Table S-3. Selected syndromes with activation of a mutant cell from germline or mosaic mutation in a GTP-binding protein coupled receptor or in a nearby downstream protein.

<table>
<thead>
<tr>
<th>Syndrome &amp; Molecule</th>
<th>Mutated Molecule</th>
<th>Hormone over- secreted</th>
<th>Comments including about hyperplasia involving the same cells as expressing the mutant protein</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Familial hypocalciuric hypercalcemia</td>
<td>CaS-R</td>
<td>PTH</td>
<td>Parathyroid hyperplasia is absent or minimal</td>
<td>Marx SJ 2014</td>
</tr>
<tr>
<td>Precocious puberty</td>
<td>Kiss1-R</td>
<td>LH</td>
<td>One case. No information about histology. Over-secretion of LH is secondary and from a cell, downstream of the mutated cell</td>
<td>Teles MG, Bianco SD, et al 2008</td>
</tr>
<tr>
<td>X-linked acromegaly and gigantism</td>
<td>GPR101</td>
<td>GH, Prl</td>
<td>Extracellular ligands unknown. Mutant cell not known. Secretion by mutated or by its downstream cell may be GHRH. Somatotrope overfunction is secondary and shows GH adenoma in most cases</td>
<td>Trivellin G, Daly AF et al 2014</td>
</tr>
<tr>
<td>Jansen osteodystrophy</td>
<td>PTH1-R</td>
<td>Cartilage</td>
<td>Hyperplasia of osteoblasts and osteoblast precursors in mouse model</td>
<td>Calvi LM, Sims NA et al 2001</td>
</tr>
<tr>
<td>Multiple enchondromas</td>
<td>PTH1-R</td>
<td>Cartilage</td>
<td>One case. Increased chondrocyte proliferation in mouse model</td>
<td>Hopyan S, Gokgoz N et al 2002</td>
</tr>
<tr>
<td>Condition</td>
<td>Gene</td>
<td>Protein</td>
<td>Enzyme</td>
<td>Effect</td>
</tr>
<tr>
<td>-----------------------------------------------</td>
<td>------</td>
<td>---------</td>
<td>--------</td>
<td>------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Inappropriate nephrogenic antidiuresis</td>
<td>AVP-R2</td>
<td>None</td>
<td>None</td>
<td>No information about renal histology from mutation in man or mouse</td>
</tr>
<tr>
<td>Congenital stationary night blindness</td>
<td>Rhodopsin</td>
<td>None</td>
<td>None</td>
<td>Rhodopsin $RHO\ G90D$ activating mutation; most other mutations inactivate rhodopsin and cause retinitis pigmentosa</td>
</tr>
</tbody>
</table>

From Mutation in an Alpha-subunit of a Heterotrimeric GTP-binding Protein

<table>
<thead>
<tr>
<th>Condition</th>
<th>Gene</th>
<th>Protein</th>
<th>Enzyme</th>
<th>Effect</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Familial hypocalciuric hypercalcemia</td>
<td>Ga11</td>
<td>PTH</td>
<td>Parathyroid gland histology not documented. Perhaps hyperplasia is absent or minimal (due to similarity to FHH from mutated CaS-R (below))</td>
<td>Nesbitt MA, Hannan FM, et al 2013</td>
<td></td>
</tr>
<tr>
<td>McCune-Albright syndrome</td>
<td>Gas</td>
<td>Cortisol</td>
<td>Nodules and adenomas more predominant than hyperplasia in adrenal cortex, pituitary, gonad. Mutation is post-zygotic and expressed as mosaic, but likely to be lethal to the embryo if in the germline</td>
<td>Weinstein LS, Shenker A, et al 1991 Carney JA, Young WF, et al 2011</td>
<td></td>
</tr>
</tbody>
</table>

From Mutant Protein that Activates Cyclic AMP-like Signal

<table>
<thead>
<tr>
<th>Condition</th>
<th>Gene</th>
<th>Protein</th>
<th>Enzyme</th>
<th>Effect</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACTH-independent Cushing syndrome</td>
<td>PKA R1A</td>
<td>Cortisol</td>
<td>Pigmented micronodular adrenocortical hyperplasia. With tumors outside of adrenal cortex (myxoma, lentigines etc) is Carney Complex</td>
<td>Carney JA, Gordon et al 1985 Bertherat J 2006 Stratakia CA 2008</td>
<td></td>
</tr>
</tbody>
</table>
& Syndromes were excluded if they had predominant hyperplasia

Abbreviations: Alpha-11 subunit of heterotrimeric GTP-binding protein Ga11; Stimulatory alpha subunit of heterotrimeric GTP-binding protein Gas; CaS-R calcium sensing receptor CaS-R; Type 1 receptor for kisspeptin Kiss-1R; glucagon receptor Gcg-R; Type 1 receptor for PTHrP and PTH PTHrP-1R; Type 2 receptor for arginine vasopressin AVP-R2

* For each syndrome, the available information is not sufficient to establish that predominating hyperplasia or hormone over-secretion is present in the same tissues that are expressing the mutation. Each of these syndromes with hormone oversecretion was excluded from the study group with predominating hyperplasia in the mutated cells (See Supplementary Table S-1 for similar examples of excluded syndromes).

Agarwal SK, Mateo C, Marx SJ 2009 Rare germline mutations in cyclin-dependent kinase inhibitor genes in MEN1 and related states. J Clin Endocrinol Metab/94 1826-34.


Beckers A, Aaltonen LA, Daly AF, Karhu A 2013 Familial isolated pituitary adenomas (FIPA) and the pituitary adenoma predisposition due to mutations in the aryl hydrocarbon receptor interacting protein (AIP) gene. Endocr Rev/34 239-77.


Scholl UI, Nelson-Williams C, Yue P 2012 et al Hypertension with or without adrenal hyperplasia due to different inherited mutations in the potassium channel KCNJ5. Proc Nat Acad Sci (USA)/109 2533-2538.


