

Low IgE Is Insufficiently Sensitive to Guide Genetic Testing of *STAT3* Gain-of-Function Mutations

To the Editor:

We read with great interest the letter by Johnson et al. on the value of below reference serum IgE concentration in the diagnosis of hypermorphic or gain-of-function (GoF)¹ signal transducer and activator of transcription 3 (*STAT3*) mutations (MIM: 615952) (1). As noted by the authors, previously published literature does not support the proposal that IgE <2 kU/mL would be reliable in differentiating individuals in need of genetic testing (2–4). Johnson et al. report total IgE concentrations in kilounits per liter, equivalent to International units per milliliter (5). Based on 6 patients with *STAT3* GoF, they suggest that this feature could be used to guide genetic testing. Because we collectively follow a large cohort either carrying previously published activating *STAT3* mutations or novel mutations with gain of *STAT3* luciferase reporter activity, we decided to collect and measure IgE concentrations in this cohort to validate the suggestion of Johnson et al.

To test the notion proposed by Johnson et al., we determined IgE concentrations from an international cohort of known germline *STAT3* GoF patients, all of whom had genetically verified and hyperactivating *STAT3* mutations confirmed by an abnormal luciferase assay demonstrating enhanced transcriptional activity. Written informed consent was obtained from patients. The study was conducted in accor-

dance to the principles of the Helsinki Declaration and was approved by local ethics committees. IgE concentrations in our cohort were tested in local accredited clinical laboratories using IgE calibrators traceable to the 2nd International Reference Preparation 75/502 of Human Serum Immunoglobulin E from the World Health Organization and by using the recommended reference intervals; only those assays with 5h percentile cutoff values ≤2 were included. In reporting, our centers variably used International units per milliliter or kilounits per liter (2, 3, 5).

Of the 23 patients (present age, 3–44; 52% females) assessed in our study that fulfill the above criteria, the results of 11 have previously been published (2–4), whereas the results of the remaining 12 will be published in separate articles. All patients had either multiorgan autoimmunity and/or autoimmune lymphoproliferative syndrome-like features, often accompanied by poor growth. These led to the identification of disease-causing mutations in 21 patients. Indications for genetic testing were family screening in 1 and disseminated nontuberculous mycobacterial disease in another affected individual.

Of the 23 patients in our extended cohort, 9 had serum IgE concentrations >2 IU/mL or kU/mL (2.4–146, median <2, mean 28.3, see Fig. 1). This gives serum IgE concentrations <2 (IU/mL or kU/mL) a sensitivity of 61% (95% CI, 39%–80%), a value that is too low to guide clinical genetic testing. Whether those *STAT3* GoF patients with serum IgE concentrations <2 IU/mL or kU/mL represent a phenotypic subgroup (e.g., neonatal diabetes, autoimmune lymphoproliferative syndrome-like, patients with failure to thrive) will require further study and identification of additional patients to provide a larger patient cohort.

Currently, *STAT3* GoF is known to cause a wide spectrum of

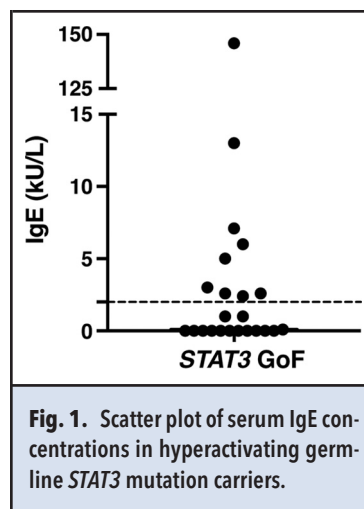


Fig. 1. Scatter plot of serum IgE concentrations in hyperactivating germline *STAT3* mutation carriers.

autoimmune disorders including cytopenias; lymphoproliferation; enteritis; type 1 diabetes; skin, lung, and thyroid disorders; and arthritis. In a substantial subset of patients, *STAT3* GoF mutations also lead to short stature; severe bacterial, viral, fungal, and mycobacterial infections; hypogammaglobulinemia; and malignancy. Thus, *STAT3* GoF syndrome is a multisystem disorder potentially leading to severe early-onset multisystem organ dysfunction and large granular lymphocytic leukemia (3–4). Clinically, stem cell transplantation has been reported to halt disease progression (4). This, however, requires further study. Also, when a novel monogenic immunologic disease has been published, its phenotype later typically evolves into a significantly broader clinical and immunologic phenotype. We thus strongly recommend genetic testing for *STAT3* GoF with high index of suspicion, irrespective of serum IgE concentrations.

Author Contributions: All authors confirmed they have contributed to the intellectual content of this paper and have met the following 3 requirements: (a) significant contributions to the conception and design, acquisition of data, or analysis and interpretation of data; (b) drafting or revising the article for intellectual content; and (c) final approval of the published article.

Authors' Disclosures or Potential Conflicts of Interest: Upon manuscript submission, all authors completed the author disclosure form. Disclosures and/or potential conflicts of interest:

Employment or Leadership: None declared.

Consultant or Advisory Role: None declared.

Stock Ownership: None declared.

Honoraria: None declared.

Research Funding: S.G. Tangye, National Health and Medical Research Council of Australia; J.D. Milner, NIAID, NIH intramural funding; M. Seppänen, Helsinki University Hospital Research Funds.

Expert Testimony: None declared.

Patents: None declared.

Other Remuneration: L.R. Forbes, Clinical Immunology Society.

Acknowledgments: We acknowledge the contributions of our patients and those of Olive Eckstein MD, Tiphonie Vogel MD PhD, and Michael A. Weinreich PhD, who provided data for this analysis.

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Stuart G. Tangye^{2,3}

Lisa R. Forbes⁴

Jennifer Leiding⁵

Kahn Preece⁶

Ashish R. Kumar⁷

Eleonora Gambineri⁸

Joshua D. Milner⁹

Megan A. Cooper¹⁰

Mikko Seppänen^{11*}

² Immunology Division, Garvan Institute of Medical Research Darlinghurst, New South Wales Australia

³ St Vincent's Clinical School, Faculty of Medicine University of NSW, Sydney, Australia

⁴ Section of Immunology, Allergy, & Rheumatology, Department of Pediatrics, Baylor College of Medicine, Center for Human Immunobiology, Texas Children's Hospital, Houston, TX

⁵ Division of Allergy and Immunology Department of Pediatrics, University of South Florida, St Petersburg, FL

⁶ Pediatric Allergy and Immunology Department Starship Children's Hospital Auckland, New Zealand

⁷ Cancer and Blood Diseases Institute Division of Bone Marrow Transplantation and Immune Deficiency and Department of Pediatrics, Cincinnati Children's Hospital Medical Center and University

of Cincinnati, Cincinnati, OH

⁸ Department of NEUROFARBA, Section of Child's Health, University of Florence and BMT Unit, Department of Hematology-Oncology, Anna Meyer Children's Hospital, Florence Italy

⁹ Genetics and Pathogenesis of Allergy Section, Laboratory of Allergic Diseases, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, MD

¹⁰ Departments of Pediatrics, Division of Rheumatology and Department of Pathology and Immunology Washington University School of Medicine, St. Louis, MO

¹¹ Adult Immunodeficiency Unit Infectious Diseases, Inflammation Center and Rare Diseases Center Children's Hospital, University of Helsinki and Helsinki University Hospital, Helsinki, Finland

* Address correspondence to this author at: Rare Disease Center, Children's Hospital University of Helsinki and Helsinki University Hospital Lastenlinnankatu 2, 00029, Finland Fax +358-9-47174703 E-mail mikko.seppanen@hus.fi

Previously published online at DOI: 10.1373/clinchem.2017.273458

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