New genetic cause of gigantism and FIPA

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Context: Acromegaly and gigantism result from excessive production and secretion of growth hormone (GH), usually by a pituitary adenoma, and are considered as very rare conditions. Gigantism occurs in the period of linear growth and is poorly understood disorder. Although previous studies have identified the various alterations in predisposing genes in somatotropinomas, genetic cause in majority of cases of acromegaly and gigantism remains unclear.

Aim: We studied gigantism for genetic defects.

Methods: We conducted an international study (clinical and genetic) on the pituitary gigantism. In total 208 patients were enrolled with growth hormone excess and abnormal growth for age or final height > 2SD above country local standards. Genome-wide analyses was performed in 46 patients with gigantism and 248 patients with acromegaly.

Results: Genetic or hereditary characteristics were observed in 46% of patients and included FIPA, McCune- Albright syndrome, Carney complex and MEN type 1. AIP mutations accounted for about one third of cases. We observed a microduplication in a region of about 500 kb on chromosome Xq26.3 in samples from 17 patients with gigantism. Four were obtained from members of two FIPA families, and 13 were sporadic cases. All sporadic cases had an original duplication, while familial cases had inherited identical duplications. In all patients, the disease appeared in infancy. None of patients with gigantism that do not bear the Xq26.3 microduplication, has grown excessively before age of 5 years. Genomic characterization of Xq26.3 region suggests that microduplications are generated during chromosome replication. Patients with X-linked infantile gigantism have a common area of overlap that involves four genes, including GPR101 gene, which encodes a receptor coupled to a G protein with seven transmembrane domains. Only this gene is strongly overexpressed in pituitary tumors from two patients with infantile gigantism.

Conclusions: A new pediatric syndrome (we called X-LAG for X-linked acrogigantism) is caused by the genomic microduplication on chromosome Xq26.3 and characterized by early onset of gigantism resulting from an excess of growth hormone. X-LAG syndrome is most likely caused by duplication of GPR101 gene.