

From FIPA to gigantism

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Over 15 years ago, the syndrome of Familial Isolated Pituitary Adenomas (FIPA) was defined in Liege as a familial association of pituitary adenomas arising in the absence of other clinical signs of hereditary syndromes such as multiple endocrine neoplasia type 1 or Carney complex. All types of secretory adenomas can occur in this context and FIPA families can either be homogenous (the same secretory type of adenoma in all affected members) or heterogenous. It was later found that mutations in the *AIP* (Aryl hydrocarbon receptor Interacting Protein) gene were responsible for 15-20% of FIPA cases, with GH-secreting adenomas being well represented in the *AIP*-mutated group. Acromegalic patients that are *AIP*-mutated have a particularly severe phenotype with early disease onset, invasive adenomas, poor response to somatostatin analogues and need for multiple treatment courses.

Recently, a new type of FIPA has been discovered, in the context of a novel pituitary disease called X-linked acro-gigantism (X-LAG). This disease causes early-onset gigantism due to massive GH hypersecretion. Children affected start accelerating their growth rate before the age of 3, reaching what are most likely the tallest heights reported in history. These children present some acromegalic features (acral enlargement and coarse facial traits) and biologically, prolactin hypersecretion is associated. The cause of this syndrome is a microduplication of a region on the X chromosome containing 4 genes, out of which *GPR101* is most probably the one responsible for the phenotype. Activating mutations of this gene were also found in sporadic acromegaly cases. This discovery represents a new cause of gigantism and FIPA, due to a novel genetic mechanism in pituitary pathophysiology. It unveils new regulatory pathways of the growth hormone axis and could help identify targets for novel treatment possibilities in growth-hormone related diseases.