

## Familial Acromegaly

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The majority of pituitary adenomas occur sporadically, however, familial adenomas account for 3-5% of all pituitary adenomas. Familial growth hormone (GH)-secreting pituitary adenoma [also known as familial somatotropinoma (FS) or familial acromegaly] is a rare clinical entity. Familial GH-secreting pituitary adenoma is associated with three separate clinical syndromes: multiple endocrine neoplasia type 1 (*MEN1*), Carney complex (CNC) and isolated FS (IFS) which is included in the spectrum of familial isolated pituitary adenoma (FIPA). Mutations in *MEN1* and the protein kinase A regulatory subunit 1 (*PRKAR1A*) genes are found in the majority of *MEN1* and CNC patients, respectively. The *MEN-1* gene, which codes the nuclear protein menin, has been identified and a large number of inactivating mutations have been recognized in *MEN-1*. Pituitary tumor types in *MEN-1* are similar to those occurring sporadically and only about 10% are GH-secreting adenomas (somatotropinomas). The gene associated with CNC encodes the protein kinase A regulatory subunit 1, an inactivation which leads to enhanced the activity of the GH-releasing hormone-induced signal transduction pathway. This pathway exerts proliferative effects in somatotropes. Therefore, pituitary hyperplasia is common in CNC. In the late 1990's, a clinical condition called familial isolated pituitary adenomas (FIPA) was described in the presence of two or more pituitary adenomas of any type that were unrelated to *MEN1* or CNC. After that, FIPA

was started increasingly to be recognized as an autosomal dominant disease with low or variable penetrance, caused by heterozygous germline mutations of the aryl hydrocarbon receptor interacting protein (AIP) gene. FIPA families comprise approximately 2% of pituitary adenomas and represent a clinical entity with homogeneous (such as IFS) or heterogeneous pituitary adenoma types occurring within the same kindred. IFS accounts for 18% of all FIPA cases. The aryl hydrocarbon receptor *AIP* gene is involved in about 15% of FIPAs, in about 50% of IFS and in a small proportion of acromegalic patients with sporadic presentation. Familial acromegaly and gigantism only account for a very tiny proportion of all pituitary adenomas, but AIP mutations are very common in gigantism. Goliath is a giant first defined in the Bible and a literal interpretation of the verses suggests that his brother and three sons were also of giant stature. In addition, the Hugo brothers, also known in France as "the Giants of the Alps", were two famous giants at the end of the 20<sup>th</sup> century. Interestingly, Goliath's family tree and Hugo brothers are suggestive of a hereditary autosomal dominant pituitary gene, such as AIP, causing early onset and familial acromegaly or gigantism. Recently, a research team extracted and analyzed the DNA from the skeleton of an 18<sup>th</sup> century acromegaly patient Charles Bryne (1761-1783), so-called "Irish Giant" and identified a specific germline mutation in the *AIP* gene. It is now discovered that the same AIP mutation has been passed on from him to four Northern Irish families who presented with gigantism, acromegaly, or prolactinoma. Evidence suggests that, especially in *MEN1* and FIPA, tumors are more aggressive and affect patients at a younger age, therefore proves show that early diagnosis may prevent excessive growth.

**Key words:** Familial acromegaly, *MEN1*, carney complex, FIPA, IFS, AIP gene