STUDY POPULATION. Three families with a dominantly inherited complex of cold-induced urticaria, antibody deficiency, and susceptibility to infection and autoimmunity.

METHODS. Immunophenotyping, including flow cytometry, analysis of serum immunoglobulins and autoantibodies, lymphocyte stimulation, and enzymatic assays, was used. Genetic studies, including linkage analysis, targeted Sanger sequencing, and next-generation whole-genome sequencing, were performed.

RESULTS. Cold-induced urticaria occurred in all affected subjects. Other, variable manifestations included atopy, granulomatous rash, autoimmune thyroiditis, antinuclear antibodies, sinopulmonary infections, and common variable immunodeficiency. Levels of serum IgM and IgA, circulating natural killer cells, and class-switched memory B cells were reduced. Linkage analysis led to the identification of an interval on chromosome 16q that included PLCG2, which encodes phospholipase Cγ2, a signaling molecule expressed in B cells, natural killer cells, and mast cells. Genomic sequencing identified 3 distinct in-frame deletions that co-segregated with disease. These deletions, located within a region encoding an inhibitory domain, result in protein products with constitutive phospholipase activity. PLCG2-expressing cells had diminished cellular signaling at 37°C but enhanced signaling at subphysiologic temperatures.

CONCLUSIONS. Genomic deletions in PLCG2 cause gain of function of phospholipase Cγ2, leading to signaling abnormalities in multiple leukocyte subsets and a phenotype that includes both deficient and excessive immune function.

REVIEWER COMMENTS. This is a very interesting “experiment of nature” that provides a great deal of insight into phospholipase-mediated signaling. It is fascinating that the PLCG2 mutations identified in this report could lead to both impaired and excessive immune function and that this can be affected by temperature.


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Cold Urticaria, Immunodeficiency, and Autoimmunity Related to PLCG2 Deletions


PURPOSE OF THE STUDY. To perform Mendelian analysis of 3 families with cold-induced urticaria and identify and elucidate immunologic pathways and mechanisms.
Stockholm, Sweden; 2024 children were included based on available questionnaire data and blood analysis at 0, 4, and 8 years of age.

METHODS. This is a prospective, population-based study that analyzed data collected longitudinally from a birth to age 8 years. Baseline data were collected at enrollment with further assessment via questionnaires mailed to subjects at ages 1, 2, 4, and 8 years with regard to allergy-related disease manifestations. At age 4 and 8 years, subjects with reported allergic disease were invited for an in-person visit that included (1) ISAAC-rhinoconjunctivitis questionnaire, (2) clinical assessments for asthma, eczema, food allergy, and oral allergy syndrome, and (3) blood samples for specific IgE to 8 inhalant allergens (Phadiatop test followed by specific ImmunoCAP IgE to individual allergens). Subjects were divided into 4 rhinitis groups: allergic rhinitis (AR), nonallergic rhinitis (NAR), allergic sensitization without rhinitis (AS), and neither rhinitis nor sensitization.

RESULTS. The median age at enrollment was 3 months. The proportion of children with AR increased from 5.4% to 14% from age 4 to 8 years; there was a slight decrease from 8.1% to 6.3% for NAR. From age 4 years to age 8 years, in children with (1) AR, 87% had persistent disease; (2) NAR, 73% underwent remission and 5.6% developed AR; (3) AS, 56% developed AR including 49% remaining after others were excluded for other atopic disease; and (4) no rhinitis or sensitization, 4% developed AR. Both AR and NAR were associated with asthma, eczema, and food allergy, and 25% of 8-year-olds with AR also had oral allergy syndrome due to birch pollen sensitization.

CONCLUSIONS. Fewer preschool age children with AR experienced remission compared to those with NAR. Allergen sensitization, and not symptoms of rhinitis, preceded development of AR. Oral allergy syndrome was common among children with AR in Sweden.

REVIEWER COMMENTS. This large, longitudinal study of young children provides important clinical information regarding rhinitis symptoms and the natural history of atopic disease. In particular, few children with AR and early allergen sensitization at age 4 years experience remission by age 8 years, yet most children with NAR experience resolution of symptoms during the same time frame. These prognostic factors support early evaluation, testing, intervention, and consistent follow-up of children with AR and allergen sensitization. Oral allergy syndrome may be an important comorbid factor in birch-sensitized children but cannot be generalized to other inhalant allergens or non-Swedish populations. The major limitation of the study is the basis of data collection from questionnaires; however, these data combined with sensitization data and longitudinal symptoms profiling support the diagnostic categories used and the conclusions gained.

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Asthma

PATHOPHYSIOLOGY

Early Childhood Overweight and Asthma and Allergic Sensitization at 8 Years of Age


PURPOSE OF THE STUDY. To examine the associations between high BMI and changes in BMI during the first 7 years of life and asthma and allergic sensitization at age 8 years.

STUDY POPULATION. A birth cohort of 2075 newborn infants followed for 8 years in Sweden as part of a broader prospective epidemiologic study of atopic families (the BAMSE study).

METHODS. Parental questionnaires provided information about environmental exposures and health outcomes including allergic disease and asthma. Allergic sensitization was determined by assessing allergen-specific IgE to dust mites, cat, dog, horse, Cladosporium, birch, timothy, mugwort, milk, egg, codfish, soy, peanut, and wheat. Height and weight data during the study period were obtained from preschool and school health care records.

RESULTS. A high BMI (≥85th percentile) at age 1, 4, and/or 7 years of age was associated with an increased risk of asthma at age 8 years. No such association was observed among children with high BMI at 12 and/or 18 months or at 4 years who developed a normal BMI by age 7 years. The risk was increased among children with high BMI at age 7 years regardless of their earlier weight. Increased risk of sensitization to inhalant allergens was also observed in children with high BMI at age 7 years.

CONCLUSIONS. High BMI during the first 4 years does not increase the risk of asthma at school age among children who have normal weight by age 7 years. High BMI at 7 years is associated with an increased risk of asthma and sensitization to inhalant allergens at age 8 years.

REVIEWER COMMENTS. This study adds further evidence that current elevated BMI is associated with asthma, whereas previous elevations of BMI are not. These results are similar to those of a previous Dutch study (Scholtens S et al. J Allergy Clin Immunol. 2009;123:1312–1318). This observation
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