GPR101 orphan receptor: A novel cause of growth hormone deregulation

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X-Linked Acrogigantism Syndrome (X-LAG) and GPR101, an Orphan GPCR

**Pituitary gigantism** is a rare endocrine disease due to GH hypersecretion before fusion of the epiphyses, usually caused by a pituitary adenoma (1). Nearly half of pituitary gigantism cases have a genetic cause (2); mutations in the AIP gene are the most frequently identified (29%). The next most common cause (10%) is X-linked acrogigantism (X-LAG) syndrome, a recently described disorder that accounts for most cases of early childhood-onset pituitary gigantism (3). X-LAG syndrome has a consistent phenotype of gigantism beginning usually within the first 12 months of life and diagnosis is made generally before the age of 5 years (Fig. 1A,B) (3,4).

Patients develop large mixed GH and prolactin secreting adenomas and/or hyperplasia (Fig. 1C). Overgrowth can be severe if the effects of GH excess are not adequately controlled and many of the tallest humans in history share the early-onset phenotype that is characteristic of X-LAG syndrome (5, 6). Some X-LAG patients have moderate GHRH excess, which suggests that hypothalamic dysregulation (Fig. 1D) might accompany/cause the pituitary tumorigenesis (7).

**X-LAG** is a genomic disorder due to microduplications on chromosome Xq26.3 (Fig. 1E,F). X-LAG is usually sporadic, but it can present as familial isolated pituitary adenomas (FIPA) (3,4,8). In all cases of X-LAG syndrome, only the gene GPR101 is duplicated and upregulated in the tumors of patients (Fig. 2A).

GPR101 is an orphan G-protein coupled receptor (GPCR), the physiology of which is still unexplored. GPR101 is temporally expressed in the human medial neonatal pituitary beginning at 14 weeks (Fig. 2B), reaching a maximum at 34 weeks to term, thereafter decreasing (10).

Many important aspects of the pharmacology and molecular biology of GPR101 remain to be determined. To address this, we performed an *in vitro* study to characterize the G protein coupling and arrestin recruitment to GPR101 and specific mutations in HEK cells expressing human GPR101 (Fig. 3, 4 & 5).

Initial results indicate that GPR101 is a highly constitutively active GPCR that is coupled to Gs; known mutations of GPR101 had only a minor effect on CAMP levels. In addition GPR101 constitutively recruits arrestin 3.

Further experiments are envisaged to better understand the signaling pathways related to GPR101 and to focus on the identification of potential ligands.

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**References:**