X-linked acrogigantism

X-linked acrogigantism (X-LAG), a condition of infant-onset acrogigantism marked by elevated GH, IGF-1, and prolactin (PRL), is extremely rare. Thirty-three cases, including three kindreds, have been reported. These patients have pituitary adenomas that are thought to be mixed lactotrophs and somatotrophs.

Pituitary tumors are undergoing a transformation in histopathologic and molecular classification, coincident with the continued refinement of increasingly powerful methods of genomic annotation and discovery.

Sporadic pituitary adenomas are associated with relatively few recurrent somatic mutations. Recurrent mutations occur largely in subsets of hormone-producing tumors, including GNAS and GPR101 in somatotroph adenomas and USP8 in corticotroph adenomas. Additionally, they manifest with a dichotomous signature of copy number alterations, ranging from almost none to widespread genome instability, while microduplication of chromosome Xq26.3, containing the GNAS gene, defines X-linked acrogigantism. Papillary craniopharyngiomas are defined by BRAF V600E mutations while β-catenin alterations characterize adamantinomatous craniopharyngiomas. Genomic annotation of pituitary tumors is defining increasing subsets of neuroendocrine adenohypophyseal tumors and craniopharyngiomas, offering rationale-based pharmacologic targets and potential biomarkers for clinical outcome [1)].

Non-syndromic pituitary gigantism can result from AIP mutations or the identified Xq26.3 microduplication causing X-linked acrogigantism (XLAG). Within Xq26.3, GPR101 is believed to be the causative gene, and the c.924G > C (p.E308D) variant in this orphan G protein-coupled receptor has been suggested to play a role in the pathogenesis of acromegaly.We studied 153 patients (58 females and 95 males) with pituitary gigantism. AIP mutation-negative cases were screened for GPR101 duplication through copy number variation droplet digital PCR and high-density aCGH. The genetic,

clinical and histopathological features of XLAG patients were studied in detail. 395 peripheral blood and 193 pituitary tumor DNA samples from acromegaly patients were tested for GPR101 variants.We identified 12 patients (10 females and 2 males; 7.8 %) with XLAG. In one subject, the duplicated region only contained GPR101, but not the other three genes in found to be duplicated in the previously reported patients, defining a new smallest region of overlap of duplications. While females presented with germline mutations, the two male patients harbored the mutation in a mosaic state. Nine patients had pituitary adenomas, while three had hyperplasia. The comparison of the features of XLAG, AIP-positive and GPR101&AIP-negative patients revealed significant differences in sex distribution, age at onset, height, prolactin co-secretion and histological features. The pathological features of XLAG-related adenomas were remarkably similar. These tumors had a sinusoidal and lobular architecture. Sparsely and densely granulated somatotrophs were admixed with lactotrophs; follicle-like structures and calcifications were commonly observed. Patients with sporadic of familial acromegaly did not have an increased prevalence of the c.924G > C (p.E308D) GPR101 variant compared to public databases.In conclusion, XLAG can result from germline or somatic duplication of GPR101. Duplication of GPR101 alone is sufficient for the development of XLAG, implicating it as the causative gene within the Xq26.3 region. The pathological features of XLAG-associated pituitary adenomas are typical and, together with the clinical phenotype, should prompt genetic testing [2].

Case reports

The patient's mother, diagnosed with acrogigantism at 21 months, underwent pituitary tumor excision at 24 months. For over 30 years, stable PRL, GH, and IGF-1 concentrations and serial imaging studies indicated no tumor recurrence. During pre-conception planning, X-LAG was diagnosed: single-nucleotide polymorphism (SNP) microarray showed chromosome Xq26.3 microduplication. After conception, SNP microarray on a chorionic villus sample showed the same microduplication in the fetus, confirming familial X-LAG. The infant grew rapidly with rising PRL, GH, and IGF-1 concentrations and an enlarging suprasellar pituitary mass, despite treatment with bromocriptine. At 15 months, he underwent tumor resection. The pituitary adenoma resembled the mother's pituitary adenoma, with tumor cells arranged in trabeculae and glandular structures. In both cases, many tumor cells expressed PRL, GH, and PIT1. Furthermore, the tumor expressed other lineage-specific transcription factors, as well as SOX2 and OCT4, demonstrating the multipotentiality of X-LAG tumors. Both showed an elevated Ki-67 proliferation index-5.6% (mother) and 8.5% (infant)-the highest reported in X-LAG.

This is the first prenatally diagnosed case of X-LAG. Clinical follow-up and biochemical evaluation have provided insight into the natural history of this disease. Expression of stem cell markers and several cell lineage-specific transcription factors suggests that these tumors are multipotential. [3].

References

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