

## GNAS genotype and clinical phenotype in acromegalic patients

<sup>1</sup>연세대학교 의과대학 내과학교실, <sup>2</sup>연세대학교 의과대학 신경외과교실

\*황윤아<sup>1</sup>, 정혜인<sup>1</sup>, 구철룡<sup>1</sup>, 김다함<sup>1</sup>, 문주형<sup>2</sup>, 김의현<sup>2</sup>, 김선호<sup>2</sup>, 이은직<sup>1</sup>

**Background/Aims:** Guanine nucleotide-binding protein,  $\alpha$  stimulating (GNAS) gene has been associated with GH secreting pituitary adenoma. Approximately 40% of patients with acromegaly have GNAS mutation. In this study, we investigated the prevalence of GNAS mutation in Korean acromegalic patients and assessed whether mutation correlates with the biochemical or clinical characteristics. **Methods:** We studied acromegalic patients underwent surgery from July 2005 to January 2007 in Severance Hospital. Genomic DNA of tumors was extracted from surgically resected tissue. Sequence of GNAS gene was analyzed, containing two hotspots of activating somatic mutations in codons 201 and 227. We evaluated the age, gender, GH, IGF-1 levels and immunohistochemical staining results of tumor. Biochemical remission of acromegaly was defined as normal serum IGF-1 level or less than 1ng/ml of nadir GH concentration after oral glucose tolerance test (OGTT). Each patient was followed-up at least 10 years. **Results:** Among 126 acromegalic subjects, 75 subjects presented GNAS mutations (59.5%). Among the GNAS mutant patient, 61 subjects (81%) had mutation in codon 201. The group without GNAS mutation (GNAS-) was 76.5% female, and the one with mutation (GNAS+) was 48.0% female ( $p=0.006$ ). Two groups were similar in age distribution and Hardy classification. GNAS+ group had higher prevalence of overall GH expression in immunohistochemical staining (98.7% vs. 92.2%,  $p=0.015$ ). GNAS mutation is associated with higher IGF-1 level preoperatively (791.3 vs. 697.0ng/ml,  $p=0.045$ ). Immediate postoperative basal GH (0.9 vs. 1.0ng/ml,  $p=0.191$ ) and nadir GH (0.3 vs. 0.6ng/ml,  $p=0.012$ ) in OGTT was lower in GNAS+ group. Surgical remission rates were significantly higher in GNAS+ group, evaluated both at immediately and at 6 months after operation (70.7% vs. 54.9%,  $p=0.011$ ; 85.3% vs. 82.4%,  $p=0.007$ , respectively). **Conclusions:** GNAS mutations were frequently found in Korean acromegalic patients. GNAS mutation positive tumors tend to have higher preoperative IGF-1 level, surgical remission rate and lower immediate postoperative nadir GH on OGTT. Identifying the GNAS mutation would be helpful in predicting patient's clinical features and prognosis.

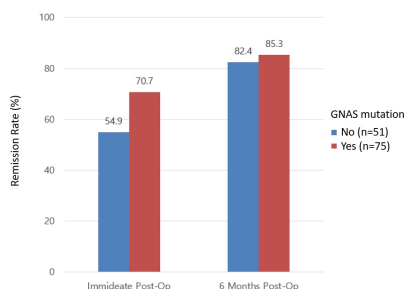


Figure 1. Surgical remission rate after operation (cutoff value : GH < 1.0 ng/mL after OGTT)