Filaggrin gene defects and risk of developing allergic sensitisation and allergic disorders: systematic review and meta-analysis
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CRD summary
This review concluded that filaggrin gene defects increased the risk of allergic sensitisation and allergic disorders, but restoring skin barrier function early in life in individuals with filaggrin defects could prevent development of disorders. The authors’ conclusions regarding increased risk appeared to reflect the evidence, but the conclusion regarding skin barrier function was speculative and should be interpreted with caution.

Authors’ objectives
To assess whether filaggrin gene defects increase the risk of developing allergic sensitisation and allergic disorders and could be used to identify candidates for preventative treatment.

Searching
MEDLINE, EMBASE, Science Citations Index, and BIOSIS Previews were searched from inception to December 2008 without language restrictions. Search terms were reported. UK National Research Register, ClinicalTrials.gov, Index to Theses and Digital Dissertations were searched for unpublished data and ongoing trials. SIGLE was searched for grey literature. In addition, references of included studies and reference citations using ISI Web of Knowledge were searched for additional studies.

Study selection
Any genetic epidemiological study (family or case-control) investigating the relationship between filaggrin gene defects and allergic sensitisation or allergic disorders in humans of any ages and ethnic group were eligible for inclusion. Outcomes of interest were atopic eczema or dermatitis, food allergy, asthma, allergic rhinitis and anaphylaxis in addition to relevant immunological factors relating to the risk of allergic sensitisation assessed by positive skin prick testing or increased levels of allergen specific Immunoglobulin E (IgE).

Included studies were mostly conducted in western Europe and North America. Where reported, the setting was usually in hospital. Most studies included participants with the filaggrin gene mutations R501X and 2282del4. In some studies carriers were compared to non-carriers. Patients had atopic dermatitis (persistent or early onset) or eczema. Diagnoses were made using the following methods: assessed by a dermatologist or allergologist according to various definitions; Hanfin and Rajka criteria; Williams et al criteria; questionnaires or scales; increased IgE levels; or skin prick tests. Most studies were matched for ethnicity and some were also matched for sex and/or age.

Two reviewers screened papers for inclusion. Disagreements were resolved by discussion.

Assessment of study quality
A customised checklist was developed to assess the quality of the included studies, including criteria on participant selection, validity of the approach to genotyping, population stratification and statistical considerations. Studies were described as high, medium or poor quality. The authors did not state how many reviewers performed the validity assessment.

Data extraction
Odds ratios and their 95% confidence intervals were calculated for individual case control studies. For familial studies, the transmission of possible alleles A and B from parents to an affected offspring were translated into odds ratios. P values for the association between filaggrin gene defects and outcomes of interest were also extracted. Where there was a zero in the contingency table, 0.5 was added. Study authors were contacted for further details if necessary. The authors did not state how many reviewers performed the data extraction.

Methods of synthesis
Where possible, a random-effects model was used to combine odds ratios and their 95% confidence intervals. Subgroup analyses were conducted for the two most common mutations (R501X and 2282del4). Sensitivity analyses were conducted for study quality, hospital setting and disease severity (persistent or early onset). Where meta-analysis was not possible, data were presented as a narrative synthesis and reported in the review.

Statistical heterogeneity was assessed using the Cochran’s Q (p value) and $I^2$ tests. Publication bias was assessed using funnel plots.

**Results of the review**

Twenty four studies were included in the review: four family/case control studies (n=1,785 families, n=1,263 cases, n=2,084 controls); 14 case control studies (n=2,559, n=5,807); three family studies (n=1,342 families); two cross-sectional studies (n=3,973); and one cohort study (n=882). Studies were classed as B or C in terms of quality, but it was unclear what level of quality this represented.

**Allergic sensitisation**

Combined filaggrin gene defects were shown to increase the risk of allergic sensitisation, odds ratio 1.57 (95% confidence interval: 1.20, 2.07; two case-control study arms) and odds ratio 1.91 (95% confidence interval: 1.44, 2.54; five family study arms). However, there was evidence of statistical heterogeneity (p<0.001, $I^2=72.20$).

**Atopic eczema/dermatitis**

Combined filaggrin gene defects increased the risk of atopic dermatitis, odds ratio 4.78 (95% confidence interval: 3.31, 6.92; 11 case control study arms) and odds ratio 1.99 (95% confidence interval: 1.72, 2.31; six family study arms). Subgroup analyses and sensitivity analyses confirmed the positive associations. One cohort study showed that filaggrin gene mutations increased the risk of eczema during the first year of life in a Danish cohort, odds ratio 2.26 (95% confidence interval: 1.27, 4.00) and an English cohort, odds ratio 1.95 (95% confidence interval: 1.13, 3.36).

**Allergic rhinitis**

Combined filaggrin gene defects were shown to increase the risk of allergic rhinitis in participants with atopic dermatitis, odds ratio 2.84 (95% confidence interval: 2.08, 3.88; two case-control study arms), odds ratio 2.46 (95% confidence interval: 1.61, 3.76; two family study arms) and in patients without atopic dermatitis, odds ratio 1.78 (95% confidence interval: 1.16, 2.73; two case control study arms).

**Asthma**

There was no significant increase in the risk of asthma in participants with combined filaggrin gene defects without atopic dermatitis or eczema (one family study and three case-control studies). However, participants with combined filaggrin gene defects with atopic dermatitis or eczema were shown to be at increased risk of developing asthma, odds ratio 2.79 (95% confidence interval: 1.77, 4.41; five case-control studies), odds ratio 2.30 (95% confidence interval: 1.66, 3.18; seven family study arms).

Subgroup analyses for gene mutations R501X and 2282del4 showed positive associations in terms of sensitisation, atopic eczema/dermatitis and asthma.

There were no studies assessing the association between filaggrin gene defects and the risk of developing food allergies or anaphylaxis. Where publication bias was assessed, this was not found to be present.

**Authors’ conclusions**

Filaggrin gene defects increase the risk of developing allergic sensitisation, atopic eczema and allergic rhinitis. Restoring skin barrier function early in life in individuals with filaggrin defects may help prevent the development of sensitisation and stop the development and progression of allergic disease.
CRD commentary
The review question was clear and was supported by appropriate inclusion criteria. A comprehensive literature search was undertaken without language restrictions, thereby minimising the risk of language bias. A search for unpublished literature was included, thus reducing the possibility that potentially relevant studies may have been missed. Publication bias was assessed for certain associations and was not found to be present. Validity was assessed, but as the tool was developed by the authors and they did not state how many reviewers performed the validity assessment, it was unclear how reliable the validity assessment was. Two reviewers assessed relevant papers for inclusion, but it was not clear how many reviewers performed the data extraction, thus reviewer error and bias could not be ruled out. Included studies were matched on certain participant characteristics. Appropriate methods were used to combine the studies and investigate statistical heterogeneity. The authors’ conclusions regarding increased risk appeared to reflect the evidence available, but their conclusion regarding restoring skin barrier function was speculative and should be interpreted with caution. Uncertainties surrounding the validity of the included studies and the potential for reviewer error and bias should also be taken into consideration when interpreting the conclusions.

Implications of the review for practice and research
Practice: The authors did not state any implications for practice.

Research: The authors stated that there was a need for further research to investigate the possible role of filaggrin gene defects on other systemic atopic allergic disorders such as food allergy and anaphylaxis. The authors also recommended the following additional research: prospective epidemiological studies, family-based designs, research focusing on the mechanisms through which defective skin function impacts on the presentation of antigens and the possible association with immune modulation. Studies of individuals with filaggrin gene defects who do not develop atopy or atopic allergic conditions would also be useful. There was also a need for further research to identify high-risk individuals, so that preventative measures could be introduced to restore the barrier function of the skin or measures to avoid allergens in infants with filaggrin defects.

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This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.