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Next Generation Sequencing in Endocrine Practice

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Abstract

With the completion of the Human Genome Project and advances in genomic sequencing technologies, the use of clinical molecular diagnostics has grown tremendously over the last decade. Next-generation sequencing (NGS) has overcome many of the practical roadblocks that had slowed the adoption of molecular testing for routine clinical diagnosis. In endocrinology, targeted NGS now complements biochemical testing and imaging studies. The goal of this review is to provide clinicians with a guide to the application of NGS to genetic testing for endocrine conditions, by compiling a list of established gene mutations detectable by NGS, and highlighting key phenotypic features of these disorders. As we outline in this review, the clinical utility of NGS-based molecular testing for endocrine disorders is very high. Identifying an exact genetic etiology improves understanding of the disease, provides clear explanation to families about the cause, and guides decisions about screening, prevention and/or treatment.

Keywords

gene; mutation; hypophosphatasia; hormone; adrenal; vitamin D; PTH; thyroid; gonad; pituitary

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INTRODUCTION

The diagnostic approach to endocrine diseases has traditionally been based on a constellation of physical findings, biochemical testing, and imaging studies. With advances in genomics and sequencing technologies, the role of genetic diagnosis in endocrinology has taken on greater importance. The etiology of endocrinopathies is multifactorial and, when genetically determined, is frequently multigenic [1]. Yet, a significant number of endocrine disorders demonstrate Mendelian transmission, suggesting disease-causing mutations. Identification of a mutation can complement biochemical studies and provide diagnostic clues for early detection and treatment.

Historically, the use of molecular testing has been sparse, due to its expense and technical difficulty. As recently as ten years ago, DNA sequencing for medical diagnosis was unusual, performed only when there was a very strong clinical rationale to seek a genetic diagnosis. Tests were difficult to obtain, turn-around was slow, and results were often difficult to interpret; many tests were only available on a research basis. However, the transition from Sanger sequencing to high-throughput next-generation sequencing (NGS) technologies has dramatically decreased the costs and time involved in obtaining high quality DNA sequence data.

Much of this transformation derives from the fact that NGS methods allow clinicians to investigate candidate genes “in parallel” rather than “in series”. Due to its cost, Sanger sequencing typically involves a serial process of sequencing one candidate gene after another, starting with the highest probability genes and proceeding to lower-probability genes, in a process referred to as “a genetic odyssey”. The genetic odyssey can involve months of frustrating and expensive searching. In contrast, NGS - in which the cost of adding additional genes to a sequencing panel is minimal - permits all genes-of-interest to be sequenced simultaneously. The parallel nature of NGS therefore allows for the rapid query of multiple loci at once, including an analysis as broad as that of the entire exome or genome [2–4].

In clinical practice, then, a managing physician can quickly analyze all of the genes in a cellular pathway. It is worth noting that the benefits of this kind of parallel analysis offer more than an increase in speed and decrease in cost. Indeed, evidence is emerging that multiple “hits” (mutations) in the same pathway or in related pathways are important disease modifiers, even in disorders with classical Mendelian inheritance [5]. In other words, since a “genetic odyssey” using Sanger sequencing typically ends once a genetic “hit” is found, it risks returning an incomplete picture of diseases even when successful. The unbiased NGS-based approach, in contrast, suffers from no such ascertainment bias. NGS has been rapidly adopted in the molecular genetics community and is widely available for clinical testing. Due to the quickly decreasing cost, marked increase in availability, and significant clinical utility, molecular sequencing as a clinical diagnostic test is fast moving from the purview of academic medical geneticists into the realm of multispecialty clinical care.

Targeted NGS promises to revolutionize the diagnosis of endocrine conditions. However, the utilization of NGS is hampered by a number of factors, including uncertainty about the

selection of genes that could be tested for presence of mutations. Thus, the goal of this review is to provide clinicians with a guide to NGS-based genetic testing for endocrine conditions.

MATERIAL AND METHODS

Next-generation sequencing

Targeted NGS of *ALPL* gene was performed at the University of Minnesota Medical Center, Molecular Diagnostics Laboratory and the University of Minnesota Genomics Center. Genomic DNA was extracted from the blood sample. Sequencing libraries were prepared and sequence capture performed according to Illumina protocols utilizing the TruSight One Sequencing Panel, with one minor modification. DNA libraries from clinical samples were pooled for sequence capture in groups of 10 samples (9 clinical samples plus one control sample) rather than pools of 12 samples, as recommended in the standard Illumina protocol, in order to increase read depth per sample. The enriched DNA libraries were sequenced on an Illumina HiSeq 2500 instrument using paired-end 100-bp sequencing reads, generating ≥ 20M reads (4 Gb) per sample. Raw sequencing reads were mapped to the reference genome using Burrows-Wheeler Alignment [2]. Raw alignment files were realigned in the neighborhood of indels, and recalibrated for base quality accuracy using the Genome Analysis Tool Kit (GATK) [3, 4]. Point mutation and indel calls in exons and adjoining intronic regions were made using the GATK Unified Genotyper. Variants were interpreted according to guidance issued by the American College of Medical Genetics [6]. Known variants with a minor allele frequency >0.01 (1%) in the 1000 genomes dataset are considered unlikely to be the cause of rare Mendelian phenotypes. Coverage is excellent under our protocol, with >20x coverage at 100% of the loci in *ALPL*, yielding a sensitivity of >95% and a specificity of >99% for all subtypes of hypophosphatasia.

Methods of data acquisition

The list of endocrine disorders and selected syndromes with multiple endocrinopathies was limited to those that are due to mutations detectable by NGS that are included in the TruSight One Sequencing Panel. Disorders of bone and mineral metabolism were limited to vitamin D deficiency and resistance, parathyroid diseases, hypophosphatasia, and hypophosphatemic rickets due to elevated FGF23 levels. Gonadal disorders were limited to those that are caused by abnormal hormone synthesis or action (*CYP21A2* mutations were excluded due to presence of pseudogenes). Inclusion of an extensive and a rapidly growing number of disorders of sex development was deemed to be outside the scope of this review. Diseases caused by chromosomal abnormalities, disorders of glucose and insulin metabolism, obesity, and lipid disorders were excluded. Individual diseases were cross-referenced against Online Mendelian Inheritance in Man (OMIM) database (http://omim.org) to provide gene and disease identifiers. Tables were constructed and most salient clinical phenotypes were listed as a guide to clinical presentation.

APPROACH TO DISEASE PROCESS AND CLINICAL IMPLICATIONS OF GENETIC TESTING

Disorders of bone and mineral metabolism

Patients with parathyroid or vitamin D disorders may come to medical attention because of either acute symptoms such as hypocalcemic seizures or more chronic manifestations of hypo- or hypercalcemia, including paresthesias, renal calculi, weakness, anorexia, polydipsia or polyuria. Phenotypically, skeletal deformities (genu varum, epiphyseal widening) may point to the diagnosis of rickets. Characteristic facial appearance (micrognathia, short palpebral fissures, prominent nose with relatively deficient alae, smooth philtrum, small ears), and presence of congenital heart defects may trigger an evaluation for DiGeorge syndrome. Short stature, obesity, and short forth metacarpals in a patient with an elevated parathyroid hormone (PTH) level and low calcium level raises a possibility of pseudohypoparathyroidism. Confirmatory biochemical testing includes measurement of calcium, phosphorus, PTH, vitamin D, alkaline phosphatase and other related blood, urine, and imaging studies.

While biochemical testing and imaging studies help categorize the disorder into broader diagnostic groups, mutational analysis serves not only as a confirmatory diagnostic study, but also brings in a greater level of diagnostic precision (Table 1). For example, because of its implications for other endocrine systems, it is important to confirm a diagnostic suspicion of Albright hereditary osteodystrophy by testing for mutations in *GNAS* gene [7]. Because this disorder is due to post-zygotic somatic mutations, the ability of NGS sequencing to detect mosaicism (which is not detected by traditional Sanger sequencing) improves the sensitivity of molecular testing at this locus [8]. Knowing that the mutation is present will prompt the health care provider to test for other associated endocrinopathies, resulting from resistance to TSH, gonadotropins, GHRH, or antidiuretic hormone. Identification of a loss-of-function mutation in *VDR* provides a genetic basis for the elevated level of 1,25-dihydroxyvitamin D level [9], ruling out an increased production of 1,25-dihydroxyvitamin D by monocytic cells in non-endocrine granulomatous or neoplastic conditions. Identification of *CDC73* mutation allows early diagnosis of other family members and prompt intervention to prevent long-term consequences, such as renal calculi. In the case of the hyperparathyroidism-jaw tumor syndrome, confirmation of *CDC73* may alleviate the anxiety that the jaw tumor is of neoplastic nature, and guide further therapy [10]. Identification of mutations in patients with frequent fractures, particularly infants, that indicate osteogenesis imperfecta or other underlying bone diseases (e.g. hypophosphatasia, disorders of vitamin D metabolism) have important medical and legal implications, for example in cases of suspected child abuse [11].

NGS not only serves as a confirmatory test for the known mutations, but may also identify new mutations, or improve our understanding of the clinical implications of the known pathogenic mutations. For example, hypophosphatasia (HPP) is a rare inherited disorder characterized by low level of tissue-nonspecific alkaline phosphatase (ALP) due to loss-of-function mutations in the *ALPL* gene. The disease has a wide spectrum of clinical presentation, including (from the most to the least severe) the perinatal (usually lethal),

infantile, childhood and adult forms. p.His381Arg mutation (previously referred to as p.H364R) has been reported in conjunction with a second missense *ALPL* mutation in one case of a lethal autosomal recessive hypophosphatasia [12]. The case below illustrates that it can also be associated with a mild, childhood form of HPP.

A case of hypophosphatasia—The patient is a 3.9 years old boy who presented with premature loss of primary teeth starting at 2.5 years of age. His growth has been normal (height and growth velocity at the 49th percentile). He began walking at 14 months. He has had no history of fractures, gait abnormalities, bone pain, or poor muscle tone. He had low ALP level (59 U/L, normal range 110–320), elevated urine phosphoethanolamine (350 nanomoles/mg creatinine, normal range 18–150), markedly elevated vitamin B6 (641 nmol/L, normal range 20–125), normal calcium, phosphorus, and 25-hydroxyvitamin D levels, mildly elevated 1,25-dihydroxyvitamin D level (80 pg/mL, normal range 15–75), low iPTH level (4 pg/mL, normal range 12–72), and no evidence of rickets on a hand radiograph. NGS identified a heterozygous missense mutation c.1142A>G (p.His381Arg) in *ALPL*, indicating that this mutation can occur not only in a lethal autosomal recessive HPP, but also a mild, presumably autosomal dominant, form due to haploinsufficiency. His mother also has a low ALP level (29 U/L, normal range 40–150), but has no history of fractures, bone pain, or premature loss of teeth. His father has a normal ALP level. Maternal great-grandmother had rickets in her youth. Paternal grandmother started wearing dentures between the age of 40 and 50 years. Molecular analysis of *ALPL* in other family members has not been performed.

Adrenal disorders

Endocrine diseases of the adrenal gland occur as a result of hyper- or hypofunction of one or more layers of the adrenal cortex. Congenital defects may be suspected prenatally or at birth on the basis of physical findings (virilization of XX female infants), as a result of newborn screening (congenital adrenal hyperplasia) or symptomatic electrolyte abnormalities (hypoglycemia, hyponatremic seizures). In other cases they may present later in childhood as symptoms manifest over time (precocious pubertal changes, cushingoid features), or are unmasked by other illnesses or events (adrenal crises). The evaluation that follows differs depending on what hormonal derangement is first detected and whether it is deficient or in excess, but in each case the clinician must differentiate primary adrenal disease from other disorders affecting adrenal pathways (e.g. pituitary/hypothalamic dysregulation in central hypocortisolism, downstream receptor defects in pseudohypoaldosteronism, etc.). Once this is established, a more extensive investigation for associated comorbidities often ensues. In some circumstances it may be difficult to differentiate organic disease from transient, functional hormonal derangements, or iatrogenic causes as a result of prolonged glucocorticoid treatment, leading to repeated ACTH stimulation testing and imaging studies.

The ability to obtain targeted genetic information early in the diagnostic process provides valuable information with implications for diagnosis and treatment (Table 2). For example, detection of a mutation in *POMC* [13] or *TBX19* [14] would obviate the need for ongoing monitoring of other pituitary functions. In other cases, molecular diagnosis can confirm a diagnosis that requires intensive monitoring (autoimmune polyendocrinopathy syndrome) or

allow early detection not possible using biochemical testing alone. For example, X-linked adrenoleukodystrophy (a peroxisomal disorder affecting the adrenal cortex, the central nervous system, and the testes) is confirmed biochemically by finding elevated very long-chain fatty acids [15]. However, heterozygous females may have normal levels of very long-chain fatty acids and only detection of a mutation in *ABCD1* gene [16] can reliably establish heterozygosity, which has significant implications for the offspring of a carrier and siblings of the proband. Early diagnosis of ALD prompts evaluation of adrenal function pre-symptomatically and can prevent adrenal crisis. Early intervention with hematopoietic cell transplantation to halt cerebral manifestations can improve neurological outcome and survival [17]. NGS may also be used to refine a diagnosis and allow selection of a precise treatment course (e.g. subtypes of congenital adrenal hyperplasia). In addition, the ability to perform genetic testing based on a panel of genes associated with a particular hormonal abnormality can also help to identify and thereby guide the management of rare disorders that might otherwise be difficult to recognize.

Gonadal disorders

Abnormal sex hormone synthesis or action may be suspected in infancy or even prenatally on the basis of abnormal or ambiguous genitalia, or a mismatch between sex phenotype and karyotype obtained for other reasons. In other cases, diagnosis may be delayed until much later when puberty does not progress normally, or even later when premature menopause or fertility problems arise. In general, diagnosis is challenging as there is a great deal of phenotypic overlap between different gonadal disorders. Traditionally, the first step is a karyotype for genetic sex determination followed by a combination of imaging and hormonal studies. Even after all of these steps, many of these disorders are simply categorized in a descriptive fashion that, although useful for treatment, may leave families and practitioners with uncertainty about future sexual development, gender identity, fertility and the possible emergence of associated comorbidities.

Genotypic characterization of patients with gonadal disorders is valuable, providing key information about prognosis and the need for screening for associated comorbidities, and guiding the nature or timing of therapeutic interventions (Table 3). For example, subjects with mutations in *WT1* would require ongoing assessment of kidney function, and, depending on the specific mutation, may need to be screened for Wilms tumor [18]. In other cases, genotypic characterization may provide key information about the anticipated impact of puberty (e.g. likelihood of virilization at puberty with *HSD17B3* [19] mutations that may influence choice of gender-rearing or whether to remove or relocate ectopic gonads.

Pituitary and hypothalamic diseases

The clinical phenotype for patients with combined pituitary hormone deficiencies tends to include characteristic facial features with prominent foreheads, midface hypoplasia, depressed nasal bridges, and short noses with anteverted nostrils. The presence of these features would prompt a workup for pituitary hormone deficiencies and, based on the identified hormone anomalies, lead to confirmatory sequencing for the suspected gene such as *PIT1* (*POU1F1*) [20] (Table 4).

NGS can be used in patients with pituitary anomalies to characterize them by genotype as well as phenotype. Such characterization allows for prediction of future anomalies based on the understanding of the molecular basis of embryonic pituitary development and the key genes that affect the cellular differentiation of pituitary cells [20]. Genes such as *HESX1*, *LHX3*, and *LHX4* affect immature pituitary progenitor cells and therefore would be expected to impact all 5 mature pituitary cell types and their resultant hormones. By contrast, *PIT1* (*POU1F1*) controls somatotrope, thyrotrope and lactotrope differentiation but not gonadotrope or corticotrope development. Thus, patients with identified *PIT1* (*POU1F1*) mutations require screening for development of new GH and TSH anomalies but not LH, FSH or ACTH/cortisol anomalies.

Thyroid disorders

The etiology for most cases of congenital hypothyroidism stems from either primary defects in thyroid hormone synthesis and/or secretion, and secondary abnormalities of the hypothalamic-pituitary-thyroidal axis that result in reduced thyrotrope activity. The advent of newborn screening programs to detect congenital hypothyroidism has drastically reduced unrecognized and untreated cases. The benefits of early treatment in such infants are well documented and are a glowing example of the utility and cost effective nature of screening programs. However, the underlying etiology for hypothyroidism is often left undetermined. Moreover, “milder” cases of hypothyroidism are increasingly recognized where modest TSH elevation may or may not have a genetic basis or be clinically relevant, leaving a clinician with uncertainty whether treatment is indicated. Utilizing NGS to screen this population would create a stronger rationale for treatment or observation, and would further reveal potential mutations in known thyroid associated genes (Table 5).

In addition, several congenital thyroid disorders are associated with other endocrinopathies that require screening and treatment. For example, mutations in *GLIS3* result in central hypothyroidism but can also result in neonatal diabetes, congenital glaucoma, and deafness [21, 22]. Through the use of NGS, an infant with evidence for central hypothyroidism could be accurately and rapidly tested and any associated medical problems identified. Moreover, identification of mutations can also have direct impact on preventive and therapeutic decisions. For example, confirmation of *RET* mutation helps determine the timing of prophylactic early thyroidectomy [23] in addition to increasing awareness of associated disorders that patients have to be tested for as discussed earlier. Thus, in thyroid disease, NGS can provide valuable clinical data for diagnostic, prognostic, and family genetic counseling purposes.

Selected syndromes with multiple endocrinopathies

Many well-known syndromes involve multiple endocrinopathies as part of their characteristic phenotype. Often these features evolve at different times and in non-classical ways, making clinical diagnosis of even well-known syndromes challenging. For many syndromic conditions, earlier genotypic identification holds prognostic and management benefits. For conditions such as IPEX and CHARGE syndrome (Table 6), genetic identification aids in establishing a schedule for endocrine screening. For the multiple

endocrine neoplasias, genotypic identification allows for periodic monitoring for known neoplastic conditions as well as screening and counseling for relatives of the proband.

DISCUSSION

As a science, molecular genetics is only 62 years old, dating back to the description of the structure of DNA by Watson, Crick and Franklin in 1953 [24]; the number of chromosomes in a human cell was not determined until 1956 [25]. The study of DNA for diagnosis began with the discovery by Dr. Jerome Lejune in 1959 that Down syndrome was caused by an extra copy of chromosome 21 [25]. In the half-century since, clinical molecular diagnostics have “exploded.” The Human Genome Project took 13 years and was completed in 2003 [26]. In 2015, clinical laboratories are able to return the same amount of data in a matter of a few months. The technology that changed a 13-year international multisite collaborative endeavor into a simple blood test that any licensed provider can order is NGS. At the turn of the 21st century, a two-gene cancer risk Sanger sequencing based test cost about $2,500 (personal communication). Now, a complete exome study covering about 22,000 genes at a typical commercial laboratory is quoted at around $5,000 [27]. Clearly, NGS has overcome the practical obstacles to the clinical use of routine molecular testing.

NGS increases the diagnostic precision of endocrine and other disorders, which is of importance not only to the health care providers, but also to the families seeking answers and definitive diagnosis, particularly when more than one family member is affected. Knowing the exact genetic etiology improves understanding of the disease, provides clear explanation to the families about the cause, and guides the decision about screening, prevention and/or treatment of the patient and the family. NGS also generates new information, enhancing genotype-phenotype correlations and aiding in the development of genotype-oriented screening guidelines as larger established genotype cohorts are identified with increased clinical use of this technology. Registry programs with subsequent genotype-phenotype correlations could be established to better understand the relevance and genetic nature of endocrinopathies.

Although interest continues to increase in the clinical use of whole-exome sequencing or even whole-genome sequencing, routine use of this technology is not recommended [28]. Systematic targeted NGS testing of well-crafted panels avoids the major ethical and logistical pitfalls associated with incidentally discovered findings in genes unrelated to the patient’s presenting problem [29]. Furthermore, targeted NGS panels often have demonstrably better sensitivity for mutations than whole exome protocols [30].

Propagation of NGS technologies has led to greater integration of genetic counseling into endocrine practice. Genetic counselors assist with education about inheritance, benefits and limitations to testing, interpretation of risk and results, as well as identification of resources and research opportunities [31]. Genetic counselors have traditionally worked in a diverse set of specialty clinics that have counseled individuals with endocrinopathies, including pediatric (e.g. congenital adrenal hyperplasia), infertility (e.g. premature ovarian failure), and oncology (e.g. multiple endocrine neoplasias) clinics. Skills from these traditional roles are highly transferrable to an unlimited number of specialties including endocrinology.

Major issues addressed by genetic counseling for endocrinopathies include adequate informed consent and pre-test counseling, identification of at risk family members, increased identification and cascade testing for individuals at risk, increased accuracy of result interpretation, and better facilitation of the testing process and disclosure of results [32]. As costs of genetic testing decrease and genetic information evolves, genetic counselors may play an even larger role in interpreting variants, testing modifier genes, and discussing secondary findings to genetic testing.

It is important to acknowledge, however, that the current generation of high-output NGS instruments - which rely on so-called “short-read” NGS sequencing - has limitations. Most importantly, short-read sequencing has not been as successfully applied to the detection of moderate (hundreds of nucleotides) to large (gene-length or larger) insertions and deletions. Although such mutations can be detected and scored as novel breakpoints and/or copy number variations by short-read NGS, analytical methods for doing so are not as advanced as methods for detecting simple nucleotide variants (SNVs) such as point mutations and smaller indels. In particular, NGS has trouble detecting large structural variations and fails almost completely to detect variation in polymorphic repetitive sequences such as CAG repeats, intronic dinucleotide repeats, intronic polyT/polyA sequences, or triplet repeat type mutations (for example, the type of mutation that causes Fragile X syndrome) [33]. These pitfalls of short-read NGS instruments, however, are being overcome by what are sometimes referred to as “third-generation” sequencing technologies, in which reads as long as 10–30 kb are possible [34]. The combination of short-read NGS instruments with third-gen long-read sequencers is likely to fill the current “hole” in sequencing methodology. Also, when targeted sequence-capture is the primary mode of library preparation, NGS is limited to those sequences that have been captured, which is typically the coding exons and immediately adjoining intronic sequences of the analyzed genes. Sequences that reside more than 25 base pairs from a coding exon are typically not enriched and sequenced, hence mutations in these regions may not be detected by this analysis. In the case of hypophosphatasia described above, for example, we cannot exclude a possibility that a second mutation in *ALPL* is present, but is not detectable by this method, consistent with an autosomal recessive inheritance pattern. Nevertheless, heterozygosity for p.His381Arg mutation appears to be the cause of low ALP in this patient.

Future of next generation sequencing

Medicine is on the brink of entirely revising our diagnostic methodology. In the past, molecular testing was done by highly specialized medical geneticists only at the very end of a diagnostic work up in rare individuals with multiple congenital anomalies and a high clinical suspicion for a genetic “syndrome.” It is certainly possible that NGS will invert the diagnostic process, with DNA sequencing performed at the beginning of a diagnostic evaluation as an exploratory step, rather than last, as a confirmatory step. The increased availability of DNA sequence data is leading to a rapid democratization of genetics. Subspecialists outside of medical genetics already commonly order molecular testing and this will only increase. As is outlined in this paper, the direct clinical utility of molecular testing is enormous for patients with endocrine disorders. The time is now for endocrinologists to begin to utilize this technology regularly in their practice.

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References

1. Amendola E, De Luca P, Macchia PE, Terracciano D, Rosica A, Chiappetta G, Kimura S, Mansouri A, Affuso A, Arra C, Macchia V, Di Lauro R, De Felice M. A mouse model demonstrates a multigenic origin of congenital hypothyroidism. Endocrinology. 2005; 146:5038–5047. [PubMed: 16150900]
2. Li H, Durbin R. Fast and accurate short read alignment with Burrows-Wheeler transform. Bioinformatics. 2009; 25:1754–1760. [PubMed: 19451168]
3. McKenna A, Hanna M, Banks E, Sivachenko A, Cibulskis K, Kernytsky A, Garimella K, Altshuler D, Gabriel S, Daly M, DePristo MA. The Genome Analysis Toolkit: a MapReduce framework for analyzing next-generation DNA sequencing data. Genome research. 2010; 20:1297–1303. [PubMed: 20644199]
4. DePristo MA, Banks E, Poplin R, Garimella KV, Maguire JR, Hartl C, Philippakis AA, del Angel G, Rivas MA, Hanna M, McKenna A, Fennell TJ, Kernytsky AM, Sivachenko AY, Cibulskis K, Gabriel SB, Altshuler D, Daly MJ. A framework for variation discovery and genotyping using next-generation DNA sequencing data. Nature genetics. 2011; 43:491–498. [PubMed: 21478889]
5. Petrucci S, Consoli F, Valente EM. Parkinson Disease Genetics: A “Continuum” From Mendelian to Multifactorial Inheritance. Current molecular medicine. 2014
6. Richards CS, Bale S, Bellissimo DB, Das S, Grody WW, Hegde MR, Lyon E, Ward BE, A.L.Q.A.C. Molecular Subcommittee of the, ACMG recommendations for standards for interpretation and reporting of sequence variations: Revisions 2007. Genetics in medicine: official journal of the American College of Medical Genetics. 2008; 10:294–300. [PubMed: 18414213]
7. Ahrens W, Hiort O, Staedt P, Kirschner T, Marschke C, Kruse K. Analysis of the GNAS1 gene in Albright’s hereditary osteodystrophy. The Journal of clinical endocrinology and metabolism. 2001; 86:4630–4634. [PubMed: 11600516]
8. Yamaguchi K, Komura M, Yamaguchi R, Imoto S, Shimizu E, Kasuya S, Shibuya T, Hatakeyama S, Takahashi N, Ikenoue T, Hata K, Tsurita G, Shinozaki M, Suzuki Y, Sugano S, Miyano S, Furukawa Y. Detection of APC mosaicism by next-generation sequencing in an FAP patient. Journal of human genetics. 2015
9. Kudoh T, Kumagai T, Uetsuji N, Tsugawa S, Oyanagi K, Chiba Y, Minami R, Nakao T. Vitamin D dependent rickets: decreased sensitivity to 1,25-dihydroxyvitamin. D European journal of pediatrics. 1981; 137:307–311. [PubMed: 7318845]
10. 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, Hoog A, Heath H 3rd, James-Newton LA, Robinson B, Zarbo RJ, Cavaco BM, Wassif W, Perrier ND, Rosen IB, Kristoffersson U, Turnpenny PD, Farnebo LO, Besser GM, Jackson CE, Morreau H, Trent JM, Thakker RV, Marx SJ, Teh BT, Larsson C, Hobbs MR. HRPT2, encoding parafibromin, is mutated in hyperparathyroidism-jaw tumor syndrome. Nature genetics. 2002; 32:676–680. [PubMed: 12434154]
11. Marlowe A, Pepin MG, Byers PH. Testing for osteogenesis imperfecta in cases of suspected non-accidental injury. Journal of medical genetics. 2002; 39:382–386. [PubMed: 12070242]
12. Taillandier A, Cozien E, Muller F, Merrien Y, Bonnin E, Fribourg C, Simon-Bouy B, Serre JL, Bieth E, Brenner R, Cordier MP, De Bie S, Fellmann F, Freisinger P, Hesse V, Hennekam RC, Josifova D, Kerzin-Storrar L, Leporrier N, Zabot MT, Mornet E. Fifteen new mutations (−195C>T, L-12X, 298-2A>G, T117N, A159T, R229S, 997+2T>A, E274X, A331T, H364R, D389G, 1256delC, R433H, N461I, C472S) in the tissue-nonspecific alkaline phosphatase (TNSALP) gene in patients with hypophosphatasia. Human mutation. 2000; 15:293. [PubMed: 10679946]

13. Krude H, Biebermann H, Luck W, Horn R, Brabant G, Gruters A. Severe early-onset obesity, adrenal insufficiency and red hair pigmentation caused by POMC mutations in humans. Nature genetics. 1998; 19:155–157. [PubMed: 9620771]
14. Lamolet B, Pulichino AM, Lamonerie T, Gauthier Y, Brue T, Enjalbert A, Drouin J. A pituitary cell-restricted T box factor, Tpit, activates POMC transcription in cooperation with Pitx homeoproteins. Cell. 2001; 104:849–859. [PubMed: 11290323]
15. Kemp S, Berger J, Aubourg P. X-linked adrenoleukodystrophy: clinical, metabolic, genetic and pathophysiological aspects. Biochimica et biophysica acta. 2012; 1822:1465–1474. [PubMed: 22483867]
16. Mosser J, Douar AM, Sarde CO, Kioschis P, Feil R, Moser H, Poustka AM, Mandel JL, Aubourg P. Putative X-linked adrenoleukodystrophy gene shares unexpected homology with ABC transporters. Nature. 1993; 361:726–730. [PubMed: 8441467]
17. Polgreen LE, Chahla S, Miller W, Rothman S, Tolar J, Kivisto T, Nascene D, Orchard PJ, Petryk A. Early diagnosis of cerebral X-linked adrenoleukodystrophy in boys with Addison's disease improves survival and neurological outcomes. European journal of pediatrics. 2011; 170:1049–1054. [PubMed: 21279382]
18. Pritchard-Jones K, Fleming S, Davidson D, Bickmore W, Porteous D, Gosden C, Bard J, Buckler A, Pelletier J, Housman D, et al. The candidate Wilms' tumour gene is involved in genitourinary development. Nature. 1990; 346:194–197. [PubMed: 2164159]
19. Andersson S, Geissler WM, Wu L, Davis DL, Grumbach MM, New MI, Schwarz HP, Blethen SL, Mendonca BB, Bloise W, Witchel SF, Cutler GB Jr, Griffin JE, Wilson JD, Russel DW. Molecular genetics and pathophysiology of 17 beta-hydroxysteroid dehydrogenase 3 deficiency. The Journal of clinical endocrinology and metabolism. 1996; 81:130–136. [PubMed: 8550739]
20. Prince KL, Walvoord EC, Rhodes SJ. The role of homeodomain transcription factors in heritable pituitary disease. Nature reviews Endocrinology. 2011; 7:727–737.
21. Senee V, Chelala C, Duchatelet S, Feng D, Blanc H, Cossec JC, Charon C, Nicolino M, Boileau P, Cavener DR, Bougneres P, Taha D, Julier C. Mutations in GLIS3 are responsible for a rare syndrome with neonatal diabetes mellitus and congenital hypothyroidism. Nature genetics. 2006; 38:682–687. [PubMed: 16715098]
22. Taha D, Barbar M, Kanaan H, Williamson Balfe J. Neonatal diabetes mellitus, congenital hypothyroidism, hepatic fibrosis, polycystic kidneys, and congenital glaucoma: a new autosomal recessive syndrome? American journal of medical genetics Part A. 2003; 122A:269–273. [PubMed: 12966531]
23. 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, G. European Multiple Endocrine Neoplasia Study. Early malignant progression of hereditary medullary thyroid cancer. The New England journal of medicine. 2003; 349:1517–1525. [PubMed: 14561794]
24. Watson JD, Crick FH. Molecular structure of nucleic acids; a structure for deoxyribose nucleic acid. Nature. 1953; 171:737–738. [PubMed: 13054692]
25. Megarbane A, Ravel A, Mircher C, Sturtz F, Grattau Y, Rethore MO, Delabar JM, Mobley WC. The 50th anniversary of the discovery of trisomy 21: the past, present, and future of research and treatment of Down syndrome. Genetics in medicine: official journal of the American College of Medical Genetics. 2009; 11:611–616. [PubMed: 19636252]
26. Austin CP. The impact of the completed human genome sequence on the development of novel therapeutics for human disease. Annual review of medicine. 2004; 55:1–13.
27. Jiang T, Tan MS, Tan L, Yu JT. Application of next-generation sequencing technologies in Neurology. Annals of translational medicine. 2014; 2:125. [PubMed: 25568878]
28. Dorschner MO, Amendola LM, Turner EH, Robertson PD, Shirts BH, Gallego CJ, Bennett RL, Jones KL, Tokita MJ, Bennett JT, Kim JH, Rosenthal EA, Kim DS, L. National Heart, P. Blood Institute Grand Opportunity Exome Sequencing. Tabor HK, Bamshad MJ, Motulsky AG, Scott CR, Pritchard CC, Walsh T, Burke W, Raskind WH, Byers P, Hisama FM, Nickerson DA, Jarvik GP. Actionable, pathogenic incidental findings in 1,000 participants' exomes. American journal of human genetics. 2013; 93:631–640. [PubMed: 24055113]

29. Amendola LM, Dorschner MO, Robertson PD, Salama JS, Hart R, Shirts BH, Murray ML, Tokita MJ, Gallego CJ, Kim DS, Bennett JT, Crosslin DR, Ranchalis J, Jones KL, Rosenthal EA, Jarvik ER, Itsara A, Turner EH, Herman DS, Schleit J, Burt A, Jamal SM, Abrudan JL, Johnson AD, Conlin LK, Dulik MC, Santani A, Metterville DR, Kelly M, Foreman AK, Lee K, Taylor KD, Guo X, Crooks K, Kiedrowski LA, Raffel LJ, Gordon O, Machini K, Desnick RJ, Biesecker LG, Lubitz SA, Mulchandani S, Cooper GM, Joffe S, Richards CS, Yang Y, Rotter JI, Rich SS, O'Donnell CJ, Berg JS, Spinner NB, Evans JP, Fullerton SM, Leppig KA, Bennett RL, Bird T, Sybert VP, Grady WM, Tabor HK, Kim JH, Bamshad MJ, Wilfond B, Motulsky AG, Scott CR, Pritchard CC, Walsh TD, Burke W, Raskind WH, Byers P, Hisama FM, Rehm H, Nickerson DA, Jarvik GP. Actionable exomic incidental findings in 6503 participants: challenges of variant classification. Genome research. 2015

30. Consugar MB, Navarro-Gomez D, Place EM, Bujakowska KM, Sousa ME, Fonseca-Kelly ZD, Taub DG, Janessian M, Wang DY, Au ED, Sims KB, Sweetser DA, Fulton AB, Liu Q, Wiggs JL, Gai X, Pierce EA. Panel-based genetic diagnostic testing for inherited eye diseases is highly accurate and reproducible, and more sensitive for variant detection, than exome sequencing. Genetics in medicine: official journal of the American College of Medical Genetics. 2014

31. Resta R, Biesecker BB, Bennett RL, Blum S, Hahn SE, Strecker MN, Williams JL. A new definition of Genetic Counseling: National Society of Genetic Counselors' Task Force report. Journal of genetic counseling. 2006; 15:77–83. [PubMed: 16761103]

32. Matloff ET, Barnett RE. The growing role for genetic counseling in endocrinology. Current opinion in oncology. 2011; 23:28–33. [PubMed: 20842029]

33. Biesecker LG, Shianna KV, Mullikin JC. Exome sequencing: the expert view. Genome biology. 2011; 12:128. [PubMed: 21920051]

34. English AC, Salerno WJ, Hampton OA, Gonzaga-Jauregui C, Ambreth S, Ritter DI, Beck CR, Davis CF, Dahdouli M, Ma S, Carroll A, Veeraraghavan N, Bruestle J, Drees B, Hastie A, Lam ET, White S, Mishra P, Wang M, Han Y, Zhang F, Stankiewicz P, Wheeler DA, Reid JG, Muzny DM, Rogers J, Sabo A, Worley KC, Lupski JR, Boerwinkle E, Gibbs RA. Assessing structural variation in a personal genome-towards a human reference diploid genome. BMC genomics. 2015; 16:286. [PubMed: 25886820]

Table 1

DISORDERS OF BONE AND MINERAL METABOLISM

Disease	Gene	H	OMIM	Phenotype
DiGeorge syndrome	*TBX1*	AD	*602054 #188400	Hypoparathyroidism, micrognathia, low-set ears, hypertelorism, congenital heart defects, thymic hypoplasia
Hyperparathyroidism 1, familial isolated primary	*CDC73 (HRPT2)*	AD	*607393 #145000	Malaise, anorexia, pancreatitis, renal calculi, pathologic fractures
Hyperparathyroidism 2 (Hyperparathyroidism-jaw tumor syndrome)	*CDC73 (HRPT2)*	AD	*607393 #145001	Ossifying fibromas of the mandible and maxilla, renal lesions, recurrent pancreatitis
Hyperparathyroidism, neonatal severe	*CASR*	AR/AD	*601199 #239200	Failure to thrive, hypotonia, fractures of the ribs, respiratory distress
Hypoparathyroidism, familial isolated	*GCM2 (GCMB)*	AR/AD	*603716 #146200	Cataracts, intracerebral calcification on CT scan, tetany, seizures
	PTH	AR/AD	*168450 #146200	
Hypoparathyroidism-retardation-dysmorphism syndrome (HRD; Sanjad-Sakati syndrome)	*TBCE*	AR	*604934 #241410	IUGR, short stature, small hands and feet, microcephaly, micrognathia, long philtrum, low-set posteriorly rotated ears, deep-set eyes, thin lips
Hypoparathyroidism, sensorineural deafness, and renal dysplasia (Barakat syndrome)	*GATA3*	AD	*131320 #146255	Hypoparathyroidism, sensorineural deafness, renal dysplasia
Hypophosphatasia	*ALPL*	AR	*171760 #241500	Infantile form: manifests within the first 6 months of life, FTT, rickets, rib fractures, lack of ossification, craniosynostosis, hypotonia, seizures, respiratory infections/failure
	ALPL	AR	*171760 #241510	Childhood form: premature deciduous tooth loss (less than 5 years of age), rickets, short stature
	ALPL	AR/AD	*171760 #146300	Adult form: recurrent fractures, particularly metatarsal stress fractures, calcium pyrophosphate arthropathy; odontohypophosphatasia: periodontitis
Hypophosphatemic rickets	*DMP1*	AR	*600980 #241520	Rickets, early fusion of cranial sutures, nerve deafness, elevated FGF23 level
	ENPP1	AR	*173335 #613312	Hypophosphatemia, elevated FGF23 level
	FGF23	AD	*605380 #193100	Short stature, tooth abscesses, bone pain, lower limb deformities, pseudofractures (adult-onset), generalized weakness (adult-onset), elevated FGF23 level
	PHEX	X	*300550 #307800	Short stature, frontal bossing, hearing loss, recurrent dental abscesses, bone pain, lower limb deformities, pseudofractures (adult-onset), elevated FGF23 level
Idiopathic infantile hypercalcemia	*CYP24A1*	AR	*126065 #143880	Increased sensitivity to vitamin D, failure to thrive, nephrocalcinosis, hypotonia, febrile episodes
Pseudohypoparathyroidism Type IA (Albright hereditary osteodystrophy)	*GNAS (maternal)*	AD	*139320 #103580	Short stature, obesity, round face, brachydactyly, subcutaneous ossifications

Disease	Gene	H	OMIM	Phenotype
Pseudohypoparathyroidism, type IB	*STX16*	AD	*603666 #603233	Rarely brachydactyly, short metacarpals, obesity
Pseudohypoparathyroidism, type IC	*GNAS*	AD	*139320 #612462	Short stature, obesity, round face, low nasal bridge, short neck, brachydactyly, subcutaneous ossifications
Pseudopseudohypopara-thyroidism	*GNAS (paternal)*	AD	*139320 #612463	See Albright hereditary osteodystrophy
Vitamin D hydroxylation-deficient rickets, type 1A (1α-hydroxylase deficiency, vitamin D-dependent rickets, type 1)	*CYP27B1*	AR	*609506 #264700	Failure to thrive, frontal bossing, delayed tooth eruption, enlarged epiphyses, lower limb deformities
Vitamin D hydroxylation-deficient rickets, type 1B (25-hydroxylase deficiency)	*CYP2R1*	AR	*608713 #600081	FTT, frontal bossing, delayed tooth eruption enlarged epiphyses, lower limb deformities
Vitamin D-dependent rickets, type 2A (vitamin D resistant rickets)	*VDR*	AR	*601769 #277440	FTT, sensorineural deafness, delayed tooth eruption, alopecia, cutaneous cysts

*gene ID;

#disease ID;

AD, autosomal dominant; AR, autosomal recessive; FTT, failure to thrive; H, inheritance; X, X-linked.

Table 2

ADRENAL DISORDERS

Disease	Gene	H	OMIM	Phenotype
CORTISOL DEFICIENCY				
Achalasia-Addisonianism-Alacrima syndrome; AAAS (Allgrove syndrome; Triple A)	*AAAS*	AR	*605378 #231550	Alacrima, achalasia, short stature, microcephaly, CNS abnormalities, adrenal insufficiency usually in the 1st decade
ACTH deficiency	*POMC*	U	*176830 #609734	Obesity, adrenal insufficiency, red hair
	TBX19	AR	*604614 #201400	Adrenal hypoplasia, fasting hypoglycemia
Adrenal hypoplasia congenita	*NR0B1 (DAX1)*	X	*300473 #300200	Primary adrenal insufficiency, HH
Adrenoleukodystrophy	*ABCD1*	X	*300371 #300100	Adrenal insufficiency, CNS symptoms
Congenital adrenal hyperplasia	*CYP11A1*	AR	*118485 #613743	M: external genitalia can range from female to undervirilized male; F: normal genitalia; Both: can present with adrenal and salt wasting crises in the neonatal period
	CYP11B1	AR	*610613 #202010	M: hyperpigmented scrotum, postnatal virilization; F: virilized external genitalia; Both: HTN in 2/3 of the cases. Non classic forms in both sexes may present later as premature adrenarche, growth acceleration, bone advancement, PCOS, menstrual irregularity, hirsutism infertility in females.
	CYP17A1	AR	*609300 #202110	M: external genitalia can range from female to undervirilized male, lack of secondary sex characteristics; F: normal genitalia, primary amenorrhea, lack of secondary sex characteristics; Both: HTN, hypokalemia
	HSD3B2	AR	*613890 #201810	M: external genitalia can range from female to undervirilized male; F: virilized external genitalia. Both can present with adrenal and salt wasting crises in the neonatal period. Non classic forms in both sexes may present later as premature adrenarche, growth acceleration, bone advancement, PCOS, menstrual irregularity, hirsutism, infertility in females.
	POR	AR	*124015 #613571	M: May be under-masculinized at birth F: Virilized genitalia at birth despite low to normal circulating androgens Both: Impaired steroidogenesis, including cortisol; may present with or without Antley-Bixler syndrome (craniosynostosis, radiohumeral synostosis, and variable skeletal and visceral anomalies); maternal virilization may occur during pregnancy, with postpartum resolution
Congenital lipoid adrenal hyperplasia (Lipoid CAH, CLAH)	STAR	AR	*600617 #201710	M: external genitalia can range from female to undervirilized male; F: normal genitalia, ovarian cysts (may progress to torsion), premature ovarian failure; Both: severe adrenal insufficiency with salt wasting with high mortality in infancy.
Corticosteroid-binding globulin deficiency	*SERPINA6*	AD AR	*122500 #611489	Hypotension, fatigue; many patients asymptomatic

Disease	Gene	H	OMIM	Phenotype
Glucocorticoid deficiency 1 (GCCD1, Familial glucocorticoid deficiency-1, FGD1)	*MC2R (ACTHR)*	AR	*607397 #202200	FTT, tall stature, hyperpigmentation, recurrent hypoglycemic episodes
Glucocorticoid deficiency 2 (GCCD2)	*MRAP*	AR	*609196 #607398	Recurrent hypoglycemia, hyperpigmentation
Glucocorticoid deficiency 3 (GCCD3, Familial glucocorticoid deficiency 3, FGD3)	*FGD3*	AR	%609197	Recurrent hypoglycemia, hyperpigmentation
CORTISOL EXCESS				
ACTH-independent macronodular adrenal hyperplasia (AIMAH)	*GNAS1*	U	*139320 #219080	Adrenal (ACTH-independent) Cushing syndrome of adult onset (40–60 yr)
Primary pigmented nodular adrenocortical disease	*PRKAR1A*	AD	*188830 #610489	Adrenal (ACTH-independent) Cushing syndrome, truncal obesity, round face, hypertension
	PDE11A	AD	*604961 #610475	
	PDE8B	U	*603390 #614190	
ISOLATED ALDOSTERONE DEFICIENCY				
Hypoaldosteronism, congenital, due to CMO I deficiency	*CYP11B2*	AR	*124080 #203400	Familial hyperreninemic hypoaldosteronism, FTT, growth retardation, hypotension, intermittent fever
Hypoaldosteronism, congenital due to CMO II deficiency	*CYP11B2*	AR	*124080 #610600	FTT, Growth retardation, hypotension
Pseudohypoaldosteronism	*NR3C2*	AD	*600983 #177735	FTT, vomiting, diarrhea, poor feeding, metabolic acidosis; onset in infancy, improves with age, some asymptomatic
HYPERALDOSTERONISM				
Apparent mineralocorticoid excess	*HSD11B2*	AR	*614232 #218030	Low birth weight, FTT, short stature, HTN, metabolic alkalosis
Glucocorticoid-remediable aldosteronism	*CYP11B1*	AD	*610613 #103900	Adrenal hyperplasia, HTN that is suppressible by glucocorticoid treatment
Glucocorticoid resistance	*NR3C1*	AD	*138040 #615962	HTN; infertility, hirsutism, hypoglycemia, fatigue

*gene ID;

#disease ID;

AD, autosomal dominant; AR, autosomal recessive; CNS, central nervous system; F, females; FTT, failure to thrive; H, inheritance; HH, hypogonadotropic hypogonadism; HTN, hypertension; M, males; PCOS, polycystic ovary syndrome; U, inheritance unclear or unknown; X, X-linked.

Table 3

GONADAL DISORDERS

Disease	Gene	H	OMIM	Phenotype
Androgen insensitivity May be minimally affected (MAIS), partial (PAIS) or complete (CAIS)	*AR*	X	*313700 #300068	M: MAIS - normal genitalia, gynecomastia, infertility; PAIS - ambiguous genitalia with variable degrees of virilization, sparse pubic hair, gynecomastia; CAIS - female body habitus and external genitalia, tall stature, sparse pubic hair, absent facial hair, blind vaginal pouch, inguinal or abdominal testes, inguinal hernias F (carriers): normal genitalia, breast development and fertility; may have tall stature and sparse pubic hair
Aromatase deficiency	*CYP19A1*	AR	*107910 #613546	M: eunuchoid body proportions, tall stature, excess adipose tissue; F: virilization, amenorrhea, absent breast development, cystic ovaries; Both: fetal and maternal virilization (acne and hirsutism in mother resolves after delivery)
Aromatase excess syndrome	*CYP19A1*	AD/AR/X	*107910 #139300	M: gynecomastia, premature growth spurt, decreased adult stature; F: usually asymptomatic, may have macromastia, premature growth spurt, menstrual irregularity, short stature; Both: normal fertility
Estrogen resistance	*ESR1*	AR	*133430 #615363	M: axillary acanthosis nigricans, early coronary artery disease, hyperinsulinemia and impaired glucose tolerance; F: primary amenorrhea, absent breast development with no response to oral estrogen, small uterus, large polycystic ovaries, severe acne; Both: osteopenia, delayed bone age with continued growth into adulthood
17β-Hydroxysteroid Dehydrogenase Deficiency	*HSD17B3*	AR	*605573 #264300	M: undervirilized external genitalia at birth, inguinal testes, virilization at puberty, gynecomastia, infertility, hypothyroidism; F: normal genitalia and breast development; possible association with pubertal-onset hirsuitism and PCOS
Leydig cell hypoplasia (M) Luteinizing hormone resistance (F)	*LHCGR*	AR	*152790 #238320	M: Type 1 – female external genitalia, absent development of male secondary sex characteristics; Type 2 - milder with range of genital abnormalities; F: amenorrhea, infertility
McCune-Albright syndrome	*GNAS1*	SM	*139320 #174800	Peripheral precocious puberty, café au lait spots, polyostotic fibrous dysplasia, facial asymmetry, deafness, blindness, hyperthyroidism, hyperparathyroidism, Cushing syndrome, acromegaly, hyperprolactinemia, gastrointestinal polyps and pituitary adenomas.
Premature ovarian failure	*FMR1*	X	*309550 #311360	Amenorrhea, osteoporosis
	DIAPH2	U	*300108 #300511	
	POF1B	U	*300603 #300604	
	FOXL2	U	*605597 #608996	
	BMP15	X	*300247 #300510	

Disease	Gene	H	OMIM	Phenotype
	NOBOX	U	*610934 #611548	
	FIGLA	AD	*608697 #612310	
	NR5A1	U	*184757 #612964	
Testotoxicosis, familial	*LHCGR*	AD	*152790 #176410	Male-limited, gonadotropin independent, precocious puberty (usually by age 4 years) with rapid virilization, small testes, not suppressible by gonadotropin releasing hormone analogs
Testotoxicosis with pseudohypoparathyroidism type 1a	*GNAS*	U	*139320 #176410	Male-limited precocious puberty, see pseudohypoparathyroidism type 1a

*gene ID;

#disease ID;

AD, autosomal dominant; AR, autosomal recessive; F, females; H, inheritance; M, males; PCOS, polycystic ovary syndrome; SM, somatic mosaic; U, inheritance unclear or unknown; X, X-linked.

Table 4

PITUITARY AND HYPOTHALAMIC DISEASES

Disease	Gene	H	OMIM	Phenotype
Disorders of Growth				
Growth hormone deficiency, isolated	*GH1*	AR	*139250 #262400	Puppet (baby doll) facies, hypoglycemia, sexual ateleiotic dwarfism, proportionate short stature, truncal obesity, delayed dentition, delayed bone age, high-pitched voice
	GH1	AR	*139250 #612781	Short stature, delayed bone age, frontal bossing, truncal obesity
	GHRHR	AR	*139191 #612781	
	GH1	AD	*139250 #173100	Short stature, truncal obesity, delayed dentition, delayed bone age
Growth hormone insensitivity with immunodeficiency	*STAT5B*	AR	*604260 #245590	Combined GH insensitivity and immunodeficiency; physical appearance similar to Laron Syndrome.
Growth hormone insensitivity syndrome (Laron syndrome)	*GHR*	AR	*600946 #262500	Marked short stature, childlike body proportions in adults, short limbs, hip degeneration, limited elbow extensibility, small face, high-pitched voice
Kowarski Syndrome	*GH1*	AR	*139250 #262650	Short stature, delayed bone age, bioinactive GH
Panhypopituitarism				
Panhypopituitarism, X-Linked	*SOX3*	X	*313430 #312000	Panhypopituitarism, pituitary dwarfism
Pituitary hormone deficiency, combined	*POU1F1 (PIT1)*	AR/AD	*173110 #613038	Short stature, FTT, prominent forehead, midface hypoplasia, depressed nasal bridge, deep-set eyes, short nose with anteverted nostrils; mental retardation
	PROP1	AR	*601538 #262600	Short stature, neonatal hypoglycemia, hypoglycemic seizures, midface hypoplasia
	LHX3	AR	*600577 #221750	Short stature, sensorineural deafness, short neck with limited rotation, mental retardation, midface hypoplasia
	LHX4	AD	*602146 #262700	Short stature, very small sella turcica, abnormal petrous bone, hypoglycemia, midface hypoplasia
	HESX1	AD/AR	*601802 #182230	Septo-optic dysplasia, short stature, GH deficiency, hypoglycemia, optic nerve hypoplasia, absent septum pellucidum, absent corpus callosum, hypoplastic anterior pituitary, ectopic or absent posterior pituitary, midline forebrain defects, supernumerary digits, hypoplastic digits, psychomotor retardation
	OTX2	AD	*600037 #613986	Short stature, pituitary hypoplasia with ectopic posterior pituitary, midface hypoplasia
Pubertal Disorders				
FSH deficiency, isolated	*FSHB*	AR	*136530 #229070	Primary amenorrhea
Hypogonadotropic hypogonadism with or without anosmia (Kallmann syndrome)	*KAL1*	X	*300836 #308700	Absent or incomplete sexual maturation by the age of 18 years, cleft palate and sensorineural hearing loss with variable frequency, in the presence of anosmia, HH is typically called “Kallmann Syndrome”

Disease	Gene	H	OMIM	Phenotype
Hypogonadotropic hypogonadism with or without anosmia	*FGFR1*	AD	*136350 #147950	
	PROKR2	AR/AD/X	*607123 #244200	
	PROK2	AD	*607002 #610628	
	CHD7	AD	*608892 #612370	
	FGF8	AD	*600483 #612702	
	GNRHR	AD	*138850 #146110	
	KISS1R	AR/AD	*604161 #614837	
	NSMF	AD	*608137 #614838	
	TAC3	AR	*162330 #614839	
	TACR3	AR	*162332 #614840	
	GNRH1	AR	*152760 #614841	
	KISS1	AR	*603286 #614842	
	WDR11	AD	*606417 #614858	
	HS6ST1	AD	*604846 #614880	
Precocious puberty, central	*KISS1R*	AD	*604161 #176400	Isosexual precocious puberty, reduced adult height
	MKRN3	AD	*603856 #615346	
Other Pituitary/Hypothalamic Disorders				
ACTH deficiency	*POMC*	U	*176830 #609734	See “Adrenal disorders (cortisol deficiency)
	TBX19	AR	*604614 #201400	See “Adrenal disorders (cortisol deficiency)
Diabetes insipidus	*AVP*	AD	*192340 #125700	Hypertelorism, broad short nose, long philtrum, decreased bone mineral density

*gene ID;

#disease ID;

AD, autosomal dominant; AR, autosomal recessive; FTT, failure to thrive; GH, growth hormone; H, inheritance; HH, hypogonadotropic hypogonadism; U, inheritance unclear or unknown; X, X-linked.

Table 5

THYROID DISORDERS

Disease	Gene	H	OMIM	Phenotype
Hyperthyroidism, nonautoimmune	*TSHR*	AD	*603372 #609152	Activating mutation, low birth weight, tachycardia, goiter
Hypothyroidism, athyroidal with spiky hair and cleft Palate (Bamforth-Lazarus syndrome)	*FOXE1 (TTF-2)*	AR	*602617 #241850	Kinky hair, cleft palate, choanal atresia, bifid epiglottis
	POU1F1 (PIT1)	AD/AR	*173110 #613038	See “Hypopituitarism (combined pituitary hormone deficiency)”
	PROP1	AR	*601538 #262600	See “Hypopituitarism (combined pituitary hormone deficiency)”
Hypothyroidism, congenital with choreoathetosis, with or without pulmonary dysfunction	*NKX2-1 (TTF-1)*	AD	*600635 #610978	Brain-lung-thyroid syndrome: choreoathetosis, ataxia, hypotonia, respiratory distress syndrome
Hypothyroidism, congenital with neonatal diabetes mellitus	*GLIS3*	AR	*610192 #610199	Neonatal DM, congenital glaucoma, deafness
Hypothyroidism, congenital, nongoitrous	*TSHR*	AR	*603372 #275200	TSH resistance, variable severity ranging from asymptomatic to euthyroidism to hypothyroidism
	PAX8	AR/Sp	*167415 #218700	Hypothermia, lethargy, umbilical hernia, hoarse cry, macroglossia
	TSHB	AR	*188540 #275100	Growth retardation, depressed nasal bridge, macroglossia, umbilical hernia, hoarse cry
	NKX2-5	AD	*600584 #225250	Severe growth retardation, heart defects, kidney disease, liver disease
	THRA	AD	*190120 #614450	Growth retardation, macrocephaly, macroglossia, low resting heart rate, hypotonia
Thyroid carcinoma	*NTRK1*	AD	*191315 #155240	Medullary thyroid carcinoma
	RET	AD	*164761 #155240	
Thyroid dyshormonogenesis	*SLC5A5*	AR	*601843 #274400	Thyroid iodine accumulation defect, goiter, thyroid nodules, macroglossia, growth retardation
	TPO	AR	*606765 #274500	Defective oxidation and organification of iodide, goiter
	SLC26A4	AR	*605646 #274600	Pendred syndrome, thyroid hormone organification defect, sensorineural deafness, vestibular function defect, cochlear malformation, goiter, thyroid carcinoma
	TG	AR	*188450 #274700	Thyroid hormone coupling defect with iodide trapping, goiter, thyroid cancer
	IYD	AR	*612025 #274800	Iodotyrosine deiodinase deficiency, goiter, growth retardation
	DUOXA2	AR	*612772 #274900	Thyroglobulin synthesis defect, goiter

Disease	Gene	H	OMIM	Phenotype
	DUOX2	AR	*606759 #607200	Iodide organification defect
Thyroid hormone resistance, generalized (GRTH)	*THRB*	AD	*190160 #188570	Goiter, speech delay, attention deficit/ hyperactivity disorder
Thyroid hormone resistance, generalized (Refetoff Syndrome, GRTH)	*THRB*	AR	*190160 #274300	Goiter, deafness, stippled epiphyses, exophthalmos
Thyroid hormone resistance, selective pituitary (PRTH)	*THRB*	AD	*190160 #145650	Selective pituitary resistance, hyperthyroidism
T3 Resistance (Allan-Herndon-Dudley syndrome, AHDS)	*SLC16A2*	X	*300095 #300523	Microcephaly, elongated face, bitemporal narrowing, hypotonia, developmental delay, involuntary movements, joint deformities

*gene ID;

#disease ID;

AD, autosomal dominant; AR, autosomal recessive; DM, diabetes mellitus; H, inheritance; Sp, sporadic inheritance; X, X-linked.

Table 6

SELECTED SYNDROMES WITH MULTIPLE ENDOCRINOPATHIES

Disease	Gene	H	OMIM	Phenotype
Autoimmune polyendocrinopathy syndrome (APS1)	*AIRE*	AR AD	*607358 #240300	Hypoparathyroidism, adrenal insufficiency, hypogonadism, DM, chronic mucocutaneous candidiasis, hepatitis, pernicious anemia
Carney complex	*PRKAR1A*	AD	*188830 #160980	Pigmented nodular adrenocortical disease, spotty skin pigmentation, myxomas of the heart, skin, breast, schwannomas, pituitary adenomas, Sertoli cell tumors.
CHARGE syndrome	*CHD7*	AD	*608892 #214800	Short stature, GH deficiency, parathyroid hypoplasia, gonadotropin deficiency, hypothyroidism, microcephaly, square face, micrognathia, facial asymmetry, small ears, deafness, colobomas, ptosis, hypertelorism, downslanting palpebral fissures, posterior choanal atresia, cleft lip/palate.
	SEMA3E	AD	*608166 #214800	
Culler-Jones Syndrome	*GLI2*	AD	*165230 #615849	Short stature, midface hypoplasia, micropenis, polydactyly, developmental delay, panhypopituitarism
Denys-Drash syndrome	*WT1*	AD	*607102 #194080	Males: Undermasculinized (ambiguous) or female genitalia, gonadal dysgenesis with both ovarian and testicular tissue present, gonadoblastoma, Females: Usually normal external genitalia and gonads; gonadal dysgenesis, gonadoblastoma and wolffian structures have been reported Both: Nephropathy, HTN, high risk (~90%) of nephroblastoma (Wilms tumor)
Frasier syndrome	*WT1*	AD	*607102 #136680	Males: Female external genitalia Females: Normal external genitalia, primary amenorrhea Both: streak gonads, gonadoblastoma, glomerulopathy
IPEX	*FOXP3*	X	*300292 #304790	Hypothyroidism, DM, enteropathy, immunodeficiency
Kenney-Caffey syndrome	*TBCE*	AR	*604934 #244460	Hypoparathyroidism, IUGR, short stature, delayed anterior fontanel closure, small hand and feet
Microphthalmia, syndromic	*SOX2*	AD	*184429 #206900	Short stature, growth failure, microcephaly, frontal bossing, hearing loss, microphthalmia, anophthalmia, optic nerve hypoplasia, coloboma, VSD, PDA, rib abnormalities, esophageal atresia, vertebral anomalies, developmental delay
Multiple endocrine neoplasia type 1 (MEN1)	*MEN1*	AD	*613733 #131100	Hyperparathyroidism, tumors of the pancreas and anterior pituitary, facial angiofibroma, lipomas, gingival papules
Multiple endocrine neoplasia type 2A (MEN2A)	*RET*	AD	*164761 #171400	Hyperparathyroidism, medullary carcinoma of the thyroid, pheochromocytoma, cutaneous lichen amyloidosis
Multiple endocrine neoplasia type 2B (MEN2B)	*RET*	AD	*164761 #162300	Marfanoid habitus, medullary carcinoma of the thyroid, pheochromocytoma, mucosal neuromas
MEN4	*CDKN1B*	AD	*600778 #610755	Acromegaly, pituitary adenoma, renal angiomyolipoma
Prader-Willi-like syndrome	*MAGEL2*	AD	*605283 #615547	Prader-Willi-like syndrome; hypogonadism, hyperphagia, autistic features

*gene ID;

#disease ID;

AD, autosomal dominant; AR, autosomal recessive; DM, diabetes mellitus; H, inheritance; HTN, hypertension; IUGR, intrauterine growth retardation; X, X-linked.