

No association between *FADS* polymorphisms and atopic diseases in children from the GINI and LISA birth cohorts

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Keywords: atopy; children; *FADS* gene cluster; fatty acids.

The role of a disturbed metabolism of long-chain polyunsaturated fatty acids (PUFA) in the development of atopic diseases is commonly discussed (1, 2). Also defects in the PUFA generating pathway (delta6 desaturation) have been suggested to be involved in atopic patients of early onset (1). PUFA have crucial functions in the organism; for example, they are precursors of major inflammatory mediators (2).

On the genetic side of the story, the association between single nucleotide polymorphisms (SNPs) in the *FADS* genes and fatty acid levels is well established (1). The *FADS* gene cluster encodes for two fatty acid desaturases that are crucial to the metabolism of essential fatty acids (long-chain n-3 and n-6 fatty acids, i.e. PUFA) as they catalyse the key steps of delta5 and delta6 desaturation.

The direct link between *FADS* SNPs and atopic outcomes was not investigated intensely so far. Only one paper described hints for an association between minor alleles of *FADS* SNPs and less numbers of allergic rhinitis and atopic eczema in an adult cohort (1).

To broaden this topic, we used data of 2718 children born between 1997 and 99 with genotype information from two ongoing German birth cohort studies, called GINIplus and LISApplus, which share a similar design [almost yearly follow-up, details in (3, 4)].

Table 1 Association between five *FADS* gene cluster SNPs and doctor-diagnosed atopic diseases in 6-year-old children

	Prevalence yes/no	aOR* (95% CI)	P-value
rs174545			
Asthma	105/2523	0.93 (0.69–1.25)	0.63
Bronchitis†	589/2039	0.95 (0.83–1.09)	0.48
Asthma or Bronchitis	609/2019	0.94 (0.82–1.08)	0.39
Eczema‡	729/1899	1.04 (0.92–1.18)	0.53
Hay fever§	217/2411	0.94 (0.76–1.16)	0.54
rs174546			
Asthma	106/2561	0.94 (0.70–1.27)	0.70
Bronchitis†	596/2071	0.95 (0.83–1.09)	0.48
Asthma or Bronchitis	616/2051	0.94 (0.82–1.08)	0.39
Eczema‡	738/1929	1.04 (0.91–1.18)	0.59
Hay fever§	221/2446	0.93 (0.75–1.14)	0.47
rs174556			
Asthma	106/2546	0.82 (0.60–1.12)	0.21
Bronchitis†	594/2058	0.98 (0.85–1.13)	0.75
Asthma or Bronchitis	614/2038	0.95 (0.83–1.10)	0.51
Eczema‡	734/1918	1.07 (0.94–1.22)	0.32
Hay fever§	222/2430	1.00 (0.81–1.23)	0.97
rs174561			
Asthma	105/2573	0.83 (0.61–1.14)	0.26
Bronchitis†	599/2079	0.98 (0.85–1.13)	0.79
Asthma or Bronchitis	619/2059	0.96 (0.83–1.10)	0.54
Eczema‡	742/1936	1.08 (0.94–1.23)	0.28
Hay fever§	219/2459	1.00 (0.81–1.24)	1.00
rs3834458			
Asthma	110/2718	0.89 (0.67–1.20)	0.45
Bronchitis†	636/2192	0.94 (0.82–1.08)	0.37
Asthma or Bronchitis	657/2171	0.93 (0.81–1.06)	0.29
Eczema‡	776/2052	1.05 (0.93–1.19)	0.46
Hay fever§	235/2593	0.93 (0.76–1.14)	0.49

*Adjusted for sex (male=reference) and study centre (Munich=reference).

†obstructive bronchitis.

‡atopic eczema.

§allergic rhinitis/allergic rhinoconjunctivitis. SNPs, single nucleotide polymorphisms.

Genotyping of the *FADS* SNPs rs174545, rs174546, rs174556, rs174561 and rs3834458 was carried out with MALDI-TOF MS as described in (5). The *FADS* gene cluster region shows highly preserved LD structure.

Parentally reported doctor's diagnosis of allergic rhinitis/rhinoconjunctivitis ('hay fever'), allergic eczema ('eczema'), asthma and obstructive bronchitis or the report of corresponding persistent or recurrent symptoms in the study questionnaires were used for the definition of outcomes as described before (5). All diagnoses ever during the first 6 years of life were used to define the outcomes.

Logistic regression analyses were performed between each SNP and each outcome using SAS (SAS Institute Inc., Cary, NC, USA, version 9.1). The regression models were adjusted for sex and the study centres (Munich, Wesel, Bad Honnef and Leipzig).

None of the atopic outcomes were associated with any of the SNPs encoding the *FADS* gene cluster (Table 1).

Strong effects of *FADS* SNPs on the blood fatty acid composition were shown previously (1). Also the association between fatty acids and atopic diseases was shown as well established. Thus, we considered a link between *FADS* SNPs and atopic diseases as biologically plausible. We decided on children as study subjects with the assumption that they have had less exposure to environmental factors that contribute to development of atopic diseases than adults and would hence

dilute the association of interest in this paper. However, our hypothesis could not be substantiated.

Many different pathways influence development of atopic diseases, and a heterogeneous combination of genetic and environmental factors plays roles. Possibly, the *FADS* pathway is not strong enough to stick out among the others.

One could speculate that the *FADS* effects constitute later in life so that they cannot be detected in our 6-year-old children. Furthermore, there are numerous regulatory mechanisms that modify the pathway from genetics to disease so that the effects of SNPs might be relativised and alleviated.

Both of our birth cohort studies are large in participant numbers and have well-defined outcomes, but as we used data at 6 years we may have not captured effects that become important later in life. Finally, power calculations with the genetic power calculator (6) showed that the effects of the studied associations are not sufficient.

Although biologically plausible, we did not find any direct association between *FADS* SNPs and atopic outcomes in children at age of 6.

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Accepted for publication 29 June 2010
Allergy 2010
© 2010 John Wiley & Sons A/S
DOI: 10.1111/j.1398-9995.2010.02457.x

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