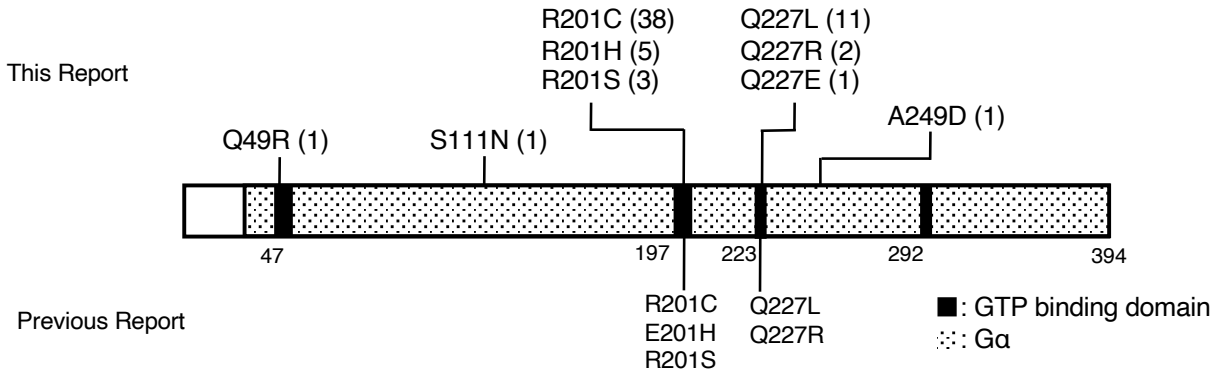
Supplemental Figure 1

a



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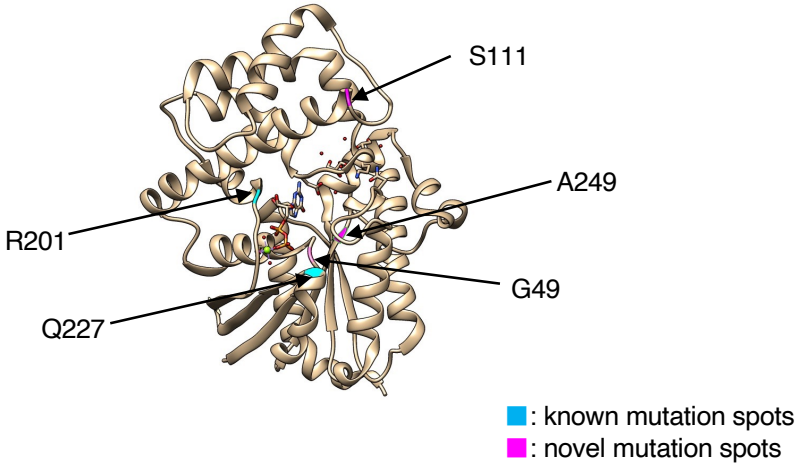
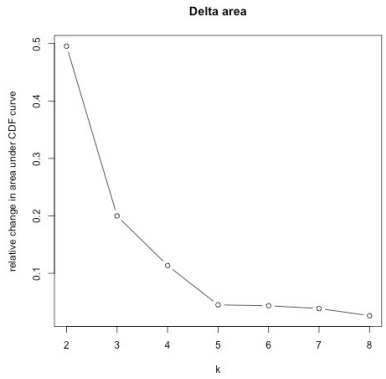
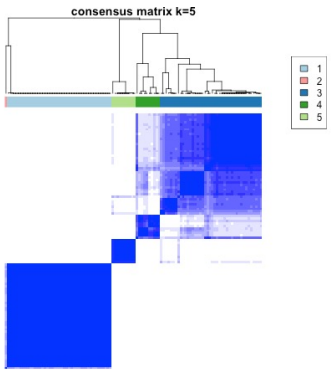
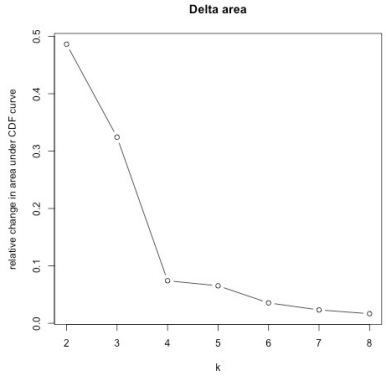


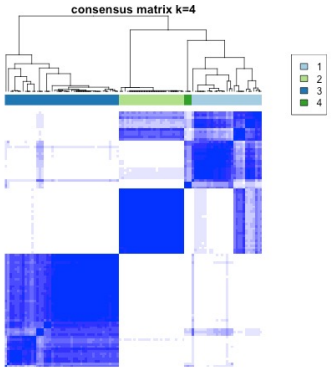
Supplemental Figure 2



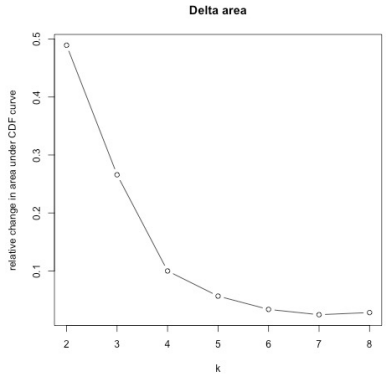


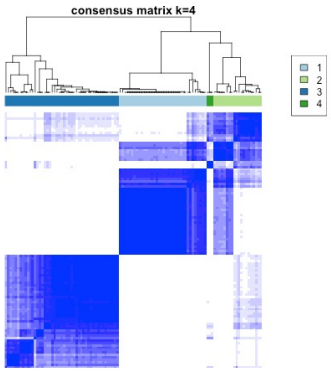
RNAseq
K=5





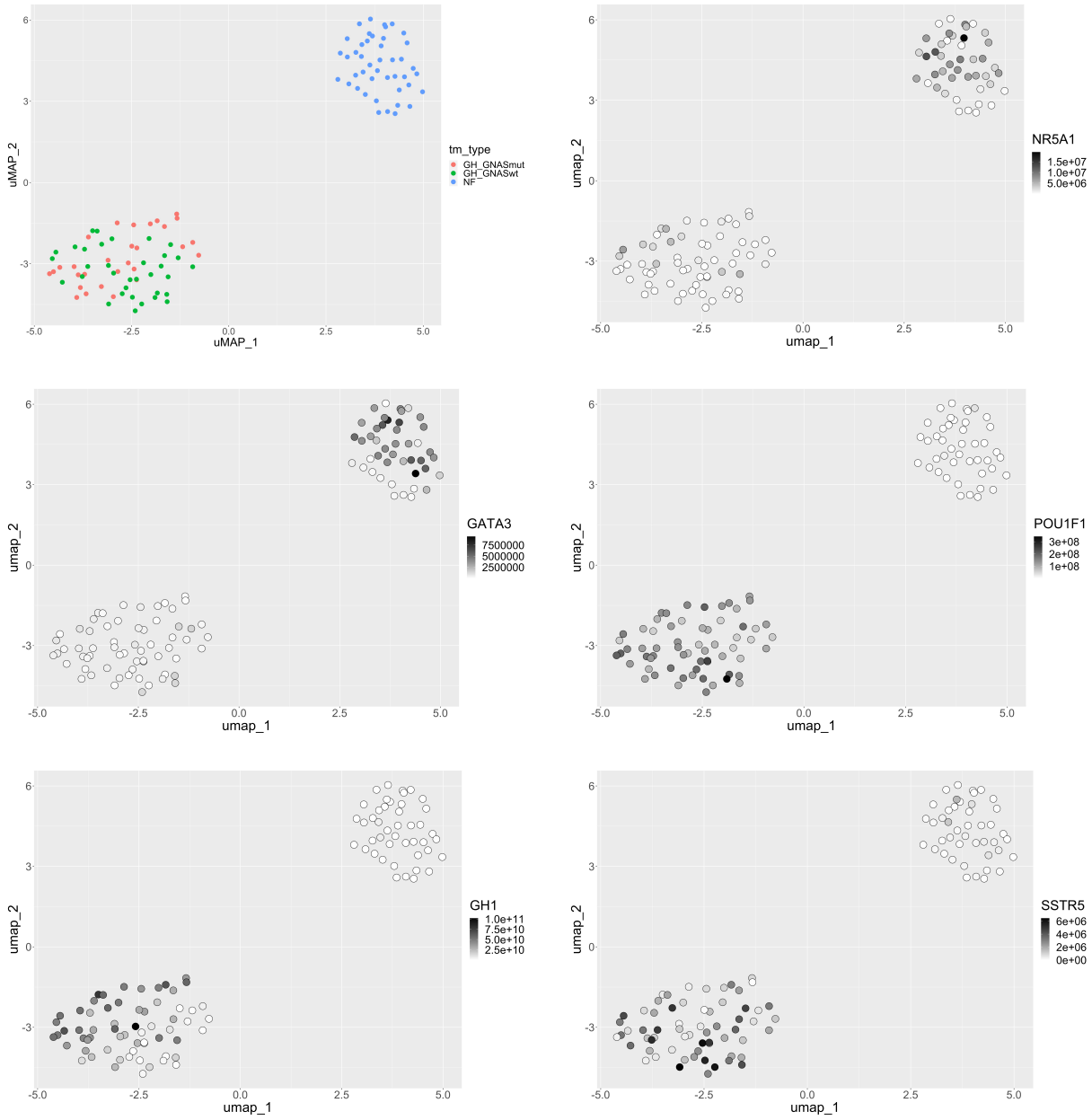
Proteomics
K=4



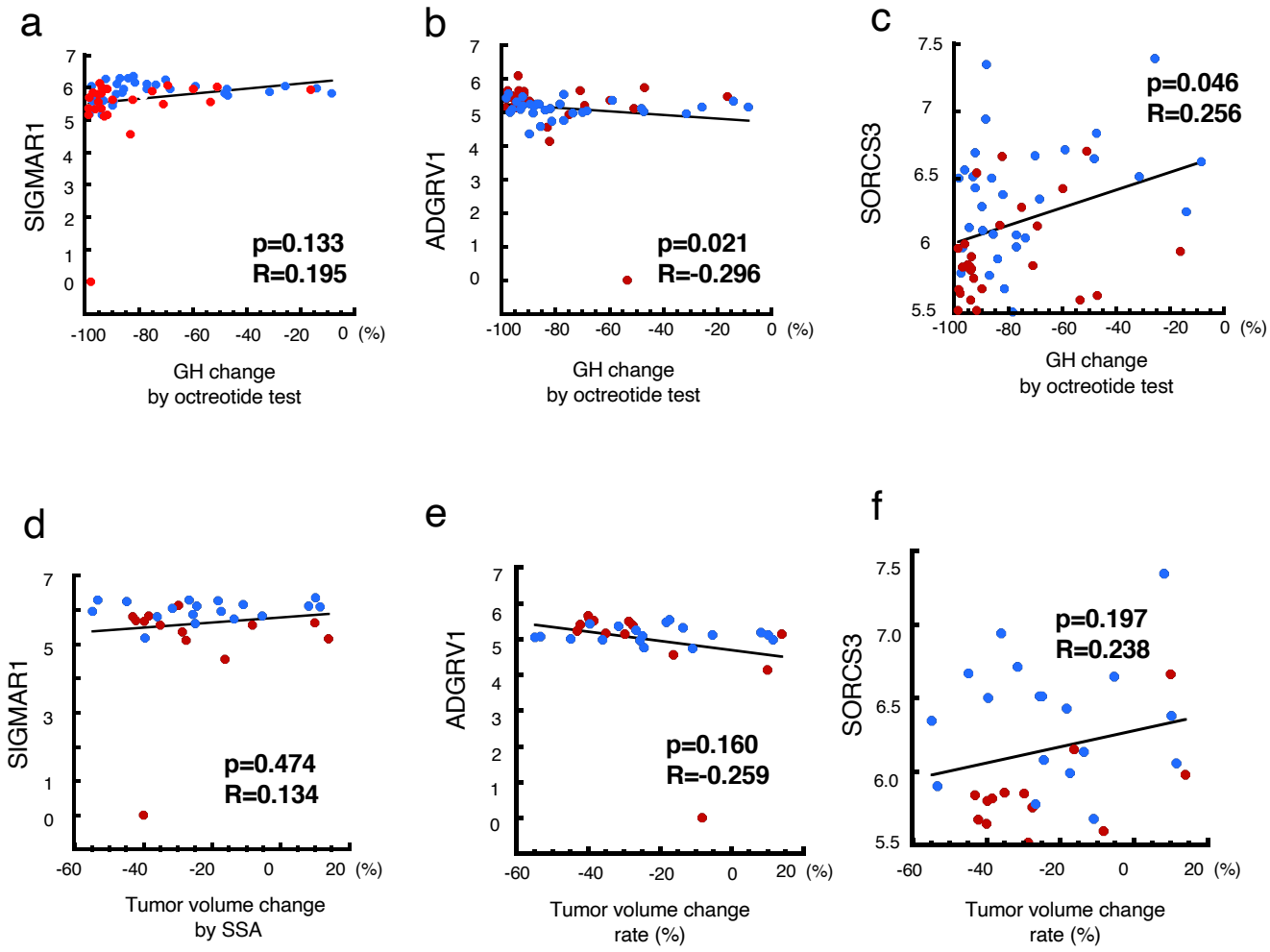


Transomics
K=4

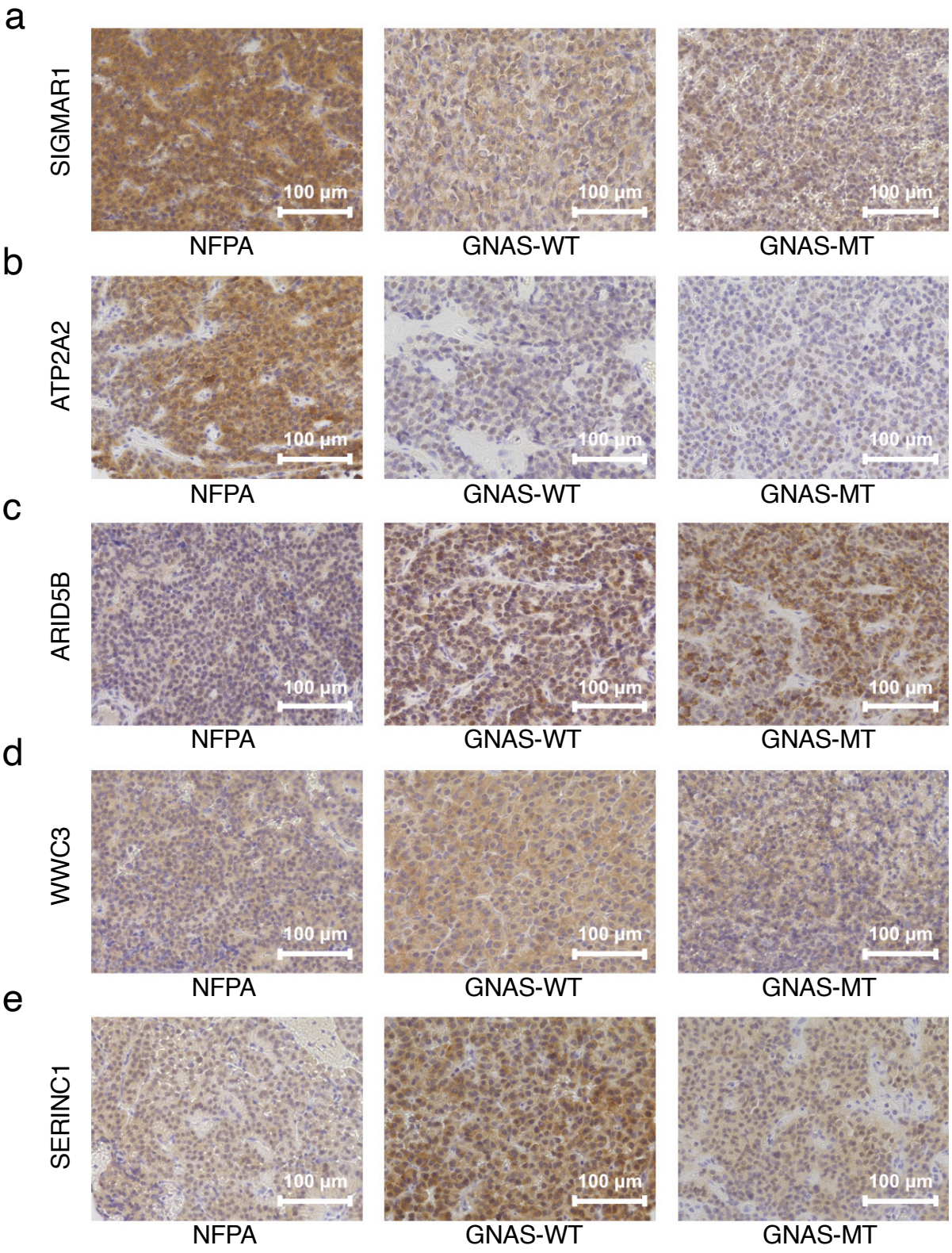
Supplemental Figure 3



Supplemental Figure 4



Supplemental Figure 5



Supplemental material

Supplemental Figure 1. (a) Two-dimensional structure of the Gsα protein. *GNAS* mutations detected in our cohort are described at the top of the schema. Mutational hotspots detected in previous reports are described at the bottom of the schema. (b) Crystal structure of the Gsα protein (PDB: 6AU6). Blue-labeled amino acids indicate known *GNAS* mutations, whereas magenta amino acids indicate novel mutations identified in the present study.

Supplemental Figure 2. Graph showing cluster metrics (y-axis) as a function of the number of cluster K (x-axis). RNA sequence, proteomics, and multi-omics results are shown.

Supplemental Figure 3. Uniform manifold approximation and projection (UMAP) analysis showing the clusters of non-functional pituitary adenomas and growth hormone (GH)-producing adenomas depending on tumor types: nuclear receptor subfamily 5 group A member 1 (NR5A1), GATA-binding protein 3 (GATA3), POU class 1 homeobox 1 (POU1F1), GH1, and somatostatin receptor 5 (SSTR5) using multi-omics data.

Supplemental Figure 4. Correlations between (a) sigma nonopioid intracellular receptor-1 (SIGMAR1), (b) adhesion G protein–coupled receptor V1 (ADGRV1), and (c) sortilin-related VPS10

domain–containing receptor 3 (SORCS3) protein expression level and the growth hormone (GH) change rate in the octreotide loading test (%). Correlations between (d) SIGMAR1, (e) ADGRV1, and (f) SORCS3 protein expression levels and the tumor volume change rate in the somatostatin analog (SSA) test (%). The protein expression value was log (base 10) transformed. Data were analyzed by Pearson's correlation analysis.

Supplemental Figure 5. Immunohistochemistry of new differentially expressed candidates in non-target proteomics. Sections were stained for (a) sigma nonopioid intracellular receptor-1 (SIGMAR1), (b) sarcoplasmic/endoplasmic reticulum calcium ATPase 2 (ATP2A2), (c) AT-rich interaction domain 5B (ARID5B), (d) WWC family member 3 (WWC3), and (e) serine incorporator 1 (SERINC1).

Supplemental Table 1. Clinical and genetics infomations of all acromegaly patients.

Supplemental Table 2. Genes analyzed by target capture sequence.

Supplemental Table 3. Clinical infomations of all patients with non-functional pitutiary adenoma.

Supplemental Table 4. KEGG analysis of molecular groups that showed significantly higher expression fluctuations in cluster 3 compared to cluster 1 in consensus clustering-based proteomics.

Supplemental Table 5. Gene ontology terms of molecular groups that showed significant expression fluctuations with and without GNAS mutations in proteomics.