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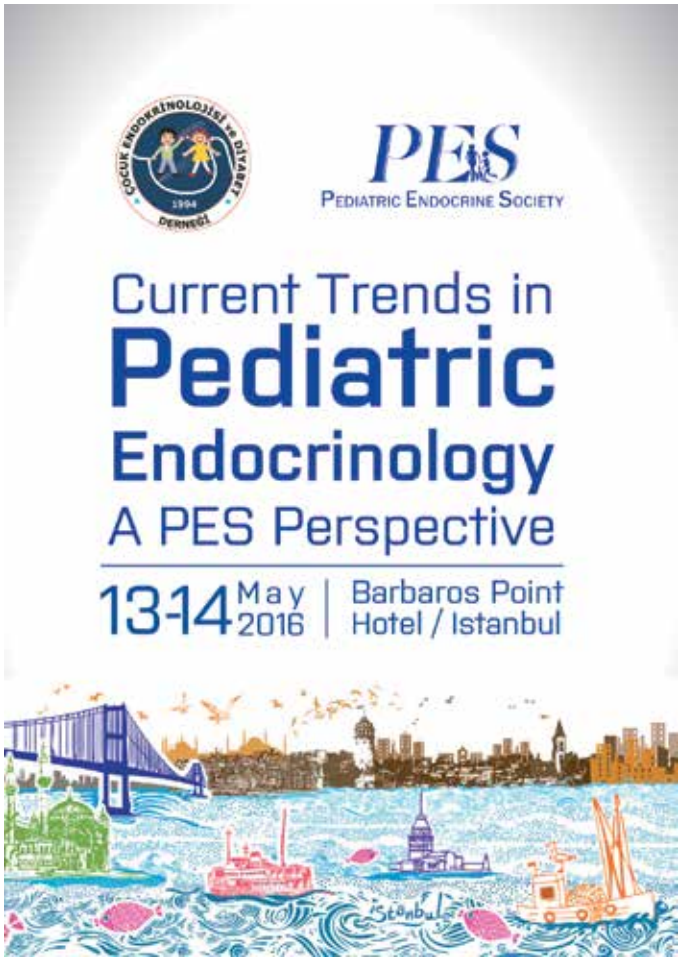

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What is already known on this topic?
What this study adds?
These two items must be completed before submission. Each item should include at most 2-3 sentences and at most 50 words focusing on what is known and what this study adds.
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All clinical investigations described in submitted manuscripts must have been conducted in accordance with the guidelines in the Declaration of Helsinki and has been formally approved by the appropriate institutional review committees. All manuscripts must indicate that such approval was obtained and that informed consent was obtained from subjects in all experiments involving humans. The study populations should be described in detail. Subjects must be identified only by number or letter, not by initials or names. Photographs of patients' faces should be included only if scientifically relevant. Authors must obtain written consent from the patient for use of such photographs.

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Sample References

Papers Published in Periodical Journals: Gungor N, Saad R, Janosky J, Arslanian S. Validation of surrogate estimates of insulin sensitivity and insulin secretion in children and adolescents. J Pediatr 2004;144:47-55.

Papers Only Published with DOI Numbers: Knops NB, Sneeuw KC, Brand R, Hile ET, de Ouden AL, Wit JM, Verloove-Vanhorick SP. Catch-up growth up to ten years of age in children born very preterm or with very low birth weight. BMC Pediatrics 2005 doi: 10.1186/1471-2431-5-26.

Book Chapters: Darendeliler F. Growth Hormone Treatment in Rare Disorders: The KIGS Experience. In: Ranke MB, Price DA, Reiter EO (eds). Growth Hormone Therapy in Pediatrics: 20 Years of KIGS. Basel, Karger, 2007;213-239.

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Dear Colleagues,

We are very pleased to note that "Current Trends in Pediatric Endocrinology: A PES Perspective" meeting was successfully held in İstanbul on 13-14 May 2016 with 72 participants. This is the first Current Trends meeting done with the North American Pediatric Endocrine Society. The aim was to discuss interesting topics with the well-known specialists.

Via this interactive scientific event, we aimed to build a bridge between Pediatric Endocrine Society and our national society in terms of educational collaboration. The meeting included presentations and discussions regarding current advances on pseudohypoparathyrodism, disorders of sex development, bionic pancreas, next generation sequencing, long-acting growth hormone, genetics of growth disorders, Turner syndrome, long-acting GnRH analogs, genetic disorders of adrenal development, and congenital adrenal hyperplasia. Additionally, important news from PES and ENDO meetings in 2016 were announced and six unique case presentations were made.

We would like to thank all speakers and participants who contributed to this influential scientific meeting for making this educational event possible.

Guest Editor

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Current Perspectives on Pseudohypoparathyroidism-New Classification

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Pseudohypoparathyroidism (PHP) is a rare disease caused by impairments in the parathyroid hormone (PTH) signaling pathway and was first described by Fuller Albright and colleagues in 1942 (1). The current classification is based on the presence or absence of Albright hereditary osteodystrophy (AHO) characterized by brachydactyly, rounded face, short stature, obesity, and subcutaneous ossifications and, the presence or absence of PTH or multiple hormonal resistance together with an in vivo response to exogenous PTH and the results of an in vitro assay to measure Gsα activity (2). However, this classification do not include recently described other related diseases like acrodysostosis (Acro) or progressive osseous heteroplasia (POH), as well as clinical and genetic/epigenetic background of the different subtypes.

The *GNAS* complex locus encodes the alpha-subunit of the stimulatory G protein (Gsα), a ubiquitous signaling protein mediating the actions of many hormones, and gives rise to other gene products, most of which exhibit exclusively monoallelic expression. Although, Gsα is expressed biallelically in most tissues, paternal Gsα expression is silenced in some tissues with poorly understood mechanisms that involve differential methylation within *GNAS* (2).

Current classification of the disease is given in the Table 1 below:

However, this classification could not include all features of the disease like in the following cases: PHP1b patients show mild TSH resistance and AHO features in several cases have and a recent study showed mildly diminished erythrocyte Gsα activity (3,4). In a subset of patients with PHP1a, also shows methylation defects in *GNAS* identical to that of PHP1b.

Additionally, mild resistance to PTH was described in patients having a paternal *GNAS* mutation, known as pseudopseudohypoparathyroidism (5), demonstrating that the hormonal resistance is not restricted to the maternally inherited mutations.

In this description of the disease, patients with methylation defects having AHO feature can be classified as PHP1c (6).

Additionally, two other diseases are caused by the defects involved in signaling pathway of Gsα, acrodysostosis caused by heterozygous mutations in PRKAR1A and PDE4D (7,8) and hypertension and brachydactyly syndrome (HTNB) caused by heterozygous mutations in PDE3A have been identified (9).

For all these reasons, the EuroPHP network suggested a new classification that encompasses all disorders with impairments in PTH and/or PTHrP cAMP-mediated pathway and proposed the name inactivating PTH/PTHrP signalling disorder (iPPSD) with the following classification (10).

iPPSD1: Loss of function mutation in PTH1R

iPPSD2: Loss of function mutation in Gsα coding exons

iPPSD3: Methylation change(s) at one or more *GNAS*, differentially methylated regions associated with or without a genetic (deletion) or cytogenetic (UPD) defect,

iPPSD4: PRKAR1A mutations

iPPSD5: PDE4D mutations

iPPSD6: PDE3A mutations

iPPSDx: Lack of genetic/epigenetic defect identified following molecular investigation of known genes described above.

As a conclusion, the new classification will cover the recent findings and lead to a more straightforward definition of the disease.

Table 1. Current classification of the disease

	Defect	Parental origin	PTH resistance	Additional hormone resistance	AHO features	Urinary cAMP and phosphate to PTH	Erythrocyte Gsα activity
PHP1a	Gsα coding mutation	Maternal	Yes	Yes	Yes	Blunted	Reduced
PHP1c	Gsα coding mutation	Maternal	Yes	Yes	Yes	Blunted	Normal
PPHP	Gsα coding mutation	Paternal	No	No	Yes	Normal	Reduced
POH	Gsα coding mutation	Paternal	No	No	No	Normal	Reduced
PHP1b	Methylation defect in DMR of *GNAS*	Maternal	Yes	No	No	Blunted	Normal

Gsα: alpha-subunit of the stimulatory G protein, PHP: pseudohypoparathyroidism, POH: progressive osseous heteroplasia, PTH: parathyroid hormone, AHO: Albright hereditary osteodystrophy, DMR: differentially methylated region, cAMP: cyclic adenosine monophosphate, PPHP: pseudopseudohypoparathyroidism

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Disorders/Differences of Sex Development: A World of Uncertainty

Eric Vilain
Department of Human Genetics,
David Geffen School of Medicine, UCLA,
Los Angeles, California, United States of America

Disorders/Differences of sex development (DSD) are congenital conditions in which development of chromosomal, gonadal, or anatomic sex is atypical (1). DSD encompass a very large spectrum of phenotypes, from minor malformations (hypospadias, undescended testes, hypertrophy of the clitoris) to sexual ambiguity of the genitalia. In the aggregate, DSD have an estimated incidence of about 1% and can result in serious consequences for fertility, cancer risk, behavioral health, and quality of life. In addition, recently, the debate about the management of intersex patients has intensified over issues of gender assignment and the indication for early genital surgery. Yet, the scientific data on patient outcome have remained scarce. The main obstacles to the optimal management of these patients with DSD have been a combination of lack of controlled outcome data and the lack of understanding of their pathophysiology, which prevents precise diagnostic categorization of patients. Despite much progress in the past 15 years, the molecular mechanisms underlying mammalian sex determination are still far from understood, and the molecular basis of sex reversal in the majority of XY patients (>50%) and a significant minority of XX patients (about 10%) cannot yet be explained.

Such conditions can be stressful for patients and their families and have historically been difficult to diagnose, especially at the genetic level. In particular, for cases of 46,XY gonadal dysgenesis, once variants in SRY and NR5A1 have been ruled out, there are few other single gene tests available. We used exome sequencing followed by analysis with a list of all known human DSD-associated genes to investigate the underlying genetic etiology of 46,XY DSD patients who had not previously received a genetic diagnosis. We were able to identify a likely genetic diagnosis in more than a third of cases, including 22.5% with a pathogenic finding and an additional 12.5% with likely pathogenic findings. In addition, 15% had variants of uncertain clinical significance (VUS) that may be reclassified as literature evolves (2). Exome sequencing allowed a remarkable and unprecedented level of genetic diagnostic success in this cohort, especially considering that, for most patients, all other endocrine and genetic testing had been exhausted. Early identification of the genetic cause of a DSD will in many cases streamline and direct the clinical management of the patient, with more focused endocrine and imaging studies and better informed surgical decisions. When unaffected parents are also genotyped, there is the additional possibility of identifying novel genes that will further enhance our understanding of these complex conditions and allow for better care and prognostic information for the patients and their families (3).

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Automating Glycemic Management in Diabetes Mellitus with a Bionic Pancreas

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An artificial or bionic pancreas combines a continuous glucose monitor, mathematical algorithms, and drug delivery pumps to automatically regulate blood glucose levels for patients with diabetes mellitus (1,2). Our bihormonal bionic pancreas delivers both insulin and glucagon under the control of autonomously adaptive algorithms that require no information about the patient other than body weight to start, and can quickly adapt to changing insulin needs (3). No carbohydrate counting is required, and qualitative meal announcements are optional. If continuous glucose monitoring is interrupted, intermittent glucose measurements can be substituted until continuous monitoring is reestablished. The bionic pancreas achieved lower mean glucose values with less hypoglycemia vs. conventional insulin pump therapy or sensor augmented pump therapy in volunteers with type 1 diabetes ranging in age from 6 to 76 years in outpatient settings, including diabetes camp studies in adolescents and pre-adolescents and a home use study in adults (4,5,6). For nearly all subjects, the bionic pancreas achieved mean glucose values below those recommended by professional societies for optimal prevention of microvascular complications. Equally important, the bionic pancreas drastically reduces the burden of diabetes management, increases user satisfaction, and reduces diabetes-related distress when compared to usual care. Use of micro-dose glucagon is well tolerated and is not associated with any reduction in effectiveness or adverse safety signals in studies up to 11 days in length.

Approval of a bihormonal system will require approval of a stable glucagon or glucagon analog for chronic intermittent use. There are at least two stable glucagon formulations or analogs that are in clinical trials and could be used in the bionic pancreas in the near term. An insulin-only version of the system is also able to provide effective glycemic regulation, but with modestly higher amounts of hypoglycemia when obtaining the same mean glucose achieved (7). Pivotal registration trials designed to support approval of a fully integrated bionic pancreas device (the iLet) by the U.S. Food and Drug Administration are planned for 2017 with the goal of availability to patients as early as 2018 for the insulin-only system and as early as 2019 for a bihormonal system. The size and duration of the trial for the bihormonal system is largely determined by the requirements for approval of glucagon for chronic intermittent administration.

Automated glucose control may have utility in other patient populations. A preliminary study suggest that the insulin-only version of the bionic pancreas may be effective in the treatment of patients with type 2 diabetes using multiple daily injections of insulin (unpublished data). A glucagon-only version of the device dramatically reduced hypoglycemia in patients managing their own insulin therapy (8) and may be useful in treating post-bariatric hypoglycemia and congenital hyperinsulinism. Future studies with the bionic pancreas will include these populations, as well as specialized populations of patients with type 1 diabetes, including very young children, newly diagnosed patients, the elderly, and patients with severe hypoglycemia unawareness.

Automated glycemic management with a bionic pancreas is feasible and is likely to change the clinical management of patients with insulin-requiring diabetes within the next five years.

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Use of Next Generation Sequencing in Clinical Practice: The Example of Disorders/Differences of Sex Development

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Disorders/Differences of sex development (DSD) are congenital conditions in which development of chromosomal, gonadal, or anatomic sex is atypical (1). DSD are chronic medical conditions collectively affecting ~1% of the population (2,3), frequently requiring life-long care by multiple specialists, and carrying a significant public health burden (1). Some are associated with life-threatening events, such as adrenal crises in congenital adrenal hyperplasia (4). DSD are also associated with increased infertility, cancer, gender dysphoria risks, psychosocial distress, and pervasive challenges to health-related quality of life for patients and families (5,6,7).

DSD are broadly classified into three categories: sex chromosome DSD, 46,XY DSD, and 46,XX DSD and are further classified according to the type of gonad found in the patient (ovary, testis, ovotestis). Currently, known etiologies include disorders of gonadal development and disorders in androgen synthesis or action, and are considered Mendelian (reviewed in Ref. 3). Sex development in humans is divided into two sequential steps: sex determination and sex differentiation. Sex determination refers to the expression of gene networks that direct the development of undifferentiated bipotential gonads into either testes or ovaries. Once developed, testes and ovaries secrete hormones that promote further sex differentiation of the body throughout embryonic development and adulthood (8). Mutations have been identified in genes that control both steps, leading to DSD (9).

Standard genetic diagnosis for DSD is typically limited to genotyping just one or two genes, chosen as likely candidates based on disease phenotype. However, because of phenotypic overlap in various DSD conditions, serial single candidate gene testing is highly inefficient: diagnostic yields of 30% for 46,XY gonadal dysgenesis, 80% for 46,XX testicular DSD, and 10% for ovotesticular DSD are widely quoted with traditional single-gene testing methods (reviewed in Ref. 8). With this approach, limited to known genes and to genes for which clinical testing is available in the country, most patients do not receive a definitive diagnosis.

We were able to increase significantly the diagnostic success for DSD using whole exome sequencing (WES), with the identification of disease-causing and likely pathogenic variants in a third of a cohort of 46,XY patients (10). We have therefore proposed a shift in the diagnostic approach to DSD to use WES as a first-line clinical test, which could lead to faster and more accurate diagnosis, and orient further clinical management, limiting unnecessary, costly, and often invasive endocrine testing and imaging (2). However, many remain unexplained (over half of the XY cases, a significant minority of XX cases, including most ovotesticular DSD, and most syndromic cases). In addition, the very large phenotypic variability in cases with known variants in the same gene is unexplained. We propose that the of use whole-genome sequencing will dramatically improve upon exome sequencing, covering both coding and non-coding parts of the genome more uniformly, as an approach to not only improve diagnostic yield, but also to identify novel genes and regulatory elements involved in DSD.

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Long-acting Growth Hormone Formulations: Structure and Activity

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Human growth hormone (hGH) has been available as a therapeutic agent since the middle of the 1950's (1). It is a 191 amino acid single chain peptide and was obtained from human pituitaries because animal growth hormones are inactive in primates (species specificity). For children, the main activity is to stimulate height velocity. In addition in children and those at adult height, hGH has extensive metabolic activities in part by the generation of insulin-like growth factor 1 on protein, carbohydrate, and adipose tissue.

Since the mid-1980's, virtually all hGH preparations have been biosynthetic, yielding a much greater supply and avoiding the prospect of Creutzfeldt-Jakob disease (2). Daily administration is quite non-physiologic, for it does not mimic the pulsatile nature of the secretion of hGH. It has a half-life of approximately 3.4 hours after subcutaneous injection. Daily administration of recombinant (r)hGH remains inconvenient for it may be painful and distressing to some patients. This may lead to non-compliance with reduced efficacy and thus increased health costs.

Long-acting endocrine drug formulations have long been part of the armamentarium of endocrinologists, for example, gonadotropin-releasing hormone agonist analogs, testosterone, medroxyprogesterone acetate, hCG (as long-acting luteinizing hormone), and multiple analogs of insulin. Pharmaceutical companies have used various strategies to lengthen the plasma half-life (and activity) of the native rhGH or an analog of it (3).

- Depot formulations with rhGH encapsulated in a biodegradable polymer or micro-particles of rhGH dispersed in a biodegradable polymer,

- PEGylation (PEG) specific site long chain polymers of PEG added to the native molecule,

- Pro-drug rhGH transiently bound to a PEG carrier with self-cleaving linker; a point mutation in rhGH to which a long chain with a terminal fatty acid is added. The latter interacts non-covalently with albumin,

- Fusion proteins: examples include hydrophilic amino acid tails (XTEN), the C-terminal peptide of hCG (CTP), albumin itself and several with immunoglobulin fragments.

Pharmaceutical agents in all classes are in at least phase 1 trials with many in phases 2 and 3 for children and adults.

Preliminary data indicate height velocities comparable to those noted with equivalent doses of rhGH obtained from the two very large registry data bases-National Cooperative Growth Study and Kabi International Growth Study. Each preparation appears safe and efficacious with a hint of less decline in height velocity in the second and perhaps third years as previously noted in virtually all studies with rhGH over 3 decades.

Virtually all agents require pivotal phase 3 studies before acceptance by the regulatory authorities. Given that the profiles (pharmacokinetic and pharmacodynamic) are even less "physiologic" than for daily therapy with rhGH and have addition biological material, long-term safety studies are mandatory.

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The Genetics of Growth and Growth Disorders: From the Hypothalamus to the Epiphysis

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At least 423 common variants with low effect size have been identified by genome-wide association studies (GWAS) to have an effect on height in normal range. Mutations in >130 genes have been found in patients with short stature and in 16 with overgrowth (1,2). The SHOX gene appears to be the "master controller" of human height. Rare deleterious gene mutations affecting height have been described throughout the growth hormone-releasing hormone (GHRH)- GH- insulin-like growth factor-1 (IGF-I) pathway (3), involving the GHRH receptor, pituitary-specific transcription factors, GH, the GH receptor (Laron syndrome), post-GH receptor JAK/STAT signaling (STAT5B), IGF-I, and the type 1 IGF (IGF-1) receptor. More recently, studies have concentrated on investigations of target tissue defects involving the endochondral growth plate and its hormonal regulators. The schema below (4) has been developed in which various growth plate-centered genes have been linked to severe and mild forms of short stature, as well as to tall stature, depending on whether mutations are homozygous or heterozygous, and whether they are inhibitors (red) or activators (green) of protein regulation. With increased identification of genes that regulate growth, the number of cases of "idiopathic short stature" will inevitably decrease.

Gene/ Pathway	Severe short stature	Mild short stature	Tall stature
FGFR3	Achondroplasia, hypochondroplasia, thanatophoric dwarfism	ISS	CATSHL (camptodactyly, tall stature, and hearing loss) (AD)
SHOX	Langer mesomelic dysplasia	Leri-Weill dyschondrosteosis, isolated SHOX deficiency, Turner syndrome	Klinefelter syndrome Triple X syndrome XYY syndrome
FBN1	Acromicric dysplasia, Weill-Marchesani syndrome, Geleophysic dysplasia		Marfan syndrome (AD)
NPR-2	Acromesomelic dysplasia, Maroteaux type (AR)	Non-syndromic ISS (AD)	Tall stature, scoliosis, arachnodactyly, long hallux (AD)
Ras-MAPK	Noonan, LEOPARD, Costello, NF1-Noonan, cardiofaciocutaneous syndromes		Sotos syndrome

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Turner Syndrome: Care Through the Ages

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Turner syndrome, the complete or partial absence of one of the X chromosomes, occurs approximately in 1:2,000 live born girls. Its most common signs and symptoms include short stature, gonadal dysgenesis, dysmorphic features with a wide range of disorders in multiple organ systems, especially the heart and lymphatic system.

The genetics include complete loss of one of the X chromosomes and deletions or malformations in the short or long arms of an X chromosome. These alterations result in marked phenotypic variability among individuals. It is the abnormal X chromosome that is preferentially inactivated and some may have Y chromosome material. The phenotypic variability seemingly shows that the blood karyotype may not be representative of the genetic make-up of other tissues.

In utero, the Turner genotype is approximately 99% lethal, and Turner syndrome is the leading individual cause of spontaneous first trimester pregnancy loss. This leads to the hypothesis that those fetuses with the 45,X karyotype who survive to term represent an "elite" with a critical mass of 46,XX cells necessary for survival. This may be designated occult mosaicism. The diagnosis of Turner syndrome may be made *in utero* based on nuchal translucency, cystic hygroma, or left-sided cardiac anomalies.

In childhood, there is growth failure, the characteristic phenotypic features and in the adolescent, these characteristics plus delayed or absent pubertal changes (1,2). The diagnosis is usually made from a peripheral blood karyotype, but 30 to 100 cells should be counted to discover low order mosaicism. Short stature and skeletal system anomalies are mainly due to the absence of the second *SHOX* gene on the pseudoautosomal portion of the X chromosome. In addition, there may be significant psychological and educational issues with specific challenges in visual-motor skills, visual-spatial skills, and working memory. As the girls reach adolescent age, the issue of pubertal induction becomes prominent. Proper low doses of estrogen permit the timing of puberty at the physiologic time.

One of the points of concern is at the transition from pediatric to adult care and another through adulthood give the multisystem health concerns. The medical care for the emerging adult should be based upon an agreed upon and structured transition plan to include: endocrine, cardiology, hearing and ENT, the issues of infertility and gynecology as well as the aforementioned psychology and perhaps psychiatry (3). Screening for osteoporosis, cardiovascular disease, hypertension, and the metabolic syndrome as well as psychology are important (4,5). The screening should also include celiac disease, hypothyroidism, and types 1 and 2 diabetes mellitus given that the relative risks for each exceed four-fold that of the general population.

Medical care should be directed toward any of the conditions found on screening or a more in-depth evaluation of those difficulties found on screening. Fertility and family planning remains major issues in many young adults. There are now a number of options using artificial reproductive technology, but pregnancy may be problematic.

In summary, one should make the diagnosis of Turner syndrome as soon as possible, employ rhGH therapy early, consider multiple medical and educational issues, induce puberty at the physiologic time, and have lifelong surveillance for multiple medical and psychological issues.

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Efficacy and Safety of Long-Acting Gonadotropin Releasing Hormone Analogs

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Gonadotropin-releasing hormone analog (GnRHa) therapy is an efficacious treatment for suppressing pubertal progression in young patients with central precocious puberty (CPP), is considered standard-of-care for this indication, and results in improved height and psychosocial outcomes (1). However, usage of GnRHa's in children with early-normal and/or normally-timed but rapid tempo puberty lacks clear-cut efficacy in terms of height preservation/augmentation (2). While there has been concern that GnRHa therapy may be associated with increases in body mass index and decreases in bone mineral density, available long-term data do not support these or other long-term adverse consequences (3). However, there remain conflicting data on the long-term risk of polycystic ovarian syndrome in conjunction with CPP (3). Treatment with injectable GnRHa formulations does not appear to impair gonadal function after treatment cessation, with onset or return of menarche within 1-2 years of treatment cessation, and normal rates of fertility so far in limited long-term follow-up studies (4). Because of these limited available data from females in their late teens to adulthood regarding the impact of GnRHa therapy on fertility, a long-term study investigating fertility, fecundity, and health of offspring would be a valuable addition to our understanding of the safety of this class of drugs. The ability to compare differential results among types of GnRHa therapy used is limited by the depth of the published literature. Physiological effects after treatment discontinuation with histrelin, which has only been available in US to treat children with CPP for ~9 years, have not been fully evaluated, but clearly merit further assessment and we await results from a patient registry investigating long-term follow-up of girls with CPP treated with histrelin, which will evaluate time to menarche or resumption of menses. There are currently no long-term post-treatment follow-up data on 3-monthly depot leuprolide, and such data would also be of great value.

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Genetic Defects Affecting Adrenal Development

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As a center of the steroidogenesis of critical mineralocorticoids, glucocorticoids, and androgens, the adrenal glands (and specifically, the adrenal cortex) play important roles in salt-retention, metabolism, and sexual differentiation. Therefore, defects in the adrenal development and maturation process can result in adverse physiological effects after birth. While the extent of the factors involved in proper development of the adrenal glands has yet to be fully understood, a reliance on a correctly functioning hypothalamic-pituitary-adrenal axis has been established. Genetic disorders that interfere with this communication, in addition to disorders affecting the glands themselves, typically result in various degrees of "adrenal hypoplasia" characterized clinically by small and hypofunctional adrenals. While the incidence of these conditions is relatively rare, occurring in around 1:12,500 live births, studies on individuals presenting with the condition have allowed for the categorization of these defects into: 1) secondary defects affecting adrenocorticotropic hormone (ACTH) synthesis and release from the pituitary, 2) adrenal resistance to ACTH, and 3) primary genetic defects within the adrenals. A number of mutations found in transcription factors active in the developing pituitary, such as TBX19 have been demonstrated to result in defective pro-opiomelanocortin (POMC) synthesis, the ACTH precursor. Furthermore, mutations in the processing machinery of POMC, such as PC-1, can result in defective ACTH signaling to the developing adrenals. Defects in the ACTH receptor (*MC2R*) and accessory proteins can result in adrenal glands unresponsive to ACTH, leading to reduced synthesis of steroid hormones required for downstream developmental events (1). Finally, while their ligands have yet to be identified, mutations in orphan steroid nuclear receptor proteins such as the X-linked DAX-1 and autosomal inherited SF-1 present within the adrenals can result in adrenal insufficiency, hypogonadism, and defects in male sexual differentiation (2).

Adrenal hypoplasia may be syndromic, as exemplified with IMAGe syndrome, a constellation of symptoms including intrauterine growth restriction, metaphyseal dysplasia, adrenal hypoplasia, and genital anomalies (3,4). Interestingly, a specific cluster of mutations in the proliferating cell nuclear antigen-binding domain of the *CDKN1C* gene (otherwise shown to cause Beckwith-Wiedemann, an overgrowth syndrome) is responsible for IMAGe syndrome (5).

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Congenital Adrenal Hyperplasia: Consensus Guidelines and Beyond

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Despite recent guidelines from the Endocrine Society (1) and the Congenital Adrenal Hyperplasia Research, Education, and Support (CARES) Foundation (2,3), there remain many controversies in the diagnosis, management, and treatment of patients with congenital adrenal hyperplasia (CAH). Newborn screening (NBS) for 21-hydroxylase deficiency (21-OHD) is performed to avoid early salt-wasting crises, allow early diagnosis of simple-virilizing CAH in males, and reduce delay in sex assignment in severely virilized females. NBS programs are associated with a significant number of false-positive results most often due to infant illness and/or prematurity. Thus, it still remains unclear if the cost:benefit ratio is favorable. Genotyping individuals with CAH is fraught with error due to complexity of gene duplications, deletions, and rearrangements within chromosome 6p21.3.

To diagnose non-classic CAH (NCAH)/CAH after infancy, an early-morning serum 17-hydroxyprogesterone level is the screening test of choice in symptomatic individuals. If >200 ng/dL (6 nM), an adrenocorticotropic hormone stimulation is warranted to differentiate 21-OHD from other enzyme defects and to make the diagnosis in borderline cases. Genotyping in this situation may be helpful when results of the stimulation test are equivocal.

The glucocorticoid (GC) of choice for children is hydrocortisone (HC) in tablet form. For infants, tablets may be crushed, weighed, and mixed with a small amount of liquid and delivered immediately by medication syringe, rather than from bulk suspension preparations that deliver uneven doses. Prednisone and dexamethasone are sometimes useful in treating patients refractory to HC; however, routine chronic use of long-acting potent GCs in growing patients is not recommended. All treated patients should always wear or carry medical identification indicating adrenal insufficiency.

Patients should be regularly monitored for signs of GC excess, hyperandrogenism due to inadequate GC treatment, or hypertension from excess mineralocorticoid (MC) and/or sodium. Monitoring treatment should involve consistently timed hormone measurements. Endogenous adrenal steroid secretion should not be completely suppressed to avoid effects of overtreatment. There should also be regular monitoring of height, weight, and physical examination; and bone age x-ray (after age 2 years).

Clinical or subclinical aldosterone deficiency is said to exist in all forms of 21-OHD. Patients with elevated plasma renin activity (PRA) or reduced aldosterone:PRA ratio (may) benefit from fludrocortisone (FC) therapy and adequate dietary Na. Sensitivity to MC's may vary over time with recovery from salt-wasting in some patients, probably secondary to extra-adrenal 21-hydroxylation.

All GC-treated patients should be monitored for iatrogenic Cushing syndrome, including height and weight in children, distribution of body fat, presence of pigmented striae, blood pressure, and plasma glucose. Since osteopenia and osteoporosis are rare in pediatric CAH patients, routine evaluation of bone mineral density is discouraged unless clinically indicated. Adrenal nodules have been identified more frequently in CAH patients than in general population; however, routine adrenal imaging is not recommended.

NCAH is not generally considered an absolute indication for GC or MC replacement. Children with NCAH should be treated when they have inappropriately early onset and rapid progression of pubarche and/or bone age. Adolescent females with overt virilization or erratic menses may also benefit. Asymptomatic individuals with NCAH need not be treated. Moreover, previously treated NCAH patients should be given the option of discontinuing therapy when their symptoms resolve.

The GC dosage should be increased in stressful situations such as febrile illness (>38.5 °C), gastroenteritis with dehydration, surgery with general anesthesia, and major trauma. Increased GC doses should not be given for mental and emotional stress, minor illness, and before physical exercise. Stress doses of GC should not be given to patients with NCAH unless their adrenal function is suboptimal or iatrogenically suppressed.

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Premature Pubarche, Hyperinsulinemia, Hypothyroxinemia and Hyperintensities in Basal Ganglia: All Caused by a Single Congenital Defect

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Objective: Premature pubarche is the occurrence of pubic hair <8 years of age in girls and is mostly idiopathic but can be due to various virilising conditions such as congenital adrenal hyperplasia and androgen secreting tumours. To present two cases with premature pubarche and associated endocrine problems which have not been described previously.

Case: Two girls, presented 10 years apart with the same complaint of early pubarche at age 7 years, with inappropriately low dehydroepiandrosterone sulfate levels. In addition to hyperandrogenemia (elevated testosterone and androstenedione) and advanced bone age, both had hyperinsulinemia, hypothyroxinemia, and hyperintensities in basal ganglia. The 2nd case also had symptomatic hypoglycemia. Investigations revealed a common congenital defect explaining all these manifestations.

Conclusion: Pathogenetic mechanisms leading to all these manifestations will be discussed.

A Case Report of Xp21 Contiguous Gene Syndrome: Adrenal Hypoplasia Congenita, Glycerol Kinase Deficiency, and Duchenne Muscular Dystrophy

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Objective: X-linked adrenal hypoplasia congenita (AHC) is characterized by primary adrenal insufficiency caused by deletion or mutation of the DAX-1 gene and is frequently associated with hypogonadotropic hypogonadism. It can occur as a part of Xp21 contiguous gene syndrome together with glycerol kinase deficiency and Duchenne muscular dystrophy. We report a new subject with this rare disease.

Case: Twin male sibs at the ages of 30 days were hospitalized because of feeding difficulties, vomiting, and weight loss. Parents had no consanguinity and there was no family history of endocrine or renal diseases. One of the twins died in a few hours. Other patient's physical examination revealed that weight was 2100 g (his twin's was 1800 g) and body length 49 cm; blood pressure: 70/40 mm-Hg, heart rate: 140 beats/minute, respiratory rate: 50 breaths/minute, body temperature: 36 °C. He was dehydrated and lethargic. External genitalia were well developed with intrascrotal testes of 2 mL in volume. There was no skin hyperpigmentation. Laboratory findings were as follows: Na 97 mEq/L, K 5.1 mEq/L, adrenocorticotropic hormone (ACTH) >1250 pg/mL, cortisol 6 µg/dL (3-23), plasma renin activity: 50 ng/mL/hr (3-35), 17(OH)P 18 ng/mL (0.3-1.1), dehydroepiandrosterone sulfate: 24 µg/dL (5-111), luteinizing hormone: 0.71 mU/L (0,02-7), follicle stimulating hormone: 0.43 mU/L (0.16-4.1), total testosterone 0.76 ng/mL (0.7-4). After initial therapy for adrenal crisis, hydrocortisone and fludrocortisone were given at replacement doses. Ten days later, steroid hormone treatment was halted and ACTH stimulation test (250 µg) was performed. Peak levels of cortisol, 17(OH)P, and 11-deoxycortisol were 1.02 µg/dL, 3.11 ng/mL, and 3.2 ng/mL, respectively. This test excluded defects in steroid biosynthesis associated with salt-losing congenital adrenal hyperplasia. On ultrasound examination, adrenal gland could not been visualized. Therefore, a diagnosis of AHC was established. Furthermore, we investigated for contiguous gene syndrome. Serum creatinine phosphokinase [CPK, 9974 U/L, (N:35-195)] and triglyceride [TG, 439 mg/dL, (N:0-200)] levels were markedly elevated. On follow-up period of

9 months, his motor and mental development were noted to be delayed. Array comparative genomic hybridization analysis was planned to show Xp21 deletion syndrome.

Conclusion: Serum CPK and TG levels should be measured in all male patients who present with an adrenal hypoplasia. These simple tests may help early diagnosis and appropriate genetic counseling for next pregnancy.

Pseudohypoparathyroisidm Type 1a: A Case Report

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Objective: Pseudohypoparathyroidism (PHP) is a group of disorders characterized by end-organ resistance to the parathyroid hormone (PTH). PHP type 1a includes multi-hormone resistance syndrome, Albright's hereditary osteodystrophy, and obesity and is caused by mutations in GNAS exon 1 through 13. Characteristic features of disease are hypocalcemia, hyperphosphatemia, elevated PTH, obesity, round facies, and subcutaneous calcification. The disease is inherited from affected mother. On the other hand, pseudopseudohypoparathyroidism (PPHP) occurs if the mutation is paternally inherited. In PPHP, calcium and phosphorus levels are generally normal. In this report, we want to present a boy with PHP type 1a who has normal calcium and elevated thyroid stimulating hormone (TSH) levels, which is a rare event.

Case: The 12-10/12-year-old boy was admitted with the complaint of short stature. On physical examination, brachydactyly, round facies, and short neck were observed as well, indicating PHP 1a. However, serum calcium, phosphorus, alkaline phosphatase, vitamin D, and PTH levels were normal. These results were compatible with PPHP. On the other hand, TSH levels were found to be high (8 µIU/mL, normal range 0.5-4.8 µIU/mL), free thyroxine levels slightly low (0.7 ng/dL, normal range 0.8-2.3 ng/dL), urine iodine level normal, and thyroid antibodies to be negative. These features were compatible with PHP type 1a. Therefore, genetic analyses were performed and p.D826H (C2476G>C) heterozygous mutation was found in GNAS. The genetic analyses of parents revealed maternal inheritance. As far as we know, this mutation was not reported before and was found to be high risky for being a cause of the disease according to mutation taster and human splicing finder.

Conclusion: In this report, we want to emphasize that normocalcemia can be a finding of PHP type 1a.

A Diabetic Infant with Homozygous LRBA Mutation: The Youngest Patient Reported

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Objective: Autoimmune disorders such as thyroiditis, celiac disease, or Addison disease would develop in one third of patients with type 1 diabetes. However, severe immunodeficiency is rarely found in those patients. Lipopolysaccharide-responsive beige-like anchor protein (*LRBA*) deficiency has been identified as a primary immunodeficiency characterized by antibody deficiency, recurrent infections, autoimmunity, and lymphoproliferative disorders. Common symptoms are autoimmune cytopenias, enteropathy, and lymphocytic interstitial lung disease. To date, *LRBA* gene mutation was found in only several patients with early-onset diabetes.

Case: An 8-month-old baby girl was admitted to emergency service due to polyuria, polydipsia, and tachypnea. Her parents were third cousins. Her prenatal history was uneventful. Her birth weight was 2970 g. A history of candida dermatitis was noted. Exclusive breastfeeding was made in the first six months. All vaccines were administered according to the routine schedule. Motor development was normal. Laboratory investigation was consistent with diabetic ketoacidosis: blood glucose was 324 mg/dL, blood ketone 5.9 mmol, pH 7.07, and HCO3 8 mmol. C-peptide was 0.42 ng/mL, insulin 3.3 µIU/mL, and HbA1c 7.4%. Following appropriate treatment of diabetic ketoacidosis, breastfeeding was started along with subcutaneous insulin. Islet cell antibody, anti-glutamic acid decarboxylase, and anti-insulin antibody were negative. Thyroid function tests, cortisol, and adrenocorticotropic hormone were normal. Antiendomysial antibody was negative. At 13 months of age, she presented with high fever, nasal discharge, and loss of appetite followed by cough. Viral pneumonia and acute otitis media were diagnosed. She was discharged on the 8th day of therapy. No mutation was found in the most common genes associated with neonatal diabetes (*KCJN11*, *ABCC8*, and *INS*). Sanger sequencing of *LRBA* gene revealed a homozygous splicing mutation in intron 30: c.5172-2A>G. Her parents were heterozygous for this mutation. Lymphocyte subpopulation showed normal results as CD3+ 62.6%, CD19+ 29%, CD16/56+ 7.8%, CD3+/CD4+ 40.3 %, and CD3+/CD8+ 20.4%. Serum immunoglobulin (Ig) A level was 48 mg/dL, IgG 574 mg/dL, IgM 99 mg/dL and total IgE 6 IU/mL. Anti dsDNA and ANA were negative.

Conclusion: *LRBA* gene mutation is considered to be associated with early-onset diabetes in this infant. In addition, this patient is the youngest reported case with LRBA mutation and diabetes.

Idiopathic Hypogonadotrophic Hypogonadism Caused by Inactivating Mutations in *SRA1*

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Objective: What initiates pubertal process in humans and other mammals has remained elusive. We hypothesized that gene(s) taking roles in triggering human puberty may be identified by studying a cohort of idiopathic hypogonadotropic hypogonadism (IHH) cases via autozygosity mapping coupled with whole exome sequencing.

Case: Our studies revealed three independent families in which IHH/delayed puberty was associated with inactivating *SRA1* variants. *SRA1* was the first gene to be identified to function through its protein as well as noncoding functional ribonucleic acid products. These products act as co-regulators of nuclear receptors including sex steroid receptors as well as SF-1 and LRH-1, the master regulators of steroidogenesis. Functional studies with a mutant *SRA1* construct showed a reduced co-activation of ligand-dependent activity of the estrogen receptor alpha, as assessed by luciferase reporter assay in HeLa cells.

Conclusion: Our findings strongly suggest that *SRA1* gene function is required for initiation of puberty in humans. Furthermore, *SRA1* with its alternative products and functionality may provide a potential explanation for versatility and complexity of puberty.

A Novel Missense Mutation in *HSD17B3* Gene in Two 46,XY Siblings with Female External Gelitalia

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Objective: Deficiency of 17β-hydroxysteroid dehydrogenase type 3 (17β-HSD3), which catalyzes the synthesis of testosterone from Δ4-androstenedione and is encoded by *HSD17B3*, is a rare cause of 46,XY disorders of sex development (DSD). Up to now, over 30 mutations in HSD17B3 have been reported. To report two siblings with a novel mutation in *HSD17B3* gene leading to 17β-HSD3 deficiency.

Case: A 15-year-old female patient was referred because of primary amenorrhea and signs of virilization. The chromosome analysis showed a 46,XY karyotype. Hormonal evaluation revealed a high Δ4-androstenedione level with a low serum testosterone/androstenedione (T/A) ratio. A homozygous missense mutation in *HSD17B3* resulting in a premature stop codon (p.Y287) was found. Gonadectomy was performed after the molecular diagnosis and estrogen replacement therapy was initiated. Screening of relevant mutation was performed in remaining family members. The father, mother, and a sibling were heterozygous, while a 12-year-old sibling who was raised as a female was homozygous for the same mutation. Her karyotype was 46,XY as well. Hormonal evaluation revealed a high Δ4-androstenedione level with a low serum T/A ratio. Gonadectomy was performed and estrogen replacement therapy was initiated consequently.

Conclusion: We emphasize that 17β-HSD3 deficiency should be considered in virilized female patients at puberty if the T/A ratio is less than 0.8 and the molecular analysis should be performed in both index case and the family members for precise diagnosis and genetic counselling.