Title: X-Linked Acrogigantism *GeneReview* – Acromegaly: *GPR101* variants of uncertain significance
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Acromegaly: *GPR101* Variants of Uncertain Significance

Because growth hormone (GH) excess occurring after closure of the epiphyseal cartilages results in acromegaly (rather than gigantism), the possibility that *GPR101* variants cause acromegaly has been investigated.

In the original publication [Trivellin et al 2014], the missense *GPR101* variant c.924G>C (p.Glu308Asp) was found in 4% of 248 patients with acromegaly. The variant was mostly found in tumors, and it was demonstrated to be somatic in one case. The overexpression of *GPR101* with this variant led to a modest increase in cell proliferation and GH release as compared with wild type *GPR101* in a pituitary cell line, suggesting a potential pathogenic role.

However, the allele frequency of the c.924G>C (p.Glu308Asp) variant was 0.94% in a cohort of 263 patients with acromegaly, and the frequency was not significantly different from the general population [Lecoq et al 2016]. In addition, in a large series of 579 patients [Iacovazzo et al 2016], the c.924G>C (p.Glu308Asp) *GPR101* variant was found in four patients (0.69%) and solely in germline DNA. The allele frequency (0.45%) was not significantly different from the general population (the allele frequency reported in the Exome Aggregation Consortium – ExAC – database is 0.37%), and no other rare or novel *GPR101* variants, either germline or somatic, were identified.

In two further studies that recruited 215 and 61 patients with acromegaly, the variant was not identified in any of the patients [Ferrau et al 2016, Matsumoto et al 2016]. Thus, the role of this variant in the pathogenesis of acromegaly remains uncertain.

In one of the above-mentioned studies [Lecoq et al 2016], the novel germline c.1098C>A (p.Asp366Glu) *GPR101* variant was identified in one patient (0.4%) with sporadic acromegaly. *In silico* prediction supported a pathogenic role. However, this variant was not found in an independent series of 395 acromegaly patients [Iacovazzo et al 2016]. Considering its rarity and the lack of functional studies, the significance of this variant is currently uncertain.

References

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