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. Germ-line 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.

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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.

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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 up-regulated 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 somatotroph 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.

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