EP928

# 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.1 A,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 sporadic male subjects these duplications may be mosaic **(Fig. 1G)**, with as few as 16% of duplicated cells leading to severe gigantism (9). 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 unresolved. 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.**

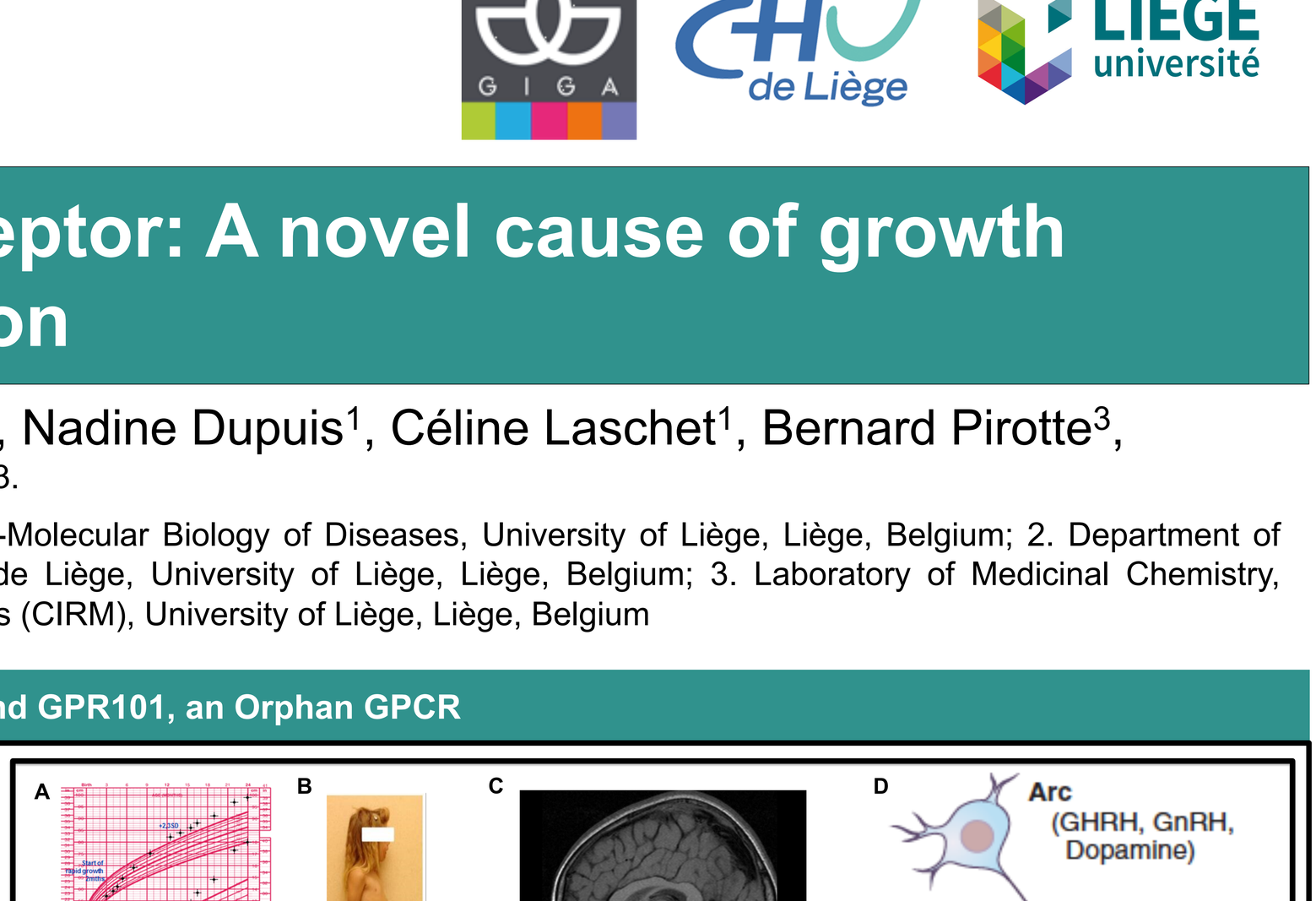


**Figure 1.**

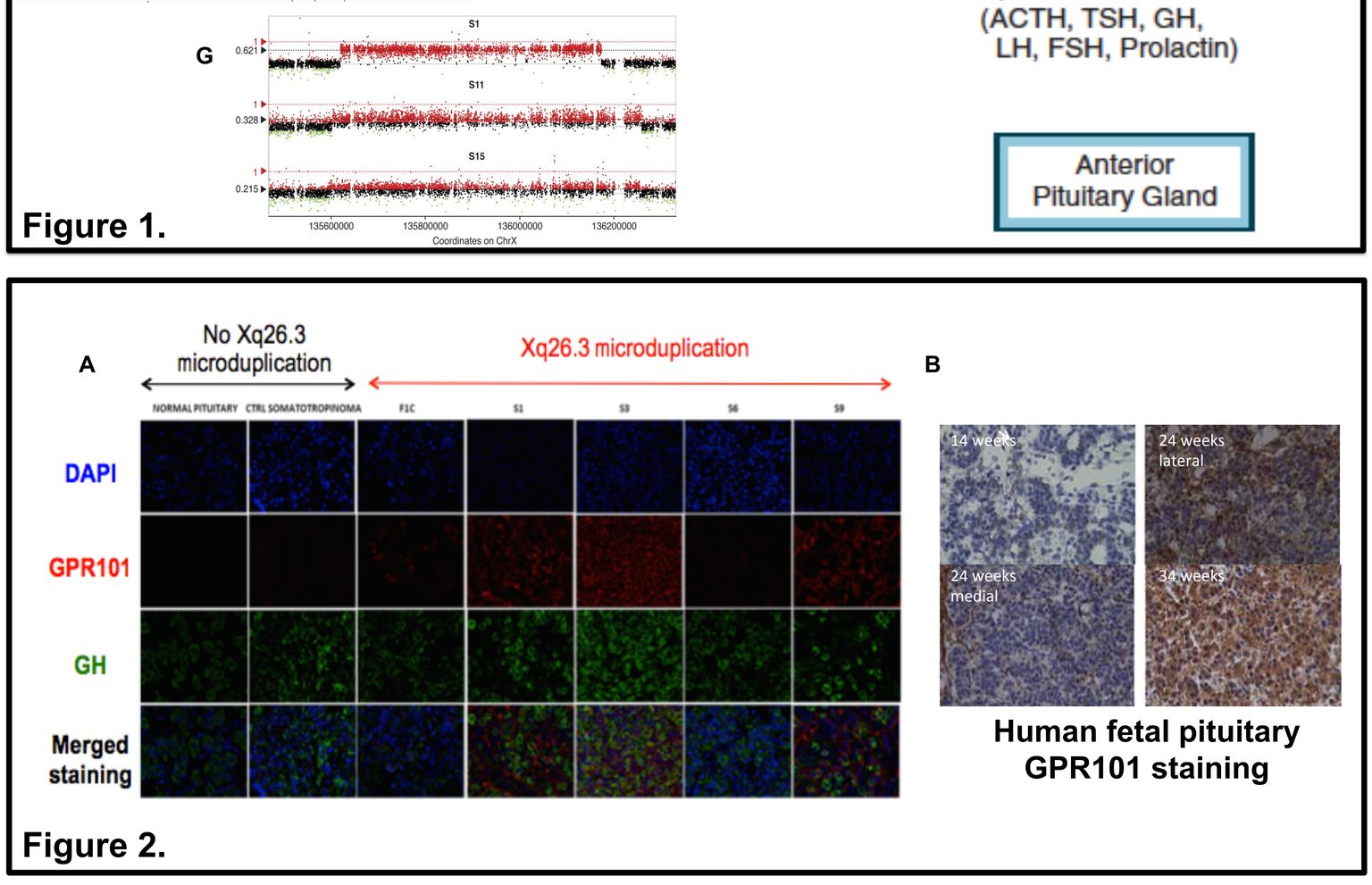


**Figure 2.**

## GPR101 characterization

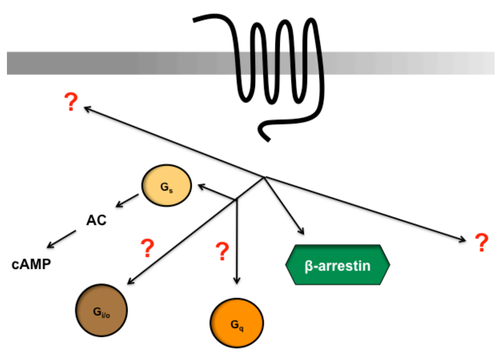


**Figure 3.**

## Gαs protein coupling to GPR101

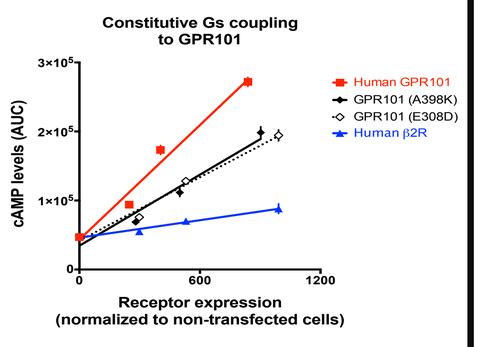


**Figure 4.**

## Arrestin 3 recruitment to GPR101

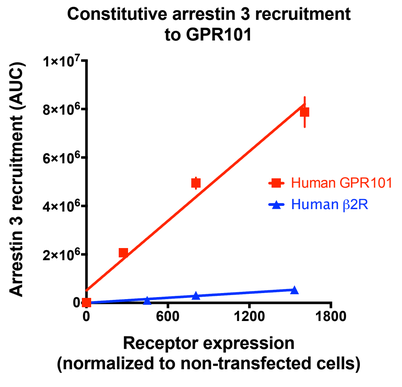


**Figure 5.**

**References:** 1. Rostomyan et al. Ann Endocrinol (Paris). 2015 Dec;76(6):643-9; 2. Rostomyan et al. Endocr Relat Cancer. 2015 Oct;22(5):745-57; 3. Trivellin et al. N Engl J Med. 2014 Dec 18;371(25):2363-74; 4. Beckers et al Endocr Relat Cancer. 2015 Jun;22(3):353-67; 5. Beckers et al Ann Endocrinol (Paris). 2017 Apr 27. pii: S0003-4266(17)30037-9; 6. Beckers et al. Endocr Relat Cancer. 2017 Feb;24(2):L17-L20.; 7. Daly et al. Endocr Relat Cancer. 2016 Mar;23(3):161-70; 8. Gordon et al. Pituitary 2016 Dec 19(6):560-564; 9. Daly et al. Endocr Relat Cancer. 2016 Apr;23(4):221-33.; 10. Trivellin et al. J Mol Endocrinol 2016; 57, 97–111.

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