Hyperplasia in glands with hormone excess

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Abstract

Five syndromes share predominantly hyperplastic glands with a primary excess of hormones: neonatal severe primary hyperparathyroidism, from homozygous mutated *CASR*, begins severely *in utero*; congenital non-autoimmune thyrotoxicosis, from mutated *TSHR*, varies from severe with fetal onset to mild with adult onset; familial male-limited precocious puberty, from mutated *LHR*, expresses testosterone oversecretion in young boys; hereditary ovarian hyperstimulation syndrome, from mutated *FSHR*, expresses symptomatic systemic vascular permeabilities during pregnancy; and familial hyperaldosteronism type IIIA, from mutated *KCNJ5*, presents in young children with hypertension and hypokalemia. The grouping of these five syndromes highlights predominant hyperplasia as a stable tissue endpoint and as their tissue stage for all of the hormone excess. Comparisons were made among this and two other groups of syndromes, forming a continuum of gland staging: predominant oversecretions express little or no hyperplasia; predominant hyperplasias express little or no neoplasia; and predominant neoplasias express nodules, adenomas, or cancers. Hyperplasias may progress (5 of 5) to neoplastic stages while predominant oversecretions rarely do (1 of 6; frequencies differ $P<0.02$). Hyperplasias do not show tumor multiplicity (0 of 5) unlike neoplasias that do (13 of 19; $P<0.02$). Hyperplasias express mutation of a plasma membrane-bound sensor (5 of 5), while neoplasias rarely do (3 of 14; $P<0.002$). In conclusion, the multiple distinguishing themes within the hyperplasias establish a robust pathophysiology. It has the shared and novel feature of mutant sensors in the plasma membrane, suggesting that these are major contributors to hyperplasia.

Key Words
- neonate
- proliferation
- GPCR
- cyclic AMP
- signal transduction
- parathyroid
- thyroid
- gonad
- adrenal cortex

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Introduction

Hyperplasia was identified long ago in pathologic tissues, including the thyroid and parathyroid, and long before the secreted hormone of each tissue had become identified (De Crecchio 1865, Hirsch 1885, Erdheim 1907). Hyperplasia is frequently a secondary state, a response to extracellular stimuli, such as in a goiter caused by thyroid-stimulating antibodies or by thyroid-stimulating hormones (TSH).

Alternately, and whether accompanied by oversecretion, hyperplasia can be a primary state, originating from an intrinsic process of the same cells (Derwahl & Studer 2002, Arnold 2011, Snow *et al*. 2012). Primary hyperplasia usually accompanies a pathologic oversecretion of a hormone from the same cells. For this, it can be divided into two broad formats. The first is subtle hyperplasia as a precursor or an accompaniment to predominating adenomas or cancers (Marx 2013, Mete & Asa 2013). The second format is predominating hyperplasia but with little or no progression to adenomas or cancer. This second format is the main subject here.

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Methods

The main foci for review were histologic staging in hormone-secretory glands, secretion processes in the glands, germline mutation, and molecular functions around the mutant protein. I analyzed reports and reviews about primary oversecretion of hormone(s), descriptions of light microscopy for the oversecreting glands, predominating hyperplasia in the hormone-secretory gland, and the origin of the syndrome from a known mutation.

The main criterion for hyperplasia of a tissue is an increase in the number of relatively normal-appearing cells (Kumar *et al*. 2010). Hyperplasia is distinct from hypertrophy, which is an increase in cell size, and it can accompany hyperplasia. Hyperplastic cells may be of uniform or mixed types. When mixed types, there is a variable decrease in the fraction with adipocytes and other stroma. The parenchymal pattern is diffuse throughout a hyperplastic tissue, in contrast to neoplasia, which is focal or multifocal. Differential immunostaining for reticulin has been used only occasionally to distinguish hyperplasia from neoplasia but mainly for hepatic or pituitary tissues (Hong *et al*. 2011, Mete & Asa 2013).

Exclusion criteria (Supplementary Table S-1, see section on supplementary data given at the end of this article) included insufficient information about gland histology, predominantly normal or near-normal tissue grade (Marx 2014), or higher grades of neoplasia (small nodules, large nodules, adenoma, or cancer). Some of the excluded syndromes were later grouped for comparisons to the reviewed group. I used Fisher's exact test to compare frequencies of features among syndrome groups.

Results

Neonatal severe primary hyperparathyroidism

Clinical Neonatal severe primary hyperparathyroidism (NSHPT) is very rare (Thompson *et al*. 1978, Cooper *et al*. 1986, Key *et al*. 1990, Arnold & Marx 2013). It includes an under-mineralized skeleton, sub-periosteal resorption, bell-shaped thorax and extremely high blood levels of calcium (20–30 mg/dl) and parathyroid hormones (PTH) (500% or more of the upper normal limit). Biallelic inactivation of the CaS-R in bone cells may contribute to the severe skeletal features (Goltzman & Hendy 2015). These severely ill neonates suffer respiratory distress, worsened by multiple rib fractures and hypotonia. They need complex support. After subtotal parathyroidectomy, hyperparathyroidism in severe form recurred rapidly, at 2 and 5 months for two cases (Thompson *et al*. 1978, Key *et al*. 1990) (see Supplement, see section on supplementary data given at the end of this article). The preferred treatment includes urgent total parathyroidectomy.

Parathyroids in NSHPT The severe skeletal expressions at birth in NSHPT indicate that harmful oversecretion of PTH had begun from the parathyroid glands of the fetus. In fact, the murine fetus with homozygous *CASR* knockout has serum PTH about 20-fold the maternal level at day 18 of gestation (Simmonds *et al*. 2010). Surgery for NSHPT at 2–12 weeks postpartum has shown a parathyroid size 4–10 times normal (Supplementary Table S-2, see section on supplementary data given at the end of this article). The histologic pattern is diffuse increase of secretory cells, mainly large clear cells and some small chief cells. In one case, polyclonality was suggested by two types of molecular genetic analysis (Corrado *et al*. 2015). Parathyroid nodularity or cancer have not been reported. However, double adenoma was identified in a variant, i.e., one case with germline biallelic inactivation of the *CASR* and a much milder onset in adulthood (Hannan *et al*. 2010).

Molecules and genes The normal *CASR* encodes the extracellular calcium sensing receptor (CaS-R). It is expressed mainly on the parathyroid cell surface but also on the renal tubular cell, the thyroidal C-cell, and elsewhere. It is central in sensing levels of extracellular calcium and in regulating PTH secretion (Brown 2013). A role in the proliferation of the parathyroid has been supported indirectly by CaS-R deficiencies in the large parathyroids of primary or secondary hyperparathyroidism and also by calcimimetic drug actions against hyperparathyroidism (Kifor *et al*. 1996, Farnebo *et al*. 1997, Miller *et al*. 2012).

Cases of NSHPT have biallelic inactivation of the *CASR* (Marx *et al*. 1985, Pollak *et al*. 1993, Hannan *et al*. 2012). The same mutation in heterozygous form expresses as familial hypocalciuric hypercalcemia (FHH) (Arnold & Marx 2013). *GNA11* and *AP2S1*, two other genes less frequently mutated in FHH heterozygotes (Nesbit *et al*. 2013*a*,*b*), have not yet been implicated in NSHPT. Of the *CASR* mutations causing NSHPT, 30% predict truncation of the CaS-R vs 3% from the *CASR* mutations causing FHH; most of the missense *CASR* mutations are clustered in a limited extracellular domain (cleft of its 'Venus fly-trap' domain) (Hannan *et al*. 2012). *In vitro*, most shift the suppression curve between extracellular Ca++ and PTH secretion toward higher Ca++ values (Pearce *et al*. 1996).

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Sporadic tumor from somatic mutation of CASR The parathyroids from common primary hyperparathyroidism show decreased sensitivity to extracellular calcium (Brown *et al*. 1979). Both primary and secondary tumors of the parathyroids show lowered concentrations of CaS-R protein (Kifor *et al*. 1996, Farnebo *et al*. 1997); however, somatic mutation of the *CASR* in the parathyroids has not been found in either of these common states (Arnold *et al*. 1995, Hosokawa *et al*. 1995, Cetani *et al*. 1999). Rare cases of FHH present with a clinical diagnosis of parathyroid adenoma (Burski *et al*. 2002, Yamauchi *et al*. 2002, Brachet *et al*. 2009, Yabuta *et al*. 2009); these have not been evaluated for a second hit at the *CASR* or at another gene.

Variants related to NSHPT Rare homozygous *CASR* mutations are expressed as a milder variant, presenting as hypocalciuric hypercalcemia in adulthood (Leitman *et al*. 2009 Hannan *et al*. 2010). A different variant of intermediate severity (serum calcium 11–15 mg/dl and PTH 300% or more of upper normal) may occur in a neonate with heterozygous mutated *CASR* but who is born to a mother without the mutation. In these cases, secondary hyperparathyroidism starting in the fetus *in utero* may worsen temporarily the otherwise mild expressions in the heterozygous neonate (Marx *et al*. 1982, Bai *et al*. 1997).

Congenital non-autoimmune thyrotoxicosis

Clinical Congenital non-autoimmune thyrotoxicosis (CNT) is rare and generally caused by the heterozygous activating mutation of the TSH receptor (TSH-R) (Kopp *et al*. 1995, Vassart 2010, Hebrant *et al*. 2011). It must be distinguished from the more frequent neonatal Graves' disease, caused by antibodies that activate the TSH-R. Severe expressions can sometimes be recognized at birth; cases with the earliest expressions show hyperthyroidism (50%), prematurity (70%), low birth weight (85%), mental retardation (60%), advanced bone age (50%), and cranial synostosis (50%) (Vassart 2010, Hebrant *et al*. 2011). Most severely affected neonates present sporadically with a new mutation (Kopp *et al*. 1995, de Roux *et al*. 1996, Gozu *et al*. 2010, Vassart 2010, Hebrant *et al*. 2011). Alternately and rarely, an affected neonate was the offspring of an affected father or mother, who had been adequately managed as a severely affected child (Supornsilchai *et al*. 2009). In some families with the TSH-R mutation, all carriers show onset of thyrotoxicosis after age 10 years (Arturi *et al*. 2002, Nishihara *et al*. 2010). Recurrence of thyrotoxicosis with CNT is likely after subtotal treatments, including after withdrawal of antithyroid drugs (Hebrant *et al*. 2011, Paschke *et al*. 2012). The usual treatment is uninterrupted antithyroid drugs and/or thyroid ablation, total or near total.

Thyroid gland in CNT The severe expressions in some cases with CNT indicate that there had been oversecretion of thyroid hormones by the fetus. Thyroid histology near parturition in CNT has not been reported, but over 50% show goiter at birth. At all older ages, there is diffuse thyroid follicular hyperplasia, with or without goiter. The average thyroid size may be increased three- to fivefold or more. There are clusters of small or large follicles, similar to toxic thyroid adenoma. At later stages, small or large nodules may occur (Gozu *et al*. 2010, Hebrant *et al*. 2011). The frequency of thyroid cancer is not increased.

Molecules and genes The normal TSH-R, LH receptor (LH-R or LH/CG-R), and FSH receptor (FSH-R) are closely related. Similarly the gonadotropin hormones, TSH, LH, FSH, and CG, are closely related (Themmen 2005, Kleinau *et al*. 2013, Jiang *et al*. 2014). All recently reported hereditary cases of CNT have had a heterozygous activating *TSHR* mutation. Most of the mutations are modeled along the transmembrane loops of the TSH-R, with a roughly similar distribution of severe and less severe mutations (Gozu *et al*. 2010). Mutation sequences from the severest cases can also be identical to mutations in sporadic adenoma. In contrast, less severe cases are from other private germline mutations. The mutated, activated TSH-R causes *in vitro* a two- to sevenfold higher basal cyclic AMP than controls (Gozu *et al*. 2010). Responsitivity to TSH *in vitro* is conserved, and apparent affinity for TSH is sometimes increased (Vassart 2010). Activating mutation of the TSH-R also stimulates thyrocyte proliferation *in vitro* (Ludgate *et al*. 1999).

Sporadic tumors from somatic mutation of the TSHR Of autonomous solitary thyroid adenomas, 50% have a somatic activating mutation of the *TSHR* (Vassart 2010, Hebrant *et al*. 2011). *TSHR* activating mutations have rarely been identified as an initiator in sporadic follicular thyroid cancer (Spambalg *et al*. 1996).

Variant from TSHR mutation, expressed as gestational thyrotoxicosis Thyrotoxicosis beginning in pregnancy is usually caused by Graves' disease or by CG activation of the normal TSH-Rs. In one family, a mother and daughter showed severe hyperthyroidism, occurring and recurring during six pregnancies of one or the other

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(Rodien *et al*. 1998). TSH was low and CG was normal for stage of gestation. A small diffuse goiter was recognized during a recurrence. The same germline change (mutation) of the *TSHR* was found in both cases. *In vitro*, this increased markedly the TSH-R sensitivity to CG but not to TSH.

Familial male-limited precocious puberty

Clinical Familial male-limited precocious puberty (FMPP) or testotoxicosis is initially recognized as male iso-sexual precocious puberty. Female carriers have no disease phenotype. Expression usually begins between ages 1 and 3 years (Beas *et al*. 1962, Egli *et al*. 1985); the occasional expression as increased genital size at birth indicates onset in the fetus of such a case (Beas *et al*. 1962, Rosenthal *et al*. 1983, Müller *et al*. 1998). Testosterone levels in blood are increased and gonadotrophins are low. Drugs against androgen synthesis or action have accomplished partial success (Reiter *et al*. 2010, Fuqua 2013).

Testis in FMPP In FMPP, there is a bilateral enlargement of the genitals, including a modest enlargement of the testes. The testis in FMPP shows hyperplasia of Leydig cells, precocious spermatogenesis, and, rarely, bilateral nodularity of Leydig cells (Gondos *et al*. 1985, Leschek *et al*. 2001, McGee & Narayan 2013).

Molecules and genes FMPP is usually attributable to germline activating mutation of the LH-R (Shenker *et al*. 1993, Themmen 2005). The germline and somatic activating *LHR* mutations *in vitro* elevate basal cyclic AMP but decrease the maximal cyclic AMP response to CG (Leschek *et al*. 2001).

Sporadic tumor arising from somatic mutation of LHR Most sporadic Leydig cell tumors have a somatically mutated *LHR*. Most adenomas show *LHRD578H*. The abnormalities of cyclic AMP regulation *in vitro* are more severe (higher basal cyclic AMP and absent response to CG) from D578H than from germline mutations; furthermore, D578H has not been identified in the germline and thus may be lethal in the very early embryo (Boot *et al*. 2011).

Hereditary ovarian hyperstimulation syndrome

Clinical When severe, hereditary ovarian hyperstimulation syndrome (OHSS) can be a life-threatening complex of ovarian enlargement and diffuse vascular permeability (ascites, pleural effusion, hemo-concentration, thromboembolism). It reflects oversecretion from the ovarian corpus luteum of pregnancy for several factors, including estrogens, progestins, and cytokines (Fiedler & Ezcurra 2012). Most frequently, OHSS occurs sporadically during the administration of exogenous FSH or CG for IVF; in this setting, FSH may have been given to compensate for a subtle deficiency of FSH. Rarely, during an unassisted pregnancy, OHSS occurs and can recur spontaneously in several pregnancies of the same woman, and it may arise in several women within a family (Smits *et al*. 2003, Vasseur *et al*. 2003). OHSS remits after delivery. The management is general support until and after delivery.

Corpus luteum of pregnancy in OHSS In OHSS, the ovaries are larger than in normal pregnancy and multicystic; there are layers of hyperplasia of luteinized granulosa and theca cells (Stocco *et al*. 2007, Meduri *et al*. 2008). The ovaries in OHSS return to normal size by 8 weeks after delivery (Smits *et al*. 2003).

Molecules and genes Most gain of function changes or mutations in the *FSHR* were in the transmembrane domains (Desai *et al*. 2013). *In vitro*, these mutations do not alter basal cyclic AMP; however, they broaden or shift the increase of cyclic AMP to lower concentrations of CG and sometimes also to TSH.

Sporadic tumor arising from somatic mutation of FSHR Mutation of the *FSHR* has not been reported in sporadic gonadal tumors.

Variant with autonomous spermatogenesis in males Normal spermatogenesis, despite undetectable FSH, was reported in two unrelated males with germline activating mutation of the *FSHR*. Undetectable FSH in one was attributed to prior surgery for a pituitary tumor and was from an unknown cause in the other (Gromoll *et al*. 1996, Casas-González *et al*. 2012). It is likely that FSH release was also inhibited by the oversecretion of inhibin or other factors from the testis.

Familial hyperaldosteronism type IIIA

Hyperaldosteronism type IIIA (HAIIIA) is HAIII with severe adrenocortical hyperplasia from germline mutations of *KCNJ5*, such as *G151R*, but notably excluding *G151E*. HAIIIB is HAIII with little or no adrenocortical hyperplasia, only from germline *KCNJ5G151E* (Scholl *et al*. 2012). Several mutations of *KCNJ5* cause 50% of sporadic aldosteronomas, but *G151E* has not caused sporadic aldosteronoma (Mulatero *et al*. 2013, Scholl & Lifton 2013).

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Clinical Familial HAIIIA is rare (Geller *et al*. 2008, Choi *et al*. 2011, Scholl *et al*. 2012, Mulatero *et al*. 2013, Scholl & Lifton 2013). It is generally recognized at ages 1–7 years as hypokalemia, mild hypertension, and very high aldosterone levels. Treatment with a blockade of the aldosterone receptors is unsuccessful, and subtotal adrenalectomy generally is followed by persistence or rapid recurrence. Total adrenalectomy is the preferred treatment.

Adrenal cortex in HAIIIA Normal secretion of aldosterone is stimulated by increases of extracellular K+ or by angiotensin II (Spat & Hunyady 2004, Bollag 2014, Romero *et al*. 2015). The renin/angiotensin system is not otherwise covered here. In HAIIIA, the adrenal cortex shows massive hyperplasia that is occasionally micronodular and mainly in the fasciculata, with atrophy in the glomerulosa (Geller *et al*. 2008, Scholl & Lifton 2013). This distribution contrasts to the glomerulosa predominant location of the normal secretion of aldosterone. The cause of this distribution of steroid synthesis is not known, but it might relate to a stronger KCNJ5 expression in the normal glomerulosa. The adrenal enlargement is age-dependent (Scholl *et al*. 2012); from extrapolation, the hyperplasia might have begun only after birth.

Molecules and genes There are more than 80 mammalian genes in the family of potassium channel subunits. Some of the inwardly rectifying K+ channels (thus 'Kir') also function as K+ sensors (Spat & Hunyady 2004, Hibino *et al*. 2010). They allow a small outflow or 'leak' of K+ from the cytoplasm to the exterior, while they restrict external Na+ from traversing inward through its K+-selective pore. Recent studies in aldosteronomas first identified Kir3.4 (encoded by the *KCNJ5* gene) as a major K+ channel subunit and a major regulator of aldosterone secretion (Choi *et al*. 2011). Kir3.4 is normally expressed in adrenal glomerulosa, nerve, and muscle (Kokunai *et al*. 2014).

Patients with HAIIIA have germline heterozygous missense mutation of *KCNJ5*. Most of its inactivating mutations in HAIII or in the sporadic aldosteronoma model to within the pore of the K+ selectivity filter (Scholl *et al*. 2012, Murthy *et al*. 2014). Most mutations are *G151R*, *T158A*, or *I157S*. A milder familial phenotype has also been recognized recently from three different mutations of *KCNJ5* that model outside of the K+ selectivity pore (Murthy *et al*. 2014). All of the evaluated germline and somatic *KCNJ5* mutations in HAIIIA, HAIIIB, or sporadic aldosteronoma cause a loss of function of Kir3.4 (Scholl & Lifton 2013). They cause a loss of K+ selectivity and thus an increased influx of Na+ through Kir3.4. Some mutations also cause a decreased surface expression of Kir3.4 (Cheng *et al*. 2014).

Another loss of function mutation, restricted to one sequence, *KCNJ5G151E*, causes HAIIIB, a different syndrome of hereditary primary hyperaldosteronism, with normal adrenocortical size and normal morphology (Mulatero *et al*. 2012, Scholl *et al*. 2012, Marx 2014).

Sporadic tumor arising from somatic mutation of KCNJ5 *KCNJ5* is mutated in 40% of sporadic aldosteronomas, more so in the aldosteronoma of women than men, and not in adrenocortical cancers (Scholl *et al*. 2012, Mulatero *et al*. 2013, Scholl & Lifton 2013). *KCNJ5* mutation also has been found selectively in the dominant nodule of sporadic multinodular adrenal glands (Dekkers *et al*. 2014). Although considered a loss of function mutations, the missense mutations of *KCNJ5* have been heterozygous in aldosteronomas, i.e., haploinsufficient or without inactivation of the normal allele (Choi *et al*. 2011).

Discussion

Broad themes among many syndromes

Broad theme: wide range of severity of a clinical feature within a syndrome I reviewed major features within five selected syndromes (Tables 1 and 2). Some of the themes were shared among the five and important, but they were also shared among many other syndromes. For example, overall clinical severity can cover a broad spectrum. The main determinant of severity of a syndrome is often the sequence of the germline mutation (Vassart 2010, Christensen *et al*. 2011, Hebrant *et al*. 2011, Murthy *et al*. 2014).

A less frequent determinant of severity is a change of gene dosage in the germline. In particular, a double dose of the mutated *CASR* causes severe expressions in the form of NSHPT, whereas a single dose of the same *CASR* mutation is expressed far more mildly as FHH (Pollak *et al*. 1993, 1994, Arnold & Marx 2013).

Broad theme: wide range of ages at onset Earlier age of onset and greater severity of expression often go together; the earliest onsets may even be lethal to the embryo. Embryonic lethality was speculated for certain mutations of the *TSHR* or of the *LHR*, mainly because those mutations had been found in sporadic tumors but not in a germline (Boot *et al*. 2011, Hebrant *et al*. 2011).

For some severely affected neonates with either CNT or NSHPT, the syndrome must have started in the fetus

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Table 1 Some clinical features of hereditary syndromes of primary hyperplasia with hormone excess (see also Table 2)

Syndrome	Normal serum stimulus of mutant sensor	Hormone oversecreted	Typical early age of onset of hormone excess	Selected comments about expressions
NSHPT	Low Ca++	PTH	In fetus	Severe defects at birth reflect onset by fetal oversecretion of PTH
CNT	TSH	T_4, T_3	In fetus	Severe defects at birth reflect onset by fetal oversecretion of iodo-thyronines
FMPP	LH	Testosterone	1–3 years	Not expressed in female carriers of the mutation
OHSS	CG	Estrogens, progestins, cytokines	Pregnant female	CG from the normal placenta stimulates the mutant FSH receptors in the corpus luteum of pregnancy
HAIIIA	K+	Aldosterone	1 year	Hyperplasia is in the adrenal fasciculata with atrophy in the adrenal glomerulosa

CNT, congenital neonatal thyrotoxicosis; NSHPT, neonatal severe primary hyperparathyroidism; HAIII, hyperaldosteronism type III; FMPP, familial male-limited precocious puberty; OHSS, ovarian hyperstimulation syndrome.

with gland hyperplasia and toxicity from an oversecreted hormone. Furthermore, some less severe forms of expression are also likely to have begun *in utero* with or without recognition of their prenatal onset *in utero* (Beas *et al*. 1962, Rosenthal *et al*. 1983, Müller *et al*. 1998). Still milder forms of expression show later onsets that are usually consistent within a family – during infancy, childhood, or adulthood. Lastly, some of the mildest carrier states have remained occult even during genetic evaluation in an adult (Nishihara *et al*. 2010). The latest onsets probably reflect the mildest forms of expression and the slowest gland enlargement over years.

An exception can be the requirement for late onset. In particular, either of the two syndromes of OHSS or gestational thyrotoxicosis can be expressed only in a female and only selectively during the unique window of her pregnancy.

Broad theme: wide time interval until postoperative recurrence Postoperative recurrence generally reflects dysfunction in residual tissues after surgery (Marx 2013). Each cell in the remnant secretory tissue carries the germline defect; furthermore, remnant cells might have already become overactive (such as predominantly monoclonal) before the time of surgery.

The average time interval until recurrence after subtotal surgery is another feature that might help characterize a syndrome. The interval until recurrence of hyperparathyroidism (severe) was 2 and 5 months in two cases of NSHPT (Thompson *et al*. 1978, Key *et al*. 1990) (see Supplement, see section on supplementary data given at the end of this article). This differs from the much longer interval of 12 years until recurrence (mild) for hyperparathyroidism in MEN1 (Rizzoli *et al*. 1985). And this also differs importantly from the even shorter average recurrence interval of 5 days (for mild hyperparathyroidism) after subtotal parathyroidectomy in FHH; the latter reflects immediate postoperative oversecretion independent of recurrent gland growth (Law & Heath 1985, Marx 2014).

The duration of the interval until postoperative recurrence was not documented in detail for the other four syndromes herein. It seems likely that hyperplasia

Table 2 Features of mutated tissue in hereditary syndromes of primary hyperplasia with hormone excess (see also Table 1)

Syndrome	Genes and germline mutations[a]	Mutated sensor molecule	Tissue over-functioning	Predominant hyperplasia	Progress to nodules or adenomas	
					Germline origin	Sporadic origin
NSHPT	*CASR*=	CaS-R	Parathyroid	Yes	Rare	No
CNT	*TSHR*+	TSH-R	Thyroid follicle	Yes	Yes	Yes
FMPP	*LHR*+	LH-R	Leydig cell of testis	Yes	Rare	Yes
OHSS	*FSHR*+	FSH-R	Corpus luteum of pregnancy	Yes	Yes	No
HAIIIA	*KCNJ5*−	Kir3.4	Adrenal cortex	Yes	Yes	Yes

CNT, congenital neonatal thyrotoxicosis; NSHPT, neonatal severe primary hyperparathyroidism; HAIII, hyperaldosteronism type III; FMPP, familial male-limited precocious puberty; OHSS, ovarian hyperstimulation syndrome; CaS-R, extracellular calcium sensing receptor; TSH-R, TSH receptor; LH-R, LH receptor; FSH-R, FSH receptor; Kir3.4 inward rectifying potassium channel subunit 3.4.
[a]Mutation types are −, heterozygous loss of function (inactivation); =, homozygous loss of function (inactivation); +, heterozygous gain of function (activation).

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from severe mutations expressed early (as in NSHPT or CNT) would recur more rapidly and that mild mutations would have a slower growth of the gland and would recur more slowly or, for some cases, not at all during prolonged follow-up (Nishihara *et al*. 2010).

Broad theme: wide relevance of the genes to neoplasia Any primary or secondary hyperplasia is typically regarded as a polyclonal process (Derwahl & Studer 2002, Arnold 2011, Mete & Asa 2013). However, monoclonal components may also be inherent parts within hyperplasia (Arnold *et al*. 1995, Diaz-Cano *et al*. 2001, Korpershoek *et al*. 2014, Hartmann *et al*. 2015).

Mutations can also contribute to sporadic cancers in diverse tissues, with any being a likely driver mutation in 0.1–5.0% of most or all common cancer types (O'Hayre *et al*. 2013, http://cancer.sanger.ac.uk/cosmic/, Forbes *et al*. 2014). For example, the large intestine from over 1000 cancers tested per gene shows mutations in the following frequencies: *CASR*, 4.5%; *TSHR*, 5.7%; *LHR*, 3.6%; *FSHR*, 2.6%; and *KCNJ5*, 1.9% (http://cancer.sanger.ac.uk/cosmic/, Forbes *et al*. 2014).

Distinguishing themes within five hyperplasia syndromes

Distinguishing theme: predominant hyperplasia as an endpoint of expression in a gland Hyperplasia results from an increased rate of cell birth and/or decreased rate of cell death in the gland. The quantitative disturbances of either process have not been analyzed herein, excepting indirectly as contributions by neoplasia-related processes (see below). I assume that, predominantly, hyperplasia herein is mainly from an increased rate of cell birth.

Beyond being an inclusion criterion herein, this histologic feature of predominant hyperplasia is a self-supporting status and a robust endpoint in a gland. It is not simply a small or brief step toward progression to adenoma or cancer.

Of course, hyperplasia in a hormone-secreting gland is not uncommon in pathology. Predominant hyperplasia is also a fundamental process in many examples of secondary excess. Furthermore, primary or secondary hyperplasia may progress to nodules, adenomas, and, occasionally, cancers (Arnold 2011, Qureshi *et al*. 2015).

Distinguishing theme: predominant hyperplasia as the cause of hormone oversecretion I focus on the process of hyperplasia and increased gland size, but hyperplasia also has a close relation or coupling with hormone oversecretion. The hyperplastic gland tissue must be the source of oversecreted hormones in these five syndromes because hyperplasia is the predominant and stable tissue type in the gland. Some other hereditary syndromes of primary hormone excess differ from these five insofar as either normal-appearing tissue, or small or large nodules, adenoma, or cancer can predominate in the gland and can be the main source of an oversecreted hormone (Supplementary Tables S-3 and S-4, see section on supplementary data given at the end of this article).

The five oversecreted hormones in these five hyperplasia syndromes represent three distinct categories of chemical: steroid, iodo-thyronine, and polypeptide. Their biosynthetic pathways are specific to their chemical structure and to the differentiated cell of secretion for each. Even the mechanisms of final 'secretion' or exit from the cell differ among the three (Spat & Hunyady 2004, Rizo & Sudhof 2012, Miot *et al*. 2013).

The partial contributions to total oversecretion of hormone may be divided among broad functions within the mutated and oversecreting cell. First, a high basal release rate may be attributable to the increased number of secreting cells. The enlarged gland may be oversecreting even despite a lower than normal secretion rate per cell (Assie *et al*. 2013). Among the five syndromes reviewed here, I estimate that the hyperplastic mass is typically increased over normal by three- to tenfold and is one major, if not the principal, determinant of the total amount of hormone secretion (Supplementary Table S-2, see section on supplementary data given at the end of this article).

Second, there may be an increased basal secretion rate per cell (Brown *et al*. 1987). This is supported by a high basal cyclic AMP level per cell *in vitro* with activating mutations of the TSH-R or the LH-R.

Third, some part of the oversecretion may be dependent on a mutant protein's responsitivity to its normal extracellular regulator (Pearce *et al*. 1996). However, among the syndromes here, most of the extracellular ligands of the mutated molecules are down-regulated in serum by the feedbacks in their syndrome (expressed as high Ca++, low TSH, low LH, low FSH, and low K+ respectively, except CG, which is not down-regulated).

Distinguishing theme: the causative mutated molecule is a sensor in the plasma membrane Four of five syndromes examined here are from the germline mutation of a gene (*CASR*, *TSHR*, *LHR*, *FSHR*) that encodes a G-protein-coupled receptor (GPCR) in the plasma membrane (Vassart & Costagliola 2011, Lefkowitz 2013) and mediates response to an extracellular ligand.

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The activating mutations of the GPCR subfamily of receptors for gonadotropins (TSR, LH, FSH) are modeled mainly within their seven transmembrane loops. The *CASR* mutations in NSHPT cause an activation of the CaS-R protein and model mainly to an extracellular domain of the CaS-R. The focus of germline mutations among these four GPCRs reflects that members of this largest of all gene families can sense highly diverse extracellular ligands, that they may transduce to diverse differentiated functions, and that their response may include hyperplasia (Katrich *et al*. 2013, Lefkowitz 2013).

KCNJ5 encodes Kir3.4, a membrane-bound protein that functions as a direct sensor for extracellular K+ (Spat & Hunyady 2004, Choi *et al*. 2011); its structure as a membrane channel is not related to the GPCRs (Hibino *et al*. 2010). Thus, each of the five mutated genes in these five syndromes encodes a plasma membrane protein that senses an extracellular regulator (O'Hayre *et al*. 2013, Vogelstein *et al*. 2013). This represents a remarkable clustering of functions in the mutated proteins. Its cause and its effects warrant further exploration.

Distinguishing theme: each of five mutated sensors regulates a downstream pathway This review included three mutation-directed pathways, immediately downstream of sensing for a serum factor (Fig. 1). These pathways can be grouped narrowly as transducing information from the plasma membrane to an adjacent intracellular messenger. They transduce from plasma membrane GPCR to cyclic AMP, from GPCR to inositol phosphates, or from plasma membrane K+ channel to cytoplasmic Ca++.

The CaS-R on the parathyroid cell transduces hypercalcemia through Gq and/or Ga11 to activate phospholipase C and thereby raise inositol phosphates and mobilize Ca++ from stores in the cytoplasm (Wettschureck *et al*. 2007, Brown 2013, Conigrave & Ward 2013, Nesbit *et al*. 2013*b*, Cocco *et al*. 2015, Hillenbrand *et al*. 2015). The lowering of extracellular Ca++ or loss of function mutations of the CaS-R as in NSHPT stimulates secretion and hyperplasia in the parathyroid cells.

Unlike the effect of rising Ca++ to inhibit the secretion of PTH, a rise of extracellular Ca++ acts through the CaS-R of thyroidal parafollicular C-cells to stimulate the secretion of calcitonin (Garrett *et al*. 1995, McGehee *et al*. 1997). It may not, however, cause hyperplasia of C-cells (Conte-Devolx *et al*. 2010). The C-cell may also respond to Ca++ in part through a plasma membrane Ca++ channel (Kantham *et al*. 2009). Overall, parathyroid cells and C-cells have contrasting hormone-secretory responses to serum calcium, with contrasts that are transduced at unknown steps.

The normal TSH-R transduces both secretion and growth in the thyrocyte mainly through Gsα and the rise of cyclic AMP (Vassart 2010, Kleinau *et al*. 2013). However, TSH-R transduction of secretion and hyperplasia has also been reported through Gq/G11 (Kero *et al*. 2007, New & Wong 2007). Similarly, the normal LH-R transduces a rise of serum LH mainly through Gs and cyclic AMP. D578H, the most severe activating human mutation of *LHR*, caused *in vitro* not only much higher basal cyclic AMP than other mutations but also much higher inositol phosphates, suggesting transduction also through a G-protein other than Gs (Boot *et al*. 2011). Lastly, the normal FSH-R transduces mainly through Gs and cyclic AMP. However, it also can transduce through different G-protein(s), causing rises of inositol phosphates and Ca++ in cytoplasm (Thomas *et al*. 2011). Normally, cyclic AMP has the potential to transduce to any of three major signaling pathways that start with one among the following molecules: protein kinase A, the guanine nucleotide exchange factor EPAC, and ion channels (Sassone-Corsi 2012).

Kir3.4 is one of four G-protein-coupled inward rectifying K+ channels; therefore, it is also termed GIRK4. It can bind directly to a cytoplasmic modulator, such as the beta-gamma portion of a heterotrimeric G-protein or regulator of G-protein signaling (RGS) (Wickman *et al*. 1994, Luscher & Slesinger 2010, Zhou *et al*. 2012, Velarde-Miranda *et al*. 2013, Bollag 2014). On the aldosterone cell, the rise of extracellular K+ or influx of Na+ depolarizes the plasma membrane. This opens a plasma membrane Ca++ channel as a major transduction step toward aldosterone secretion (Velarde-Miranda *et al*. 2013, Bollag 2014). Effectors downstream from the rises of cytoplasmic Ca++ in the aldosterone-secreting cell may include calmodulin and several calcium calmodulin-dependent kinases (Spat & Hunyady 2004, Bollag 2014).

The mechanisms for sharing predominating hyperplasia are not known and represent an important topic for future studies; for example, hyperplasia can have unique features in other diverse settings, such as the normal expansion of cartilage in the embryo or reversible development of the breast for lactation (Hassiotou & Geddes 2013, Kozhemyakina *et al*. 2015).

Distinguishing themes: features within the hyperplasia group vs two other groups with lower or higher histologic grade

Defining three groups of comparisons These five syndromes (the hyperplasia group) have important shared features that

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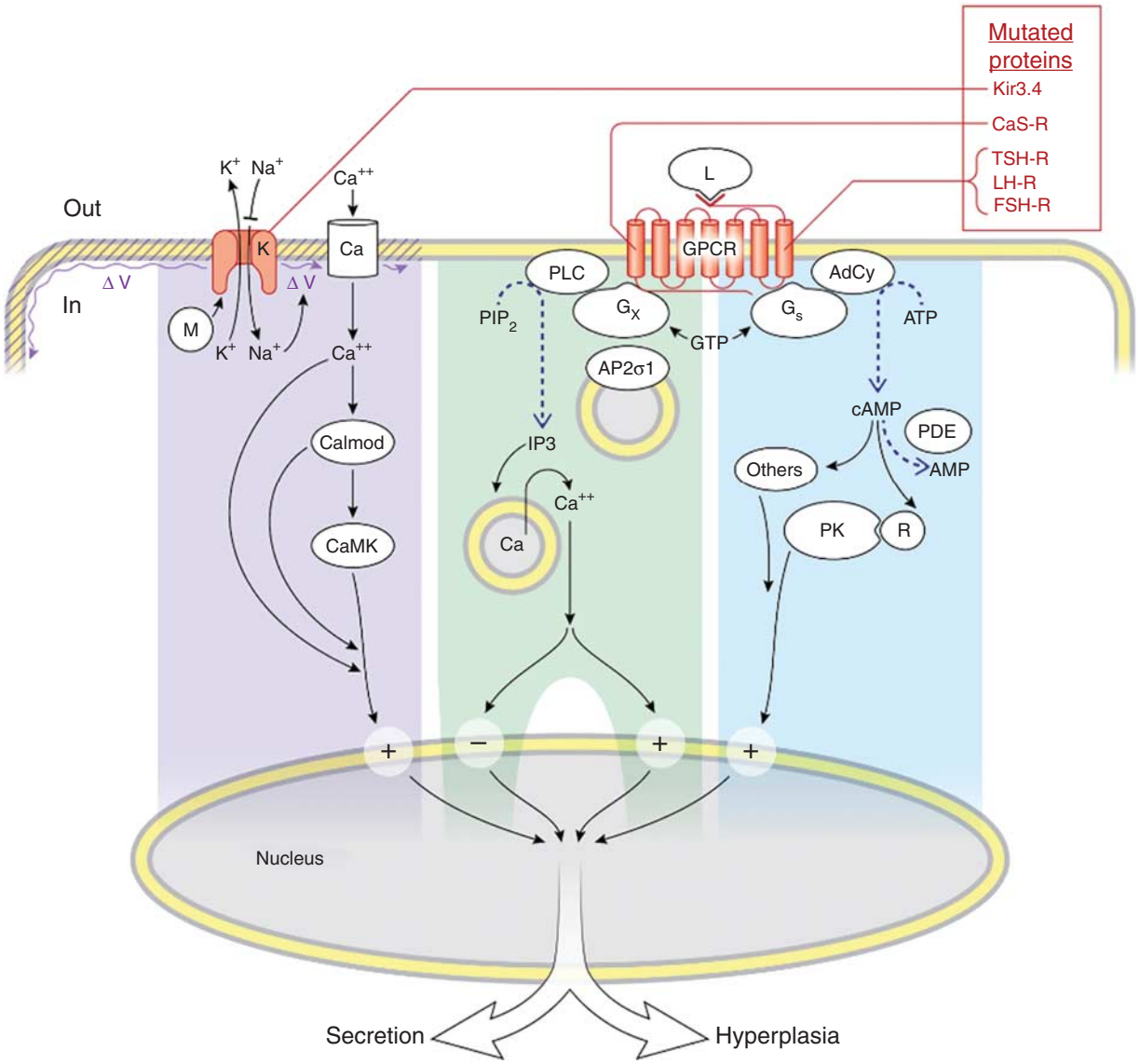

Figure 1

Overview of parts of the signaling pathways of the five mutated proteins in the five syndromes of this review. The mutated K+ channel (or Kir3.4) is shown with abnormally decreased ion selectivity of its mutation, so that fluxes of K+ and Na+ are in directions reversed from normal. Mutated proteins causing syndromes of this review are shown in red. Early downstream parts of each of three pathways are highlighted by a different background color. The pathway from Gx divides and includes a large plus or minus sign to illustrate that the CaS-R has opposite downstream effects in the parathyroid cell vs in the C-cell. By mostly unknown mechanisms, the four pathways likely converge downstream to regulate secretion and hyperplasia. (GPCR, G-protein coupled receptor; Calmod, Calmodulin; CaMK, calcium-calmodulin dependent protein kinase; K or Ca, ion channels; PLC, phospholipase C; AP2σ1, sigma subunit of AP2S1; Ad Cy, adenylyl cyclase; L, ligand; Gs, heterotrimeric stimulatory G-protein; Gx, heterotrimeric G-protein other than Gs; M, GTP-binding protein modulator of Kir3.4; PIP2, phosphatidyl inositol diphosphate; IP3, inositol triphosphate; PDE, phospho-diesterase; PK, protein kinase A catalytic subunit A; R, regulatory inhibitory subunit 1A of PKA; V, voltage of plasma membrane.

suggest both universal and distinguishing aspects in their pathophysiology. Insights about their distinguishing aspects can derive from comparison to different groups with hereditary primary excess of hormones (Supplementary Tables S-1 S-3, S-4, S-5, S-6, see section on supplementary data given at the end of this article). I compared hyperplasias to another group with primary and predominant oversecretion of hormones but little or no hyperplasia (abbreviated as the oversecretion group) (Marx 2014) (Supplementary Tables S-4 and S-6); an example is FHH. A second comparison group is dominated by adenomas or cancers (the neoplasia group) (Supplementary Tables S-1, S-3, S-5, S-6); an example is MEN1. The three groups form a continuum among three

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distinct histologic grades. Furthermore, the variables for comparison are organized for a yes or no entry, with the result that all comparisons are from simple integers.

Progression to neoplasia Hyperplasia sometimes (5 of 5 syndromes) progresses to nodules or other neoplastic features (Table 2) but oversecretion rarely does (1 of 6 syndromes; $P<0.02$; Supplementary Table S-6B, see section on supplementary data given at the end of this article). This supports the observations that many other primary hyperplastic tissues (whether or not they oversecrete a hormone) have an increased likelihood of progression to neoplastic stages (Gorgoulis *et al*. 2005, Barcellos-Hoff *et al*. 2013).

Expression as neoplasia in sporadic tissue Capability to cause sporadic neoplasia is expressed by some hyperplasias (3 of 5) (Supplementary Table S-7, see section on supplementary data given at the end of this article) and by some oversecretions (one of five; $P=0.52$). Neoplasia syndromes tend to do this more consistently than hyperplasias (15 of 16; *P* NS).

Expression as tumor multiplicity In the hyperplasia group, an underlying germline mutation is rarely expressed as a tumor in multiple tissues (0 of 5). In the neoplasia group, tumor multiplicity can be expressed by 13 of 19 syndromes (the two frequencies differ; $P<0.02$; Supplementary Table S-6C, see section on supplementary data given at the end of this article).

Focus of mutant functions is among plasma membrane sensors Another difference for the hyperplasia group is the focus of all mutant gene functions among plasma membrane sensors (5 of 5 functions) vs only 3 of 18 (*RET*, *GPR101*, *GCGN*) ($P<0.001$; Supplementary Table S-6E, see section on supplementary data given at the end of this article). The functions of most causative genes in the neoplasia group are not completely understood. It seems that functions of the mutated genes in the neoplasia group are mainly outside of the sensor-related cluster, and they probably contribute to hyperplasia and neoplasia through other pathways (Agarwal *et al*. 2009, Huang *et al*. 2012, Vogelstein *et al*. 2013, Dahia 2014, Mulligan 2014). Major clinical and molecular themes in the hyperplasia group help distinguish it from the two other comparison groups and have strengthened its robust identity.

The consistent sensor focus of the five mutant proteins on the background of this robust identity suggests that this abnormal biochemical focus on sensors is the cause of predominant hyperplasia. Because this mutated sensor might cause increase of cell numbers, there might be limits to the capacity of cell numbers to expand. Alternately, I speculate that one or more members of a down-regulating network is expressed as a counterbalance. The arrestins are but one well-identified down-regulating system for GPCRs, but others could be operational herein (Luttrell & Gesty-Palmer 2010).

This study reinforces the approach that GPCR sensor molecules can be targets for drug development (Lefkowitz 2013). Such approaches have already been successful, such as with small molecules interacting at the CaS-R (Conigrave & Ward 2013).

Supplementary data
This is linked to the online version of the paper at http://dx.doi.org/10.1530/ERC-15-0171.

Declaration of interest
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