The effect of genetic variants in the FADS gene cluster is one of the first examples for gene-nutrition interactions that influence complex phenotypes

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Genetic Variations in Polyunsaturated Fatty Acid Metabolism – Implications for Child Health?
by Eva Lattka et al.

Key insights
This article presents results from recent gene-nutrition interaction studies, discusses the implications for child health, and gives an outlook how these associations might translate into clinical practice in the future.

Current knowledge
Recent genetic association studies show that in addition to nutritional influences, the genetic background is highly important for polyunsaturated fatty acid (PUFA) composition in human tissues. Polymorphisms in the FADS genes determine the efficiency how PUFAs are processed endogenously. Furthermore, FADS genotypes modulate the effect of nutrition on complex phenotypes such as cognition and asthma risk. So far, results are inconsistent regarding the direct association of FADS polymorphisms with atopic diseases.

Practical implications
A sufficient supply of PUFA does not necessarily translate into a beneficial effect because of such gene-nutrient interactions. Once the complex network of nutritional and genetic influences is understood, well-defined dietary recommendations might be possible for optimal child health.

Recommended reading
Genetic Variations in Polyunsaturated Fatty Acid Metabolism – Implications for Child Health?

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Abstract

Sufficient nutritional supply with polyunsaturated fatty acids (PUFAs) has long been considered as beneficial for child health, especially in regard to neuronal development and allergic diseases. In recent years, genetic association studies showed that in addition to nutritional influences, the genetic background is highly important for PUFA composition in human tissues. Specifically, polymorphisms in the fatty acid desaturase genes or \textit{FADS} determine the efficiency of how PUFAs are processed endogenously. Recent gene-nutrition interaction studies suggest that these polymorphisms modulate the effect of nutritional fatty acid intake on complex phenotypes such as cognitive outcomes and asthma risk in children. These early results may provide the basis for future well-specified dietary recommendations to achieve optimal health benefit for all children. This article presents results from recent gene-nutrition interaction studies, discusses its implications for child health, and gives an outlook how this association might translate into clinical practice in the future.

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Key Messages

• Fatty acid desaturase (\textit{FADS}) genotypes are closely associated with a wide range of intermediate phenotypes such as polyunsaturated fatty acids, lipid, and glucose levels, and first evidence exists for an association with complex diseases (e.g. diabetes mellitus type 2).
• \textit{FADS} genotypes modulate the effect of nutrition on complex phenotypes such as cognition and asthma risk.
• Mendelian randomization approaches using \textit{FADS} genotypes might be useful for understanding pathways and causalities of fatty acid-related diseases better.
• Well-defined dietary recommendations might be possible in the future for optimal child health, once the complex network of nutritional and genetic influences is understood.

Key Words
Allergy · Breastfeeding · Cognition · \textit{Δ5}-Desaturase · \textit{Δ6}-Desaturase · \textit{FADS1} · \textit{FADS2} · Gene-nutrition interaction · Long-chain polyunsaturated fatty acids · Single nucleotide polymorphisms

Introduction

The genomic era opened new possibilities for gaining the first insights how a person’s genetic background might influence certain health outcomes. Hundreds of genetic
loci for various phenotypes have been identified in recent years by genome-wide association studies (GWAS). As a tool of genetic epidemiology, such studies scan for genetic markers – in most cases, single nucleotide polymorphisms (SNPs) – across the genomes of many people to find genetic variations associated with a particular disease or phenotype (table 1). The most commonly used study design is the case-control, where subjects are divided into cases and matched controls; then genotype frequencies are compared between the groups. This design is especially useful in finding genetic variations that contribute to common, complex diseases, such as atopic diseases, diabetes, heart and mental diseases.

Polymorphism association studies (GWAS) have identified many genetic loci associated with various phenotypes. These loci can be used to understand the genetic basis of diseases and traits. The most commonly used study design is the case-control, where subjects are divided into cases and matched controls; then genotype frequencies are compared between the groups. This design is especially useful in finding genetic variations that contribute to common, complex diseases, such as atopic diseases, diabetes, heart and mental diseases (fig. 1). Another design uses cohorts representing the general population to detect associations with ‘intermediate’ phenotypes such as fatty acid, lipid, metabolite or expression levels. Here, genotypes between individuals are compared to detect those alleles that contribute to especially high or low levels of the measured intermediate phenotype. Once new genetic associations are identified, researchers hope to improve understanding of pathways and to develop better strategies to detect, treat, and prevent disease.

One of the challenges of the post-genomic era is to make use of this vast amount of data and, in the best case, transfer the results into clinical practice. The main questions that researchers and clinicians aim to answer are:

- How many of the identified genetic loci translate from statistical significance to biological relevance?
- How does a certain genetic background interact with environmental influences or lifestyle factors such as nutrition or physical activity?
- Will we be able to predict disease risk based on genetic data and to give precise dietary or lifestyle recommendations to prevent disease?

This article focuses on the association of SNPs in the fatty acid desaturase (FADS) gene cluster with fatty acid levels and fatty acid-related phenotypes, which is one of the strongest and best-replicated associations identified in recent years. The biological relevance of this association and its implication for child health is discussed, current gene-nutrition interaction studies are presented, and an outlook how this association might translate into clinical practice in the future is provided.

Polyunsaturated Fatty Acids
Nutritional supply with essential ω–6 and ω–3 polyunsaturated fatty acids (PUFAs) and their long-chain derivatives such as arachidonic acid (AA) and especially docosahexaenoic acid (DHA) is considered highly important for various physiological functions in every stage of human life. Among the main functions of PUFAs is regulating cell membrane fluidity as well as acting as precursors of eicosanoids and docosanoids, which play an important role in inflammatory processes [1, 2]. In the fetal state and in early infancy, DHA is needed for proper retinal and neuronal development [3], which is reflected by the massive accumulation of DHA in the fetal retina and brain during pregnancy [4]. In recent years, much research interest has therefore been laid on the optimization of fetal DHA supply by maternal intake of DHA supplements during pregnancy and lactation. In addition to the importance of the nutritional intake of PUFAs, evidence emerged for considerable inter-individual variation in the capacity of how dietary ω–6 and ω–3 fatty acids are endogenously processed via the desaturation/elongation pathway [5]. In brief, linoleic acid and α-linolenic acid obtained from the diet are converted into longer chain fatty acids by elongation of the fatty acid carbon chain and insertion of double bonds (i.e. desaturation) via this pathway, which had been described by Sprecher [6]. A basic illustration of this pathway is given in figure 2. The rate-limiting enzymes in this pathway are the Δ5- and Δ6-desaturase, which are encoded by the genes FADS1 and FADS2, respectively [1, 7].
In 2006, the first genetic association study on the fatty acid composition in serum phospholipids revealed significant associations of SNPs in the FADS genes with several ω-6 and ω-3 PUFAs [8]. Carriers of the minor alleles of the investigated SNPs showed higher concentrations of the desaturase substrates and lower concentrations of the desaturase products compared to major allele carriers. This led to the hypothesis that minor allele carriers have less ability to endogenously convert the precursor fatty acids to their longer-chain products. In the meantime, this association was replicated in several other (candidate-gene and genome-wide) studies involving populations of European, Asian, and African descent, and including also other tissues, such as erythrocyte membrane phospholipids, adipose tissue, and breast milk [9–23].

However, FADS genotypes are not only associated with PUFA concentrations – several GWAS on complex lipid traits reported associations of FADS polymorphisms with serum phosphatidylcholines [24, 25], and the blood lipid parameters low- and high-density lipoprotein, total cholesterol, and triglycerides [26–34], suggesting that the desaturation pathway might be highly important for lipid homeostasis in the human body.

### Fatty Acid-Related Complex Diseases

In addition to lipid homeostasis, early hints were available from GWAS that demonstrated the genetically determined fatty acid composition and degree of desaturation may influence glucose homeostasis: SNPs in FADS1 and FADS2 have recently been associated with fasting glucose [32, 35], and several indices of insulin secretion and sensitivity [35–37]. Another GWAS on genetic determinants for resting heart rate found one SNP in FADS1 to be associated with the length of heart rate interval [38]. Whether SNPs in the FADS gene cluster show pleiotropic effects on all these phenotypes or whether one of these phenotypes in consequence causes the associations with all other phenotypes remains to be analyzed. However, these
widespread associations with multiple intermediate phenotypes representing different physiological processes lead to the question whether FADS genotypes also influence the development of complex fatty acid- or lipid-related phenotypes such as coronary artery, allergic, and mental disease, or glucose- and insulin-related diseases such as type 2 diabetes mellitus. Several studies analyzed the influence of FADS genotypes on such complex outcomes, but real evidence for significant associations is scarce. Table 2 summarizes the recent results of studies looking at the associations between FADS SNPs and complex outcomes. In an Italian and Korean population, FADS SNPs were associated with cardiovascular disease [19, 39]. These results were supported by a GWAS, in which hints for an association were also detected, but not at the genome-wide significance level [40]. Associations with atopic diseases were not significant in most studies [41, 42]. The only statistically significant association between one of the atopic disease entities and FADS gene variants was reported for eczema in a subgroup [41], while in the entire cohort no association was found [42]. Associations with attention-deficit/hyperactivity and bipolar disorder have been reported [40, 43] but these studies have not been replicated to date. Two studies reported significant associations of FADS SNPs with type 2 diabetes mellitus [35, 44].

Although the effect of genetic variants in the FADS gene cluster on PUFA concentrations in various tissues is extraordinarily strong [9–23], detection of really strong associations between these variants and fatty acid-related complex diseases is scarce and might be impeded by the sophisticated regulatory network of fatty acid and lipid metabolism. Several genes might be involved in the regulation of fatty acid and lipid levels and nutritional influences might play an important role as well. Gene-gene interaction and gene-nutrition interaction studies might be one of the next steps to understand this complex network better and to evaluate the biological significance of genetic background for the development of fatty acid-related complex diseases.

**Fatty Acid Genotype Interaction in Child Nutrition**

Recently, several gene-nutrition interaction studies on the effect of FADS genotypes together with nutritional influences on complex outcomes have been performed. One major field of interest when talking about fatty acids and child health is the field of mental health and neuronal development. Several studies showed a relationship between fish or fish oil intake and breastfeeding on later cognitive outcomes and different measures of intelligence in children [45–49]. It is widely hypothesized that this relation might be due to the presence of important long-chain PUFA such as DHA in fish oil and breast milk. Therefore, pregnant and lactating women are advised to achieve an average DHA intake of additional 200 mg DHA/day in order to provide optimal supply for the fetus and newborn infant [4]. Interestingly, early evidence suggests that polymorphisms in the FADS gene cluster might modulate this effect by gene-nutrition interaction. Caspi et al. [50] reported on a genetic variant in the FADS2 gene modulating the asso-

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**Fig. 2.** Schematic presentation of the desaturation/elongation pathway of ω-3 and ω-6 PUFAs (modified from [6]).
ciation between previous breastfeeding and intelligence quotient (IQ) in 2 large birth cohorts. Children who were previously breastfed and formula fed differed in their later IQ in both cohorts, but this effect was more pronounced and only significant in children carrying the major allele of the investigated SNP (rs174575). In contrast, children with the minor allele neither gained an advantage nor suffered a disadvantage from having been fed breast milk. The attempt to replicate these findings in the Avon Longitudinal Study of Parents and Children (ALSPAC) [51] showed differing effects from the Caspi study. In that study [23], all children showed benefit from having been

### Table 2. Summary of association studies of FADS polymorphisms with complex diseases

<table>
<thead>
<tr>
<th>Study</th>
<th>Subjects</th>
<th>Analyzed SNP(s)</th>
<th>Analyzed outcome</th>
<th>Main findings</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cardiovascular diseases</strong></td>
<td></td>
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<tr>
<td>Baylin et al. [11]</td>
<td>n (ca) = 1,694, n (co) = 1,694; CR</td>
<td>rs3834458</td>
<td>non-fatal acute MI in adults</td>
<td>no association between rs3834458 and non-fatal acute MI</td>
</tr>
<tr>
<td>Martinelli et al. [39]</td>
<td>n (ca) = 610, n (co) = 266; IT</td>
<td>13 SNPs in the FADS gene cluster</td>
<td>CAD in adults</td>
<td>FADS haplotypes associated with high AA/LA ratio are also associated with higher CAD risk (p = 0.02)</td>
</tr>
<tr>
<td>Kwak et al. [19]</td>
<td>n (ca) = 756, n (co) = 890; KR</td>
<td>4 SNPs in the FADS gene cluster</td>
<td>CAD in adults</td>
<td>minor T allele frequency of rs174537 significantly lower in CAD patients than in controls</td>
</tr>
<tr>
<td><strong>Atopic diseases</strong></td>
<td></td>
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<tr>
<td>Schaeffer et al. [8]</td>
<td>n (total) = 727, n (rhinitis) = 76, n (eczema) = 49; DE</td>
<td>18 SNPs in the FADS gene cluster</td>
<td>allergic rhinitis, atopic eczema, and IgE levels in adults</td>
<td>no association with IgE levels; minor alleles are protective for allergic rhinitis and atopic eczema, which is however not significant after correction for multiple testing</td>
</tr>
<tr>
<td>Rzehak et al. [41]</td>
<td>n (total) = 333, eczema = 14.1%; DE; n (total) = 542, eczema = 30.6%; NL</td>
<td>5 SNPs in FADS1/ FADS2</td>
<td>IgE levels and eczema in the first 2 years of life</td>
<td>no association with IgE levels; SNPs are significantly associated with eczema in the German (p &lt; 0.005), but not in the Dutch study</td>
</tr>
<tr>
<td>Singmann et al. [42]</td>
<td>n (total) = 2,718, asthma = 4%, bronchitis = 29%, eczema = 38%, hay fever = 9%; DE</td>
<td>5 SNPs in FADS1/ FADS2</td>
<td>asthma, bronchitis, eczema, hay fever in children</td>
<td>no association with any of the tested outcomes</td>
</tr>
<tr>
<td><strong>Diabetes</strong></td>
<td></td>
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<tr>
<td>Dupuis et al. [35]</td>
<td>n (ca) = 40,655, n (co) = 87,022; EUR</td>
<td>genome-wide study</td>
<td>T2DM [and related quantitative traits (e.g. glucose, HOMA-B, HOMA-IR)] in adults</td>
<td>major allele of SNP rs174550 is associated with higher risk of T2DM (OR = 1.04, p = 2.3 × 10⁻⁴)</td>
</tr>
<tr>
<td>Kröger et al. [44]</td>
<td>n (ca) = 649, n (co) = 2,004; DE</td>
<td>rs174546 in FADS1</td>
<td>incident T2DM in adults</td>
<td>minor allele of SNP rs174546 is associated with lower risk of T2DM when adjusted for Δ⁵-desaturase activity (RR = 0.78, p = 0.009)</td>
</tr>
<tr>
<td><strong>Mental diseases and others</strong></td>
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<tr>
<td>Brookes et al. [43]</td>
<td>n (ca) = 180, n (co) = 180; GBR</td>
<td>29 SNPs in the FADS gene cluster</td>
<td>ADHD in children and adolescents</td>
<td>SNP rs498793 is associated with ADHD (p = 0.004)</td>
</tr>
<tr>
<td>Wellcome Trust Case Control Consortium [40]</td>
<td>n (ca) = 2,000 (for each disease), n (co) = 3,000; GBR</td>
<td>genome-wide study</td>
<td>7 common diseases (bipolar disorder, CAD, Crohn’s disease, hypertension, rheumatoid arthritis, type 1 diabetes, T2DM) in adults</td>
<td>hints for association of SNP rs174548 with bipolar disorder (p = 0.048), CAD (p = 0.021), and Crohn’s disease (p = 0.027; summarized in [24])</td>
</tr>
</tbody>
</table>

n = Number of cases; ca = cases; co = controls; CR = Costa Rica; IT = Italy; KR = Korea; DE = Germany; NL = The Netherlands; EUR = individuals of European descent; GBR = Great Britain; MI = myocardial infarction; CAD = coronary artery disease; LA = linoleic acid; T2DM = type 2 diabetes mellitus; HOMA-B = homeostatic model assessment index of β-cell function; HOMA-IR = homeostatic model assessment index of insulin resistance; ADHD = attention-deficit/hyperactivity disorder; OR = odds ratio (effect per allele); RR = relative risk per allele.
breastfed irrespective of genotype (on average 8 points higher full-scale IQ in breastfed children in unadjusted analysis (3 points higher in adjusted analysis)). Children homozygous for the minor allele had the lowest IQ scores when not having been breastfed (4.3 IQ points below non-breastfed carriers of the major allele), but showed the highest benefit when having been breastfed, thereby reaching similar scores as breastfed major allele carriers (p value for interaction = 0.0091). A third study did not find any significant interactions between breastfeeding and IQ, possibly because of the smaller sample size or the later time point of IQ measurement [5]. In this third study, IQ was determined in adolescence, whereas in the ALSPAC study, IQ was assessed at 8 years. Recently, a fourth study has been published that looked at cognitive scores at 14 months (INMA-Sabadell birth cohort) and at 4 years in the replication study (AMICS INMA-Menorca Birth Cohort) [23]. Although in that study other SNPs were genotyped, sample sizes were much smaller, and the main outcome was slightly different, similar interactions as in the ALSPAC study were observed: not having been breastfed conferred a disadvantage in cognition among children being homozygous for the rs174468 allele, which corresponded to lower Δ5-desaturase activity, but not among those carrying at least one allele corresponding to high Δ5-desaturase activity [p value for interaction = 0.020 (Menorca) and 0.077 (Sabadell)]. Children who were breastfed did not differ in their cognition score irrespective of genotype. Interestingly, in that study, maternal FADS genotypes were nominally associated with children’s cognition score. The minor allele of SNP rs174627 (associated with low Δ5- and high Δ6-desaturase activity in colostrum) was related to higher child cognitive scores. Replication of these results including further interaction analyses is highly recommended. The results obtained in the ALSPAC cohort [51] suggest that breastfeeding is beneficial for all children irrespective of genetic background. However, these results (once they are replicated and confirmed) might be the first step towards the possibility for individualized recommendations and might help to guide mothers of children with a defined genetic background more easily in their decision whether to breastfeed their children or not. Those children who cannot be breastfed due to various reasons might in the future obtain individualized formula based on their genotype to achieve optimal developmental outcomes. Of note, the tested polymorphisms are very frequent in the general population (minor allele frequency of around 30% and higher in Europeans), which illustrates the high potential of public health relevance.

Gene-Nutrition Interaction and Atopic Diseases

Another field of high public interest that affects more and more children and adults, and that is considered as one of the health burdens of industrialized countries, is the field of allergic diseases. So far, inconsistent results exist on the direct association of FADS polymorphisms with atopic diseases. The only statistically significant association between FADS gene variants and atopic eczema was reported in a subgroup [41], while in the entire cohort no association was found [42]; furthermore, another study did not find significant associations with atopic disease either [8]. However, two recent gene-nutrition interaction studies suggest that FADS genotypes might indeed be important for the development of atopic disease outcomes.

In the first study, the influence of FADS genotypes on the association between dietary fatty acid intake, atopic diseases, and allergic sensitization in 10-year-old children was analyzed in 2 German prospective birth cohort studies [53]. Margarine and fatty acid intake were analyzed using a food frequency questionnaire, information on atopic diseases was collected using a questionnaire completed by the parents, and specific immunoglobulin E was measured. In this study, no direct association between FADS genotypes and allergic diseases or atopic sensitization was detected and dietary fatty acid intake was not associated with allergy in the crude analysis. However, in an additional analysis stratified by FADS genotype, a higher daily margarine intake was significantly associated with higher asthma risk only in individuals carrying two copies of the major allele. This result might explain the partly inconsistent results on dietary fatty acids and allergic outcomes and strengthens the importance of including genetic data in such studies. Although the presented study has several limitations (e.g. small sample size in stratified analysis), it seems likely that people with a certain genetic background are more sensitive to nutritional influences and more likely predisposed to the development of allergic disorders under certain nutritional conditions. The mechanisms that make FADS major allele carriers more susceptible to developing asthma are unknown. However, one could speculate that a higher percentage of inflammatory processes in major

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allele carriers might play a role in the predisposition to allergic diseases. This assumption is based on the higher capability of major allele carriers to convert n–6 fatty acids (which are highly abundant in margarine) to their longer-chain n–6 products, which are in turn precursors of pro-inflammatory eicosanoids.

The second study in the same child cohort investigated the effect of the duration of exclusive breastfeeding on ever having asthma up to 10 years of age and the influence of FADS genotypes on this association [54]. Breastfeeding is widely recognized as beneficial for a reduced risk of asthma and atopy [55], although not all results are conclusive [56]. The underlying biological mechanisms are not entirely clear, but long-chain PUFAs, which are contained in breast milk, might play one major role [57]. In that study, asthma prevalence (defined as ever having asthma up to age 10 years) decreased with increasing duration of exclusive breastfeeding (1–2 months: 13% asthma prevalence, 3–4 months: 11%, 5–6 months: 9%; p = 0.0172). Again, FADS genotypes were not directly associated with asthma prevalence, although prevalence was slightly lower in minor allele carriers. Interestingly, when looking at the effect of breastfeeding on asthma prevalence in a second analysis stratified by genotype, asthma prevalence was significantly reduced only in children who had been exclusively breastfed for at least 3 months and were carrying at least one copy of the minor allele of the investigated SNPs. In contrast, children being homozygous for the major allele showed no significant benefit from having been exclusively breastfed. This effect was also confirmed in an additional interaction analysis.

How can we interpret these results? Again, these results suggest that a certain group of children with a defined genetic background are more sensitive to nutritional influences, although a possible biological explanation is harder to find compared to the aforementioned study. Only those children who are less able to convert precursor PUFA to their longer-chain products show a benefit after at least 3 months of exclusive breastfeeding. In a previous study, it has been shown that mothers carrying the minor alleles of several polymorphisms in the FADS genes have decreased levels of the pro-inflammatory eicosanoid precursor AA in their breast milk from 1.5 to 6 months of breastfeeding [16]. Children carrying at least one minor allele are more likely to have a mother that also carries a minor allele than children being homozygous for the major allele due to rules of inheritance. These children might therefore gain advantage from the low supply with AA by maternal breast milk and their own low capability to convert precursor n–6 PUFA in breast milk to AA. In contrast, a high supply with AA during lactation might not gain any benefit for breastfed children compared to bottle-fed children in terms of asthma risk. Because maternal genotypes were not available in the presented study and breast milk fatty acids were not included, the influence of the maternal genotype and fatty acid composition on the child’s asthma risk could not be determined.

**Outlook**

Although a lot of questions remain open, these early results show a clear modulation of nutritional influences on complex outcomes by genetic variants in fatty acid metabolism (fig. 3). How can we make use of these data in the future? Optimal health outcomes during development are desirable for all children and the presented data might be a very first step towards the possibility for individual nutritional recommendations in order to achieve optimal cognitive development and the reduction of atopic disease risk. Before that goal can be achieved, more detailed studies are required under well-defined nutritional preconditions and with a sufficient and well-phenotyped number of subjects. Along with these further intervention studies on specified health outcomes, it is indispensable to focus on the biological mechanisms that make people with a certain genetic background more sensitive to nutritional influences. Once the genotype-dependent effects of nutrition on the analyzed outcomes are confirmed and biological mechanisms become clearer, individualized dietary recommendations or specific interventions might be possible.
However, dispute exists among researchers whether genotype-dependent dietary recommendations are realistic in the future due to practical, financial and ethical reasons. Still, even if it will not be feasible in the future to test every pregnant woman for her FADS genotype, knowledge of the genetic influences on dietary fatty acid conversion is critical in understanding pathways and causalities of fatty acid-related phenotypes. In this context, FADS genotypes can be very useful in future studies as surrogate variables of modifiable exposures such as desaturase activity or fatty acid supply. This approach is called the Mendelian randomization approach in genetic epidemiology [58–60] and is especially useful as alternative to such randomized controlled trials, which are difficult to conduct due to ethical reasons, e.g. trials on breastfeeding effects on disease risk.

An example of such a Mendelian randomization approach using FADS genotypes as proxy variables of desaturase activity and its potential causality in diabetes development has been published recently by Kröger et al. [44, 61]. Once the pathways and genetic influences are understood completely, refinement of current recommendations might be possible in the future to enable every child to achieve the maximum benefit with the lowest possible disease risk.

**Conclusion**

The effect of genetic variants in the FADS gene cluster is one of the first examples for gene-nutrition interactions that influence complex phenotypes. The studies summarized in this review show the high complexity of the interaction between genetic background and environmental influences and remind us that genetic association studies are only the first step in understanding the mechanisms and pathways of specific phenotypes. The great opportunity of the post-genomic era is now to integrate data from different fields and bring together geneticists, epidemiologists, nutrition experts, and clinicians in order to realize the full translational potential of the recent association findings.

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