Supplementary Table S-5. Representative syndromes with hereditary primary excess of hormone over-secreting nodules, adenomas, or cancers. Several other syndromes are described separately as incomplete parts of Supplementary S-1.

Syndrome	Genes and mutations@	Main hormones over-secreted	Main tissues over-active		Hyperplastic precursors in tissue	Cause a sporadic neoplasm	References
			Over-secreting	Not secreting			
MEN1	*MEN1*-,	PTH, Prl, gastrin insulin	Islet*, parathy pituitary	Carcinoid, dermis, adrenal cortex	Su	Y	Marx SJ, Wells SA jr 2011
MEN4	*CDKN1B*-*(CDKIs)*	PTH, Prl, gastrin insulin	Islet*, parathy pituitary	Carcinoid, dermis, adrenal cortex	Su	Y	Agarwal SK, Mateo C, et al 2009
HPT-JT	*HRPT2*-	PTH	Parathyroid	Jaw bone, kidney	Su	Y	Carpten JD, Robbins CM, et al 2002
FMTC	*RET*+	Calcitonin	C-cell		Y	Y	Albores-Saavedra J, Krueger JE 2001
MEN2A	*RET*+	Calcitonin, PTH, catecholamines	C-cell, parathy adrenal medulla		Y	Y	Machens A, Niccoli-Sire P, et al 2003
MEN2B	*RET*+	Calcitonin, catecholamines	C-cell, adrenal medulla	Nerve	Y	Y	Zenaty D, Aigrain Y, et al 2009
PGL4	*SDHB*-	Catecholamines	Adrenal medulla Kidney	Paraganglioma,	Su	?	Grogan RH, Pacak K, et al 2011
PGL1	*SDHD*-	Catecholamines	Adrenal medulla	Paraganglioma	Su	?	Mete O, Tischler AS, et al 2014

MAX	*MAX*-	Catecholamines	Adrenal medulla	Paraganglioma	Su	?	Mete O, Tischler AS, et al 2014
IPheo	*TMEM127*-	Catecholamines	Adrenal medulla		Su	?	Toledo SP,Lourenco DM jr, et al 2014
NF1	*NF1*-	Catecholamines	Adrenal medulla	Nerve	Su	Y	Welander J, Larsson C, et al 2012
VHL	*VHL*-	Catecholamines	Adrenal medulla	Kidney, retina, cerebellum, islet	Su	Y	Gossage L, Eisen T, et al 2015
DICER1	*DICER1*-	ACTH, GH	Thyroid	Lung, kidney sertoli, pineal	N	N	de Kock L, Sabbaghian N, et al 2014

& MEN1 and MEN4 are treated as expressing the same or very similar phenotype. Cases of MEN4 are too few and too similar to MEN1, to separate the MEN4 phenotype from MEN1
*Underlined tissues have high cancer potential (above 5% in adults with tumor of that tissue)
@ Mutation types are: - heterozygous loss of function (inactivation); + heterozygous gain of function (activation).

Abbreviations: Glucagon cell neoplasia GcGN; Massive macronodular adrenocortical hyperplasia MMAH; Multiple endocrine neoplasia MEN; PRKR1A; PRKACA; Familial medullary thyroid cancer FMTC; Von Hipplel Lindau Disease VHL; Paraganglioma PGL; Neurofibromatosis type I NF1; Isolated pheochromocytoma IPheo; Hyperparathyroid-Jaw tumor syndrome HPT-JT; Familial isolated pituitary adenoma FIPA; Subtle Su; Yes Y; Parathyroid parathy;

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.

Albores-Saavedra J, Krueger JE 2001 C-cell hyperplasia and medullary thyroid microcarcinoma. Endocr Pathol/12 365-377.

Arnold A, Marx SJ 2013 Familial hyperparathyroidism (Including MEN, FHH, and HPT-JT). In Primer on the Metabolic Bone Diseases and Mineral Metabolism, edn 8, pp 553-561, Eds C Rosen, R Bouillon, JE Compston, V. Rosen. John Wiley & Sons, Inc.

Assie G, Libé R, Espiard S, Rizk-Rabin M, Guimier A, Luscap W, Barreau O, Lefèvre L, Sibony M, Guignat L, Rodriguez S, Perlemoine K, René-Corail F, Letourneur F, Trabulsi B, Poussier A, Chabbert-Buffet N, Borson-Chazot F, Groussin L, Bertagna X, Stratakis CA, Ragazzon B, Bertherat J 2013 ARMC5 mutations in macronodular adrenal hyperplasia with Cushing's syndrome. N Engl J Med/369 2105-14.

Bamford S, Dawson E, Forbes S, Clements J, Pettett R, Dogan A, Flanagan A, Teague J, Futreal PA, Stratton MR, Wooster R 2004 The COSIC (Catalog of Somatic Mutations in Cancer) database and website. In the Sanger Institute Catalogue of Somatic Mutations in Cancer web site, http://www.sanger.ac.uk/cosmic. Brit J Cancer/91 355-358.

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.

Blair JW, Carachi R 1991 Neonatal primary hyperparathyroidism – A case report and review of the literature. Eur J Pediatr Surg/1 110-114.

Calvi LM, Sims NA, Hunzelman JL, Knight MC, Giovannetti A, Saxton JM, Kronenberg HM, Baron R, Schipani E 2001 Activated parathyroid hormone/parathyroid hormone-related protein receptor in osteoblastic cells differentially affects cortical and trabecular bone. J Clin Invest./107 277-86.

Carney JA, Gaillard RC, Bertherat J, Stratakis CA 2010 Familial micronodular adrenocortical disease, Cushing syndrome, and mutations of the gene encoding phosphodiesterase 11A4 (PDE11A). Am J Surg Pathol/34 547-55.

Carney JA, Young WF, Stratakis CA. Primary bimorphic adrenocortical disease: cause of hypercortisolism in McCune-Albright syndrome. Am J Surg Pathol. 2011 ;35:1311-26.

Carpten JD, Robbins CM, Villablanca A, Forsberg L, Presciuttini S, Bailey-Wilson J, Simonds WF, Gillanders EM, Kennedy AM, Chen JD, Agarwal SK, Sood R, Jones MP, Moses TY, Haven C, Petillo D, Leotlela PD, Harding B, Cameron D, Pannett AA, Höög A, Heath H III, James-Newton LA, Robinson B, Zarbo RJ, Cavaco BM, Wassif W, Perrier ND, Rosen IB, Kristoffersson U, Turnpenny PD, Farnebo L-O, Besser GM, Jackson CE, Morreau H, Trent JM, ThakkerRV, Marx SJ, Teh BT, Larsson C, Hobbs MR. *HRPT2*, encoding parafibromin, is mutated in hyperparathyroidism–jaw tumor syndrome. Nature Genetics, 32: 676-80, 2002.

Ch'ng JL, Kaiser A, Lynn J, Joplin JF 1984 Post-parathyroidectoy restoration of normal calcium homeostasis in neonatal primary hyperparathyroidism. Acta Endocr/105 350-353.

Cooper L, Wertheimer J, Levey R, Brown E, Leboff M, Wilkinson R, Anast CS 1986 Severe primary hyperparathyroidism in a neonate with two hypercalcemic parents: management with parathyroidectomy and heterotopic autotransplantation. Pediatrics/78 263-268.

Dahia PLM 2014 Pheochromocytoma and paraganglioma pathogenesis: learning from genetic heterogeneity. Nat Rev Cancer/14 108-119.

Deccaux G, Vandergherynst F, Bouke Y, Parma J, Vassart g, Vilain C. Nephrogenic syndrome of inappropriate antidiuresis in adults: high phenotypic variability in men and women from a large pedigree. J Am Soc Nephrol18: 606-612, 2007

de Kock L, Sabbaghian N, Druker H, Weber E, Hamel N, Miller S, Choong CS, Gottardo NG, Kees UR, Rednam SP, van Hest LP, Jongmans MC, Jhangiani S, Lupski JR, Zacharin M, Bouron-Dal Soglio D, Huang A, Priest JR, Perry A, Mueller S, Albrecht S, Malkin D, Grundy RG, Foulkes WD. Germ-line and somatic DICER1 mutations in pineoblastoma. Acta Neuropathol. 2014; 128:583-95

Fukumoto S FGF23-FGF receptor/klotho pathway is a new drug target for disorders of bone and mineral metabolism. Calcif Tiss Int 223: 15-29, 2015

Gilmour JR, Martin WJ 1937 The weight of the parathyroid glands. J Pathol Bacteriol/34 431-462.

Goldbloom RB, Gillis DDA, Prasad M 1972 Hereditary parathyroid hyperplasia: A surgical emergency of early infancy. Pediatr/49 514-523.

Gossage L, Eisen T & Maher ER 2015 VHL, the story of a tumour suppressor gene. Nat Rev Cancer/15 55–64.

Grantmyre EB1973 Roentgenographic features of “primary” nyperparathyroidism in infancy. J de L’Associat Canad des Radiol/24 257-260.

Grogan RH, Pacak K, Pasche L, Huynh TT, Greco RS 2011 Bilateral adrenal medullary hyperplasia associated with an SDHB mutation. J Clin Oncol/29 e200-2.

Hillman DA, Scriver CR, Pedvis S, Shragovitch I 1964 Neonatal familial primary hyperparathyroidism. N Eng J Med/270 483-488.

Hopyan S, Gokgoz N, Poon R, Gensure RC, Yu C, Cole WG, Bell RS, Jüppner H, Andrulis IL, Wunder JS, Alman BA 2002 A mutant PTH/PTHrP type I receptor in enchondromatosis. Nat Genet/30 306-10.

Horvath A, Boikos S, Giatzakis C, Robinson-White A, Groussin L, Griffin KJ, Stein E, Levine E, Delimpasi G, Hsiao HP, Keil M, Heyerdahl S, Matyakhina L, Libè R, Fratticci A, Kirschner LS, Cramer K, Gaillard RC, Bertagna X, Carney JA, Bertherat J, Bossis I, Stratakis CA 2006 A

genome-wide scan identifies mutations in the gene encoding phosphodiesterase 11A4 (PDE11A) in individuals with adrenocortical hyperplasia. Nat Genet/38 794-800.

Horvath A, Mericq V, Stratakis CA 2008 Mutation in PDE8B, a cyclic AMP-specific phosphodiesterase in adrenal hyperplasia. N Engl J Med/358 750-2.

Key L, Thorne M, Pitzer B, Volberg F, Turner C 1990 Management of neonatal hyperparathyroidism with parathyroidectomy and autotransplantation. J Pediatr/116 923-926.

Lutz P, Kane O, Pfrsdorff A, Seiller F, Sauvage P, Levy JM 1986 Neonatal primary hyperparathyroidism: Total parathyroidectomy with autotransplantation of cryopreserved parathyroid tissue. Acta Paed Scand/75 179-182.

Machens A, Niccoli-Sire P, Hoegel J, Frank-Raue K, van Vroonhoven TJ, Roeher HD, Wahl RA, Lamesch P, Raue F, Conte-Devolx B, Dralle H 2003 European Multiple Endocrine Neoplasia (EUROMEN) Study Group. Early malignant progression of hereditary medullary thyroid cancer. N Engl J Med/349 1517-25.

Marx SJ 2014 Uncoupling of secretion from size in some hormone secretory tissues. J Clin Endocrinol Metab/99 4051-4059.

Marx SJ and Wells SA Jr (In Press) Multiple Endocrine Neoplasia. In Williams Textbook of Endocrinology, edn 13. Eds S Melmed, KS Polonsky, PR Larsen, HM Kronenberg. Philadelphia: Elsevier Saunders.

Marx SJ and Wells SA Jr 2011 Multiple Endocrine Neoplasia, In Endocrinology, edn 12, pp 1728-67. Eds S Melmed, KS Polonsky, PR Larsen, HM Kronenberg. Philadelphia: Elsevier Saunders.

Mete O, Tischler AS, de Krijger R, McNicol AM, Eisenhofer G, Pacak K, Ezzat S, Asa SL 2014 Protocol for the examination of specimens from patients with pheochromocytomas and extra-adrenal paragangliomas. Arch Pathol Lab Med/138 182-88.

Nesbit MA, Hannan FM, Howles SA, Babinski VN, Head RA, Cranston T, Rust N, Hobbs MR, Heath H III, Thakker R 2013 Mutations affecting G-protein subunit a11 in hypercalcemia and hypocalcemia. N Eng J Med/368 2476-2486.

Nesbit MA, Hannan F, Howles SA, Reed AAC, Cranston T, Thakker CE, Gregory L, Rimmer AJ, Rust N, Graham U, Morrison PJ, Hunter SJ, Whyte M, McVean G, Buck D, Thakker R 2013 Mutations in AP2S1 cause familial hypocalciuric hypercalcemia type 3. Nat Genet/45 93-97.

Rhone DP 1975 Primary neonatal hyperparathyroidism: Report of a case and review of the literature. Am J Clin Pathol/64 488-499.

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.

Singhal A, Ostermaier MK, Vishnivetskiy SA, Panneels V, Homan KT, Tesmer JJ, Veprintsev D, Deupi X, Gurevich VV, Schertler GF, Standfuss J 2013 Insights into congenital stationary night blindness based on the structure of G90D rhodopsin. EMBO Rep. 2013/14 520-526.

Sipos B, Sperveslage J, Anlauf M, Hoffmeister M, Henopp T, Buch S, Hampe J, Weber A, Hammel P, Couvelard A, Höbling W, Lieb W, Böhm BO, Klöppel G 2015 Glucagon cell hyperplasia and neoplasia with and without glucagon receptor mutations. J Clin Endocrinol Metab/jc20144405 [Epub ahead of print].

Stanley CA and De Leon DD 2012 Eds. Monogenic Hyperinsulinemic Hypoglycemia Disorders. Karger Basel.

Steinmann B, Gnehm HE, Rao VH, Kind HP, Prader A 1984 Neonatal severe primary hyperparathyroidism and alkaptonuria in a boy born to related parents with familial hypocalciuric hypercalcemia. Helv Paediatr Acta/39 171-86.

Teles MG, Bianco SD, Brito VN, Trarbach EB, Kuohung W, Xu S, Seminara SB, Mendonca BB, Kaiser UB, Latronico AC 2008 A GPR54-activating mutation in a patient with central precocious puberty. N Engl J Med/358 709-15.

Thompson NW, Carpenter LC, Nishiyama RH 1978 Hereditary neonatal hyperparathyroidism. Arch Surg/113 100-103.

Toledo SP, Lourenço DM Jr, Sekiya T, Lucon AM, Baena ME, Castro CC, Bortolotto LA, Zerbini MC, Siqueira SA, Toledo RA, Dahia PL 2014 Penetrance and clinical features of pheochromocytoma in a six-generation family carrying a germline TMEM127 mutation. J Clin Endocrinol Metab/100 E308-18.

Trivellin G, Daly AF, Faucz FR, Yuan B, Rostomyan L, Larco DO, Schernthaner-Reiter MH, Szarek E, Leal LF, Caberg JH, Castermans E, Villa C, Dimopoulos A, Chittiboina P, Xekouki P, Shah N, Metzger D, Lysy PA, Ferrante E, Strebkova N, Mazerkina N, Zatelli MC, Lodish M, Horvath A, de Alexandre RB, Manning AD, Levy I, Keil MF, Sierra Mde L, Palmeira L, Coppieters W, Georges M, Naves LA, Jamar M, Bours V, Wu TJ, Choong CS, Bertherat J, Chanson P, Kamenický P, Farrell WE, Barlier A, Quezado M, Bjelobaba I, Stojilkovic SS, Wess J, Costanzi

S, Liu P, Lupski JR, Beckers A, Stratakis CA 2014 Gigantism and acromegaly due to Xq26 microduplications and GPR101 mutation. N Engl J Med/371 2363-74.

Villa C, Lagonigro MS, Magri F, Koziak M, Jaffrain-Rea ML, Brauner R, Bouligand J, Junier MP, Di Rocco F, Sainte-Rose C, Beckers A, Roux FX, Daly AF, Chiovato L 2011 Hyperplasia-adenoma sequence in pituitary tumorigenesis related to aryl hydrocarbon receptor interacting protein gene mutation. Endocr Relat Cancer/18 347-56.

Villa C, Lagonigro MS, Magri F, Koziak M, Jaffrain-Rea ML, Brauner R, Bouligand J, Junier MP, Di Rocco F, Sainte-Rose C, Beckers A, Roux FX, Daly AF, Chiovato L 2011 Hyperplasia-adenoma sequence in pituitary tumorigenesis related to aryl hydrocarbon receptor interacting protein gene mutation. Endocr Relat Cancer/18 347-56.

Weinstein LS, Shenker A, Gejman PV, Merino MJ, Friedman E, Spiegel AM 1991 Activating mutations of the stimulatory G protein in the McCune-Albright syndrome. N Engl J Med

Welander J, Larsson C, Bäckdahl M, Hareni N, Sivlér T, Brauckhoff M, Söderkvist P, Gimm O 2012 Integrative genomics reveals frequent somatic NF1 mutations in sporadic pheochromocytomas. Hum Mol Genet/21 5406-16.

Wells SA Jr, Pacini F, Robinson BG, Santoro M 2013 Multiple endocrine neoplasia type 2 and familial medullary thyroid carcinoma: an update. J Clin Endocrinol Metab/98 3149-64.

Zenaty D, Aigrain Y, Peuchmaur M, Philippe-Chomette P, Baumann C, Cornelis F, Hugot JP, Chevenne D, Barbu V, Guillausseau PJ, Schlumberger M, Carel JC, Travagli JP, Léger J 2009 Medullary thyroid carcinoma identified within the first year of life in children with hereditary multiple endocrine neoplasia type 2A (codon 634) and 2B. Eur J Endocrinol/160 807-13.