Lower prevalence of common filaggrin mutations in a community sample of atopic eczema: is disease severity important?

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Geringere Prävalenz häufiger Filaggrin-Mutationen in einer unselektionierten Neurodermitis-Kohorte: Ist der Schweregrad der Erkrankung bedeutend?


Ergebnisse: In der Patientengruppe fanden sich ein homozygoter (R501X/R501X), 4 compound heterozygote (3 R501X/2282del4, ein 2282del4/R2447X) und 17 heterozygote (10 R501X/wt, 5 2282del4/wt, 2 R2447X/wt), in der Kontrollgruppe 9 heterozygote (5 R501X/wt, 4 2282del4/wt) Individuen. Die kombinierte Prävalenz von FLG Funktionsverlust-Mutationen betrug 5 % in der Kontroll- und 9 % in der Atopie-Gruppe. In einer Subtypenanalyse zeigte die Kombination von allergischer Rhinitis und Neurodermitis eine signifikante Assoziation mit FLG Mutationen, OR = 3,7 (1,01–12,67; p = 0,024). Ebenso wurden signifikante Zusammenhänge mit berichteter Familienanamnese von Asthma bronchiale, OR = 4,35 (1,78–10,62; p = 0,0012), allergischer Rhinitis, OR = 2,33 (1,49–3,63; p = 0,0002) und Neurodermitis, OR = 5,08 (2,78–9,30; p ≤ 0,0001) gefunden. Im Gegensatz zu klinischen Studien mit prozentuell mehr schwer betroffenen Personen, zeigten FLG Mutationen in der vorliegenden Arbeit eine lediglich moderate Assoziation mit atopischen Erkrankungen.


Summary. Background: Recent studies have shown an association of loss-of-function mutations in the filaggrin gene (FLG) with ichthyosis vulgaris and atopic eczema (AE). Case selection may have distorted the hitherto reported prevalence of FLG mutations and their relation to atopic disease. The aim of the study was to determine the true population prevalence of FLG mutations in unselected children with and without reported physician diagnoses of asthma, allergic rhinitis and AE and their relationship with family history of atopic disease.

Methods: We used a nested case-control design by sampling children with reported doctor’s diagnoses of AE, asthma and allergic rhinitis and randomly selected controls from a larger cross-sectional study (n = 1263). Most common FLG mutations R501X, 2282del4, and R2447X were screened in DNA extracted from defrosted urine samples. The relationship of the combined FLG variants with atopic diseases and with reported family history of AE, asthma, and rhinitis was assessed.

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Results: In the patient group one homozygote (R501X/R501X), 4 compound heterozygotes (3 R501X/2282del4, one 2282del4/R2447X), and 17 heterozygotes (10 R501X/wt, 5 2282del4/wt, and 2 R2447X/wt), in the control group 9 heterozygotes (5 R501X/wt, 4 2282del4/wt) were detected. The combined prevalence of FLG loss-of-function alleles was 5% in the control group and 9% in the atopic sample. In a subgroup analysis, the combination of allergic rhinitis and AE showed a significant relationship with FLG mutations, OR = 3.7 (1.01–12.67, p = 0.024). Likewise, significant relations with reported family history of asthma, OR = 4.35 (1.78–10.62, p = 0.0012), allergic rhinitis, OR = 2.33 (1.49–3.63, p = 0.0002), and AE, OR = 5.08 (2.78–9.30, p ≤ 0.0001) were observed. In contrast to clinical studies with higher percentages of severely affected persons, FLG mutations here showed a moderate association with atopic disease.

Conclusions: Case selection may be responsible for overestimating the prevalence of FLG mutations in atopic disease.

Key words: Allergic rhinitis, asthma, atopic eczema, filaggrin, public health, Allergische Rhinitis, Asthma bronchiale, Neurodermitis, Filaggrin, Gesundheitswesen.

Abbreviations

AE Atopic eczema
CAMP Childhood Asthma Management Program
CI Confidence interval
DNA Desoxyribonucleic acid
FeNO Fractional exhaled nitric oxide
FEV1 Forced expiratory volume in one second
FLG Filaggrin
FVC Forced vital capacity
ISAAC International Study of Asthma and Allergies in Childhood
MAS Multicenter Allergy Study
MEFw50 Forced expiratory flow at 50% of FVC
OR Odds ratio
PCR Polymerase chain reaction
SCORAD Scoring Atopic Dermatitis system

Introduction

Mutations in the filaggrin gene (FLG) proven to impair epithelial barrier function are strongly associated with ichthyosis vulgaris and atopic eczema (AE) [1–8]. In several European studies mainly in children and young adults strong associations of FLG loss-of-function alleles with AE, allergic rhinitis, early wheeze, and asthma occurring in the context of AE have been replicated [9–18]. A meta-analysis (nine studies that had been conducted until March 2007) of FLG associations with AE revealed an overall odds ratio (OR) for case-control studies of 4.09 (95% confidence interval (CI): 2.64–6.33) and 2.06 (95% CI: 1.76–2.42) for family studies [8]. Some analyses suggested that individuals with AE who carry FLG loss-of-function alleles are more likely to show earlier onset [14, 16] and persistent disease [13]. Eventually, FLG mutations were associated with greater asthma severity [19] and risk of asthma exacerbations in asthmatic children and young adults [20]. From this overall evidence it has been concluded that FLG mutations represent the single most important risk factors for the development of AE and associated illnesses such as asthma and allergic rhinitis [8, 21]. The observed ORs did, however, show a broader range from 3 to 7, with lower risk estimates from apparently less selected, population-based studies. Recently, a clinically well-characterized case-only cohort of white children (CAMP) with mild to moderate asthma confirmed the association of FLG mutations and AE using both population-based and family-based tests of association [21]. However, no association of FLG loss-of-function alleles with asthma or asthma severity was observed in the absence of AE. This result reminds of a cautious interpretation of earlier studies where subject ascertainment was strongly driven by known family history or by disease severity. It is well known that such studies often overestimate genetic associations due to strong case selection [22, 23]. Moreover, other potential biases can induce false-positive associations [24, 25]. A recent meta-analysis of 24 studies including both case control and family studies provided convincing evidence for a strong association of common FLG mutations with AE (OR = 3.12; 95% CI: 2.57–3.79), in particular more severe and dermatologist-diagnosed disease, and asthma in the presence of AE (OR = 3.29; 95% CI: 2.84–3.82) [26].

Since a genuine interest in both, clinical and public health medicine is to better predict the occurrence and the course of these prevalent and costly diseases, broader evidence is needed for FLG loss-of-function allele associations with asthma, allergic rhinitis, and AE from true population-based studies. For further clarification of hitherto reported mutant FLG associations we used urine samples for genetic analyses from a strict community-based study of schoolchildren with a participation proportion of 85.5%.

Patients, materials, and methods

Study population

As a method of choice [27], a (nested) case-control design was established by sampling all children, aged between 8 and 11 years, from a rural area in the center of Tyrol with International Study of Asthma and Allergies in Childhood (ISAAC) reported diagnoses of AE or asthma or allergic rhinitis as cases (n = 382 = “atopic illness”) and stratified (after region) randomly selected controls without atopic illness (n = 200) from the original cross-sectional study (n = 1263). Due to missing information the final sample was reduced to n = 576. Complete genotyping information was available for 513 children. Sample size was based on power analyses using reviewed prevalence information provided by Irvine [8]. The study was approved by the ethics committee of the Innsbruck Medical University, the regional school board and all local schools.

Health outcome measures

Since the interest of the main study arm was the interplay between environment, predispositions and atopic disease symptoms, doctor’s diagnoses, medications, family history of asthma, allergic rhinitis, and AE were collected from parent reports with a...