CORRESPONDENCE

Gigantism, Acromegaly, and *GPR101* Mutations

TO THE EDITOR: Trivellin et al. (Dec. 18 issue)[1] report a recurrent activating *GPR101* mutation (p.E308D) in 11 of 248 tumor DNA samples from patients with isolated acromegaly. Of these patients, 3 carried a germline *GPR101* mutation. Two of the 3 patients are being treated at our institution and were identified among 38 patients from our cohort. This might suggest a higher prevalence of germline *GPR101* mutation among French patients with sporadic acromegaly.

We therefore screened our entire cohort of 263 patients with gigantism or acromegaly for germline mutations in *GPR101*, which encodes a G-protein–coupled receptor, and in *AIP*, which encodes aryl hydrocarbon receptor–interacting protein (Table S1 in the Supplementary Appendix, available with the full text of this letter at NEJM.org). Only 3 patients (1.1%), including the 2 patients who were reported previously, had the *GPR101* p.E308D mutation; all 3 of these patients had adult-onset sporadic acromegaly. This finding shows that the prevalence of this germline mutation in our large cohort is very similar to that reported by Trivellin et al. In addition, we identified in a patient with sporadic acromegaly a novel *GPR101* p.D366E variant (0.4%), which was not reported in the databases of the Exome Aggregation Consortium (ExAC), 1000 Genomes Project, dbSNP, or Exome Variant Server. Germline *AIP* mutations were identified in 8 of 263 patients with somatotropinomas (3.0%), of whom 6 patients (75%) have gigantism.[2] None of the 263 patients carried germline mutations in both *GPR101* and *AIP*.

Peter Kamenický, M.D., Ph.D.
INSERM, Unité 693
Le Kremlin-Bicêtre, France
peter.kamenicky@u-psud.fr

Jérôme Bouligand, Pharm.D., Ph.D.
Université Paris-Sud
Le Kremlin-Bicêtre, France

Philippe Chanson, M.D.
Hôpitaux Universitaires Paris-Sud
Le Kremlin-Bicêtre, France

No potential conflict of interest relevant to this letter was reported.

1. Trivellin G, Daly AF, Faucz FR, et al. Gigantism and acromegaly due to Xq26 microduplications and *GPR101* mutation. N Engl J Med 2014;371:2363-74.
2. Lecoq AL, Kamenický P, Guiochon-Mantel A, Chanson P. Genetic mutations in sporadic pituitary adenomas — what to screen for? Nat Rev Endocrinol 2015;11:43-54.

DOI: 10.1056/NEJMc1500340

TO THE EDITOR: Trivellin et al. report a c.924G→C substitution (p.E308D) in *GPR101* in 11 of 248 patients with acromegaly, for an allele frequency for this variant (rs73637412) of 2.86%. At the time of manuscript preparation, a search of public databases, including the 1000 Genomes Project, the Exome Variant Sever, and the GO Exome Sequencing Project of the National Heart, Lung, and Blood Institute, did not identify the c.924G→C substitution in 7600 control individuals.

THIS WEEK'S LETTERS

Recently, a new exome-sequencing data set, the ExAC Browser, has become publicly available.[1] It contains sequence data from approximately 61,500 unrelated individuals. A search of the ExAC Browser for the c.924G→C substitution shows an allele frequency of 0.55% (about 1 in 185) among Europeans and 0.36% (about 1 in 275) among the total cohort. In contrast, the population prevalence of acromegaly is estimated at only 6 per 100,000 population, with an incidence of 3 to 4 per million per year.[2] Given the frequency of the c.924G→C substitution, I would urge caution in interpreting it as a disease-associated variant.

Jasmin Roohi, M.D., Ph.D.

Johns Hopkins University
Baltimore, MD
jroohi1@jhu.edu

No potential conflict of interest relevant to this letter was reported.

1. Exome Aggregation Consortium (ExAC) home page (http://exac.broadinstitute.org).
2. Holdaway IM, Rajasoorya C. Epidemiology of acromegaly. Pituitary 1999;2:29-41.

DOI: 10.1056/NEJMc1500340

THE AUTHORS REPLY: Microduplications on chromosome Xq26.3 cause X-linked acrogigantism (X-LAG). The expression of *GPR101* (alone among the duplicated genes on Xq26.3) was highly upregulated in pituitary tumors obtained from patients with X-LAG. We therefore assessed whether genetic variants in *GPR101* were present among a large, international sample of patients with acromegaly. Sequence analysis showed a missense change, c.924G→C (p.E308D; single-nucleotide polymorphism [SNP], rs73637412) in 4.4% of patients with acromegaly, predominantly in tumor DNA, including a sample obtained from a patient in whom the mutation was not present in peripheral DNA. This finding contrasted with a low prevalence of p.E308D in online databases. In keeping with this result, Kamenický et al. indicate that p.E308D also occurs in a minority of unselected patients with acromegaly.

We found that p.E308D had functional effects: it significantly increased the release of growth hormone in somatomammotroph cells. We agree with Roohi that the frequencies of mutations vary according to the database that is used. In the current 1000 Genomes Project release, for example, c.924G accounts for only 3 of 3775 alleles (0.0008) and is not present in other databases. Also, estimates of the prevalence of rare conditions such as acromegaly (currently, 1:8000)[1] should be used cautiously when calculating overall allelic frequencies. SNP rs73637412 describes both p.E308D (encoded by c.924G→C) and its synonymous counterpart, c.924G→A. The synonymous variant is reported at a lower frequency in the ExAC Browser than in other databases, suggesting that variant-calling may explain discrepancies among online data. Accurate sequence determination is needed to distinguish between p.E308D and its synonymous variant in every sample.

Even if p.E308D is present in unaffected persons, there are other genetic defects leading to acromegaly that are also present in the general population: the penetrance of *AIP* mutations is low (20 to 40%),[2] and unaffected carriers abound.[3,4] The fact that p.E308D may also be present de novo in pituitary tumors, as well as constitutively, is supportive of this variant and possibly the new one identified by Kamenický et al. (p.D366E), since they are factors that can alter somatotrope function and that may contribute to the development of acromegaly.

Adrian F. Daly, M.B., B.Ch., Ph.D.

University of Liège
Liège, Belgium

Giampaolo Trivellin, Ph.D.
Constantine A. Stratakis, M.D., D.Sc.

Eunice Kennedy Shriver National Institute of Child Health and Human Development
Bethesda, MD
stratakc@mail.nih.gov

Since publication of their article, the authors report no further potential conflict of interest.

1. Daly AF, Rixhon M, Adam C, Dempegioti A, Tichomirowa MA, Beckers A. High prevalence of pituitary adenomas: a cross-sectional study in the province of Liege, Belgium. J Clin Endocrinol Metab 2006;91:4769-75.
2. Stratakis CA, Tichomirowa MA, Boikos S, et al. The role of germline AIP, MEN1, PRKAR1A, CDKN1B and CDKN2C mutations in causing pituitary adenomas in a large cohort of children, adolescents, and patients with genetic syndromes. Clin Genet 2010;78:457-63.
3. Beckers A, Aaltonen LA, Daly AF, Karhu A. Familial isolated pituitary adenomas (FIPA) and the pituitary adenoma predisposition due to mutations in the aryl hydrocarbon receptor interacting protein (AIP) gene. Endocr Rev 2013;34:239-77.
4. Xekouki P, Mastroyiannis SA, Avgeropoulos D, et al. Familial pituitary apoplexy as the only presentation of a novel AIP mutation. Endocr Relat Cancer 2013;20:L11-4.

DOI: 10.1056/NEJMc1500340