of allergic diseases

Self-administered questionnaires were given to mothers to collect information on the occurrence of eczema in the 7-year-old children. The questionnaire was the Japanese version of the validated International Study of Asthma and Allergies in Childhood (ISAAC) core questionnaire (ISAAC Steering Committee, 1998). Eczema was defined as (a) “Having an itchy rash that comes and goes for at least 6 months,” or (b) “Having the aforementioned itchy rash at any time during the last 12 months,” or (c) “Having the aforementioned itchy rash affect one or several of the following areas: the folds of the elbows, behind the knees, in front of the ankles, under the buttocks, or around the neck, ears, or eyes.” Wheeze was determined by an affirmative answer to the following question: “Has your child had wheezing or whistling in the chest in the last 12 months?”