



## Somatic mosaicism is implicated in the etiology of XLAG syndrome

Catégorie  
"Study  
Abstract"

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### Context

X-linked acrogigantism (X-LAG) syndrome is a newly described form of early onset inheritable pituitary gigantism caused by microduplications on chromosome Xq26.3 including the GPR101 gene.

### Aim

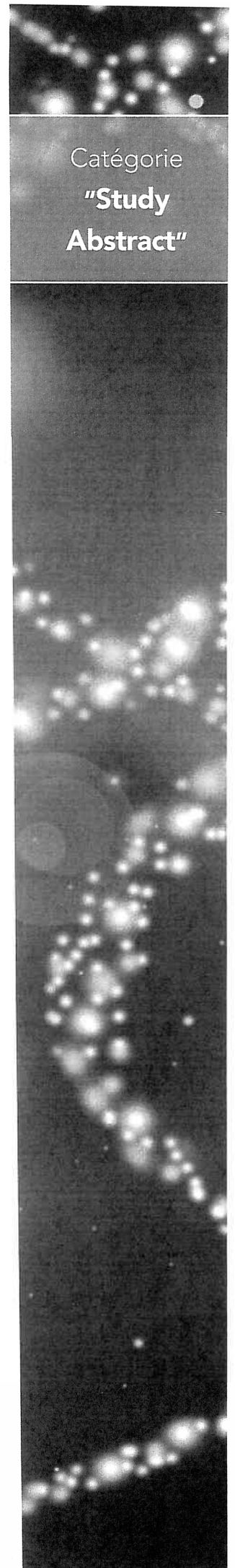
We explored the genomic pathophysiology of XLAG syndrome and studied XLAG, pituitary gigantism, or acromegaly patients for somatic mosaicism of Xq26.3 microduplications that include GPR101.

### Methods

Copy number variations (CNVs) at the GPR101 gene were assessed and compared to ZIC3 (nearest protein-coding gene on chromosome X not included in duplications causing XLAG) by droplet digital PCR (ddPCR) in 36 acromegalics (24M; age at diagnosis: 22 - 50 years), 6 acromegaly homogeneous FIPA cases, 22 pituitary gigantism patients, and 20 controls. In 18 XLAG patients (6M -3 sporadic, 3 familial, and 12 F - 11 sporadic, 1 familial) high-definition array comparative genomic hybridization (HD-aCGH) and breakpoint junction (JCT)-specific ddPCR were performed to characterize Xq26.3 duplications and quantify their level of mosaicism.

### Results

On HD-aCGH all XLAG microduplications were unique and included GPR101. All male subjects had a decreased log<sub>2</sub> ratio (LR) than expected value of LR=1, suggesting potential mosaicism, whereas there was no evidence of mosaicism in XLAG females. Males as a group had significantly lower LR values compared with female patients. Moreover, sporadically males had lower levels of Xq26.3 duplication mosaicism in blood DNA (ranged 16.1 - 53.8%) than familial XLAG males (69.1 - 78.5%). These findings were then confirmed using a personalized (JCT)-specific quantification ddPCR and the mosaicism levels obtained with this technique were consistent with the HD-aCGH results. Using a separate ddPCR technique, we studied the feasibility of identifying XLAG cases in acromegaly/gigantism patients' population by abnormalities in copy number at GPR101 vs. ZIC3. One female gigantism patient was found having increased CNV threshold for GPR101 and was subsequently diagnosed with XLAG microduplication on HD-aCGH.





## Conclusions

In this study we demonstrated using a combination of HD-aCGH and novel ddPCR approaches, for the first time, that XLAG syndrome can be caused by somatic mosaicism for duplications at chromosome Xq26.3. Sporadic males but not females with XLAG were found to have variable degrees of somatic mosaicism. Screening for changes in CNV at GPR101 by ddPCR technique may identify a potential XLAG case among pituitary gigantism population.

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