

directed Sanger sequencing, and specific ex vivo biochemical studies.

**RESULTS.** All patients had a history of significant atopic dermatitis as well as other allergic findings, including asthma, food allergy, and/or environmental allergy. Staphylococcal soft tissue infections, recurrent sinopulmonary infections, low-level Epstein-Barr virus viremia, and other viral infections were characteristic of these patients. In addition, autoimmunity was found in the majority of the patients, primarily cutaneous leukocytoclastic vasculitis or membranoproliferative glomerulonephritis. Finally, neurologic impairment that developed early in life was present in all patients. Laboratory evaluation revealed elevated IgE levels, whereas IgG, IgA, IgM, and specific antibody production to vaccines were found to be normal. The patients also demonstrated varied degrees of cytopenias. Whole-exome evaluation in the affected patients from the first family revealed a large number of single nucleotide variants that after extensive software filtering yielded 1 candidate, an autosomal recessive defect in the gene encoding phosphoglucomutase 3 (PGM3). Application of the same strategy in the second family also yielded an autosomal recessive defect in the affected patients involving the same gene, and in both families, Sanger sequencing confirmed these results. The genetic results were followed by biochemical studies that demonstrated variable defects in O- and N-linked glycosylation, thus establishing that these genetic changes yielded functional abnormalities in glycosylation.

**CONCLUSIONS.** Patients with autosomal recessive defects in PGM3 have an immunologic disorder that includes severe atopic disease, autoimmunity, and intellectual disability as well as increased susceptibility to infection.

**REVIEWER COMMENTS.** This report adds to a growing list of immune defects associated with immune dysregulation that present clinically with elevated IgE levels, atopic disease, and autoimmunity together with increased susceptibility to infection. The link between immune dysregulation and atopy is providing valuable new information regarding the underlying immunologic processes involved in the development of allergic disease. In addition, defects in glycosylation have typically been associated with neurologic disease but generally have not been linked with immune disorders. Conversely, ~50% of the proteins in humans are glycosylated, and there is an evolving appreciation that protein glycosylation plays a role in immunologic development and response. This newly defined disorder provides support for this role, and an additional report of immunologic changes in the setting of genetic defects of glycosylation (Sadat MA, Moir S, Chun TW, et al. Glycosylation, hypogammaglobulinemia, and resistance to viral infections. *N Engl J Med.* 2014;370 [17]:1615–1625) strengthens this link.

URL: [www.pediatrics.org/cgi/doi/10.1542/peds.2014–1817FFFF](http://www.pediatrics.org/cgi/doi/10.1542/peds.2014–1817FFFF)

**Thomas A. Fleisher, MD**  
Bethesda, MD

## **Glycosylation, Hypogammaglobulinemia, and Resistance to Viral Infections**

Sadat MA, Moir S, Chun TW, et al. *N Engl J Med.* 2014;370 (17):1615–1625

**PURPOSE OF THE STUDY.** The goal of this study was to elucidate viral resistance despite immunodeficiency in a rare congenital disorder of glycosylation type IIb.

**STUDY POPULATION.** The study subjects were 2 siblings presenting with multiple neurologic complications and a paradoxical immunologic phenotype characterized by severe hypogammaglobulinemia but limited clinical evidence of recurrent severe infections.

**METHODS.** An 11-year-old boy and 6-year-old girl, first and third children, born to a young, healthy, non-consanguineous couple were evaluated. They are characterized by dysmorphic features, hypotonia, seizures, global developmental delay, cerebral atrophy, optic nerve atrophy, hearing loss, and recurrent bone fractures.

**RESULTS.** The siblings had normal or increased numbers of B cells in peripheral blood but severe hypogammaglobulinemia (317 mg/dL and 142 mg/dL) with significantly shortened half-life for IgG (6 days). The patients had normal specific antibody response to polysaccharide proteins, conjugated proteins, and polysaccharide antigens but did not respond to live virus vaccines such as measles-mumps-rubella (vaccine) or varicella, which are viruses with glycosylated envelopes. These patients did not have altered susceptibility to adenovirus or parvovirus 1, which are nonenvelope viruses, or to vaccinia virus, which is an envelope virus. In contrast, the patients did have markedly reduced susceptibility to infection with HIV and influenza viruses, which are glycosylation-dependent envelope viruses.

**CONCLUSIONS.** These data seem to suggest that altered glycosylation may modify the susceptibility to infection with viruses that must undergo protein glycosylation to complete their infection cycle.

**REVIEWER COMMENTS.** This study helps us to continue to expand our understanding of genetically determined permutations of host defense that could aid in explaining these unusual and unanticipated clinical presentations.

URL: [www.pediatrics.org/cgi/doi/10.1542/peds.2014–1817GGGG](http://www.pediatrics.org/cgi/doi/10.1542/peds.2014–1817GGGG)

**Bradley E. Chipps, MD**  
Sacramento, CA

## **Lentiviral Hematopoietic Stem Cell Gene Therapy in Patients With Wiskott-Aldrich Syndrome**

Aiuti A, Biasco L, Scaramuzza S, et al. *Science.* 2013;341 (6148):1233151

**PURPOSE OF THE STUDY.** The goal of this study was to develop a clinical protocol for Wiskott-Aldrich syndrome (WAS)

## Glycosylation, Hypogammaglobulinemia, and Resistance to Viral Infections

Bradley E. Chipps

*Pediatrics* 2014;134;S182

DOI: 10.1542/peds.2014-1817GGGG

### Updated Information & Services

including high resolution figures, can be found at:  
[http://pediatrics.aappublications.org/content/134/Supplement\\_3/S182.1](http://pediatrics.aappublications.org/content/134/Supplement_3/S182.1)

### Permissions & Licensing

Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at:  
<http://www.aappublications.org/site/misc/Permissions.xhtml>

### Reprints

Information about ordering reprints can be found online:  
<http://www.aappublications.org/site/misc/reprints.xhtml>

# American Academy of Pediatrics

DEDICATED TO THE HEALTH OF ALL CHILDREN®



# PEDIATRICS®

OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

## **Glycosylation, Hypogammaglobulinemia, and Resistance to Viral Infections**

Bradley E. Chipps

*Pediatrics* 2014;134;S182

DOI: 10.1542/peds.2014-1817GGGG

The online version of this article, along with updated information and services, is located on the World Wide Web at:

[http://pediatrics.aappublications.org/content/134/Supplement\\_3/S182.1](http://pediatrics.aappublications.org/content/134/Supplement_3/S182.1)

Pediatrics is the official journal of the American Academy of Pediatrics. A monthly publication, it has been published continuously since 1948. Pediatrics is owned, published, and trademarked by the American Academy of Pediatrics, 345 Park Avenue, Itasca, Illinois, 60143. Copyright © 2014 by the American Academy of Pediatrics. All rights reserved. Print ISSN: 1073-0397.

## American Academy of Pediatrics

DEDICATED TO THE HEALTH OF ALL CHILDREN®

