CARES Connections

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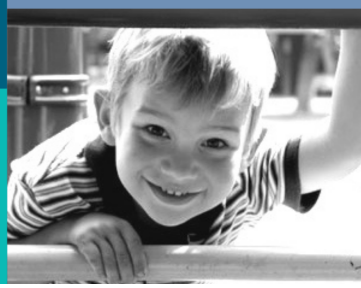
Improving health, connecting people, saving lives



In This Issue

Genetics of congenital adrenal hyperplasia and genotype-phenotype correlation

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Synthesis of adrenal steroid hormones and cortisol is mediated by five major enzymes whose impaired activity leads to the group of disorders called congenital adrenal hyperplasia (CAH). The five steroidogeneic enzymes are cytochrome P450 side chain cleavage enzyme encoded by the *CYP11A1* (cytochrome P450, family 11, subfamily A, member 1), 21 *a* hydroxylase (encoded by the *CYP21A2* gene: cytochrome P450 family 21 subfamily A member 2), 11 b hydroxylase (encoded by the *CYP11B1* gene: cytochrome P450, family 11, subfamily B, member 1), 3b-hydroxysteroid dehydrogenase 2 (encoded by the *HSD3B2* gene), and 17-hydroxylase/17, 20-lyase deficiency (encoded by the *CYP17A1* gene: cytochrome P450, family 17, subfamily A, member 1) (1-5).

This Views and Reviews centers on 21-hydroxylase deficiency CAH due to genetic defects in the CYP21A2 gene, with a focus on genotype-phenotype correlations. Pathophysiology and biochemical findings in CAH are discussed in this Views and Reviews section by Gomes et al. Depending on the degree of impairment of the 21-hydroxylase, three distinct phenotypes have been described: classical salt wasting, classical simple virilizing, and nonclassical CAH (6, 7).

Virilization of external genitalia in the female newborn, salt wasting (potentially fatal), rapid somatic growth, and skeletal maturation with a subsequent compromised adult height, precocious adrenarche and/or puberty, acne, hirsutism, irregular menses, and fertility concerns are all features of classical salt-wasting CAH. Patients with classical simple virilizing CAH present with similar features but with an intact mineralocorticoid pathway. The main distinctive clinical feature between classical and nonclassical CAH is the normal external genitalia in the newborn female with nonclassical CAH and the lack of genital ambiguity; patients with nonclassical CAH may present with mild features of hyperandrogenemia or may be asymptomatic (6, 7).

CYP21A2 GENE AND PSEUDOGENE

The *CYP21A2* gene is a 10-exon, 3.1 kb gene that is mapped on the short arm of chromosome number 6 within the major histocompatibility complex region (locus 6p21.31). The *CYP21A2* gene is specifically located within proximity of three other genes along a 730 kb region called the *RCCX* module. The three neighboring genes, *RP1*, *C4*, and *TNXB*, respectively, encode a nuclear serine/threonine protein kinase, which is the fourth complement system component, and an extracellular protein matrix called *Tenascin X* that is expressed in the skin, tendons, and blood vessels.

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A Message from the Executive Director

Dear Friend:

As I think back to December 31, 2019, I was excited about the year ahead. We were poised to celebrate CARES' 20th anniversary in style with a big Gala in Hollywood, walks across the country, and family events. However, 2020 had other plans for us all. Instead of a large gathering with fancy tuxedos and gowns, we held our Gala virtually in an intimate setting donning our 2020 uniforms (aka loungewear). In true CAH warrior fashion we made the best of it and enjoyed the heartfelt testimonials, entertainment and feeling of community as we "gathered" from coast to coast via the magic of Zoom. While it was not what any of us had anticipated, it created something special. Many who joined us had never attended a CARES Gala before, but because they did not need to travel or make special arrangements, were able to participate. We were able to connect with other people more deeply, seeing them gather around with close friends and family on their couches.

We have had to make other adjustments in 2020 – our Patient Education Conference this month, will also be held virtually. The same for our walks and other events. While we have faced many challenges, it has not all been negative. Our time in quarantine provided an opportunity for patients and parents to connect directly with some of our top experts over Zoom calls; participate in webinars from the comfort of their own homes and young patients connected with others during CARES Story Time.

We have been keeping our patients and families informed about COVID, medication shortages and considerations for sending kids back to school or adult patients back to work. Our fight to preserve surgical treatment options for patients has also continued despite COVID.

One of the highlights of 2020 was the addition of four new centers of excellence. With newly designated centers in New Jersey, Texas and Washington, patients and families now have greater access to the highest quality CAH care in the world.

While the future remains uncertain, our commitment to our patients is stronger than ever. With your support, we will embrace both the challenges and victories and continue to forge a better future for CAH patients.

RESEARCH continued from page 1

Tandem duplication, a well-established phenomenon of molecular evolution, may result in a mono-, bi-, or tri-modular RCCX module. The most common outcome of this tandem duplication is the bimodular RCCX module, RP1-C4ACYP21A1-TNXA/RP2-C4B-CYP21A2-TNXB.

The active gene encoding the 21-hydroxylase enzyme CYP21A2 and the inactive gene CYP21A1 "pseudogene" are highly similar, with 98% homology; 15 mutations render the CYP21A1 inactive. Four promoter region mutations —an intronic mutation,two frameshift mutations on exons 3 and 7, and eight single base pair missense mutations (on exons 1, 4, 7, three on exon 6, and two on exon 8)—comprise the 15 *CYP21A1*/ pseudogene mutations. Knowledge of these 15 *CYP21A1*/pseudogene mutations is vital to understanding the molecular pathophysiology of 21-hydroxylase deficiency CAH. Figure 1 demonstrates the CYP21A2 gene and its location within the RCCX module on chromosome). number 6. The location of the 15 *CYP21A1*/pseudogene mutations is also shown (7, 8).

MECHANISM OF MUTATIONS

Hundreds of *CYP21A2* disease-causing defects have been described to date, with gene conversions and deletions as the underlying mechanisms in the vast majority of cases. Other mechanisms, such as de novo mutations and uniparental disomy, have also been described (7).

Gene Conversions

Misalignment of sister chromatids during mitosis leads to exchange of genetic material between the CYP21A2 and CYP21A1. This results in transfer of CYP21A1/pseudogene mutations to the CYP21A2 gene. Pseudogene-derived CYP21A2 mutations are sometimes referred to as "common mutations" on commercial testing panels (7).

CYP21A1/Pseudogene-Derived Mutations

Four promoter region mutations (g.-103A>G, g.-110T>C, g.-113G>A, g.-126C>T). Present in the noncoding region of the CYP21 and associated with reduction of transcriptional activity to 20%.

Exon 1 mutation (g.89C>T [p.P30L]). A mild missense single base pair mutation associated with 40%-70% of 21-hydroxylase activity (9).

Intron 2 mutation (g.655C/A>G). Associated with aberrant slicing due to upstream activation of a splice acceptor site and <5% of 21-hydroxylase enzyme activity (6, 9).

Exon 3 mutation (g.707_714delGAGACTAC [p.G110fs]). A frameshift mutation associated with an eight base pair deletion, a premature termination codon, and complete loss of 21-hydroxylase enzyme activity (9).

Exon 4 mutation [g.999T>A (p.I172N)]. Associated with loss of the hydrophobic pocket and reduction of 21-hydroxylase enzyme activity to 2% (1, 6, 10).

Exon 6 mutations [g.1380T>A (p.I236N), g.1383T>A (p.V237E) and g.1389T>A (p.M239K)]. This triple mutation cluster always occurs together and is associated with a substrate-binding defect depleting the 21-hydroxylase enzyme activity to 0%. Of note, p.I236N and p.M239K do not appear to cause significant structural disruption if present alone; nevertheless, both always occur together in conjunction with the highly disruptive p.V237E (1, 9).

Exon 7 mutations [g.1683G>T (p.V281L)]. Another mild missense single base pair mutation that is associated with 20%-50% of 21-hydroxylase activity.

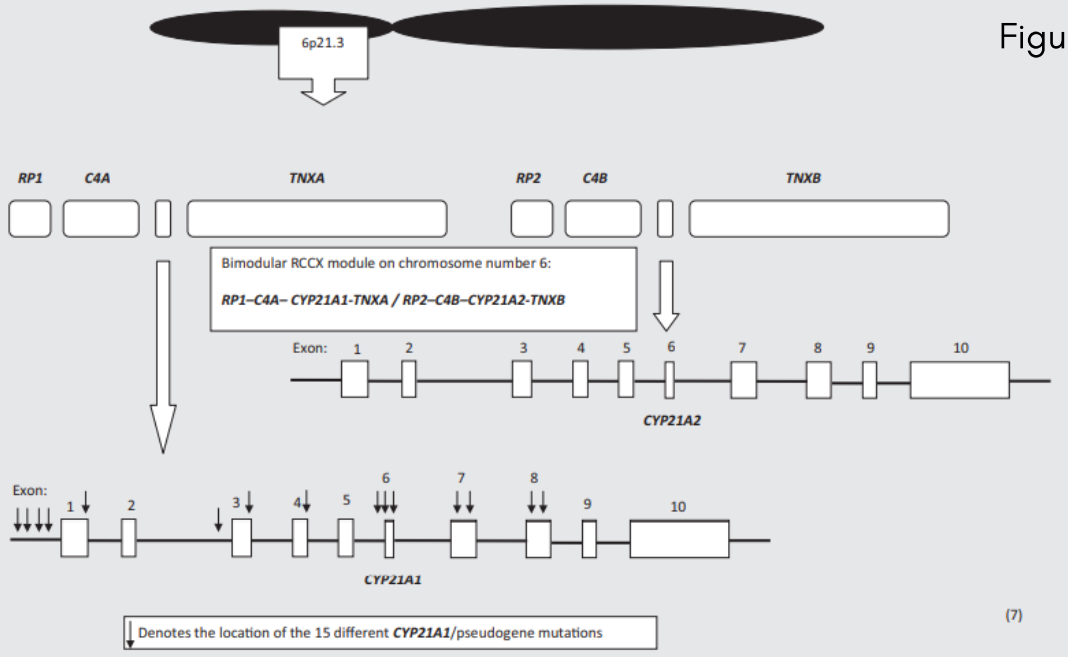
[g.1762_1763insT(p.L307fs)]. Another frameshift mutation but here associated with a single base insertion and premature termination codon associated with complete loss of 21-hydroxylase enzyme activity (9).

Exon 8 mutations [g.1994C>T (p.Q318X) and g.2108C>T(p.R356W)] Associated with disruption of H-bonding and loss of 21-hydroxylase enzyme (1).

Large Gene Deletion via Unequal Crossover

Misalignment of sister chromatids during meiosis and subsequent unequal crossover of genetic material of the RCCX module result in a chromatid with one RCCX module

Figure 1



The RCCM module: CYP21A2 and CYP21A1 gene with mutation sites.

Narasimhan. Genetics of congenital adrenal hyperplasia. Fertil Steril 2018.

(monomodular) and another chromatid with three RCCX modules (trimodular). The effect of this misalignment and unequal crossover is determined by the site of crossover. Crossover can happen at the C4, CYP21, or TNX genes, with three different resultant chimeras (7).

A simplified demonstration of the three possible scenarios and the resultant chimeric hybrids for the possible crossover sites is shown in Figure 2.

The first possible scenario (crossover site is C4) results in a trimodular RCCX chromatid with one CYP21A2 copy and two CYP21A1 copies (inheritance of this allele does not carry a risk for CAH due to the presence of an intact CYP21A2 copy) (11) and a monomodular RCCX chromatid with one CYP21A2 copy and a functional C4A/C4B chimera (inheritance of this allele does not carry a risk for CAH due to the presence of an intact CYP21A2 copy) (7). Thus, crossover at C4 does not result in 21-hydroxylase deficiency CAH because each chromosome will ultimately harbor an intact CYP21A2 (7).

The second possible scenario (crossover site is TNX) results in a monomodular RCCX chromatid with a deleted CYP21A2 and one CYP21A1 copy (clearly, inheritance of this allele is associated with risk for CAH) (11) and a trimodular RCCX chromatid with two CYP21A2 copies and one CYP21A1 copy (inheritance of this allele does not carry a risk for CAH due to the presence of an intact CYP21A2) (7). Thus, crossover at TNX may result in 21-hydroxylase deficiency CAH if the offspring inherits the chromosome with the deleted CYP21 (7).

The third possible scenario (crossover site is CYP21) re-sults in a trimodular RCCX chromatid with one CYP21A2 copy, one CYP21A1 copy, and a CYP21A1CYP21A2 chimera (inheritance of this allele does not carry a risk for CAH due to the presence of an intact CYP21A2) (11) and a monomodular RCCX chromatid with a CYP21A1CYP21A2 chimera (because CYP21A1CYP21A2 harbors mutations, the inheritance of this allele is associated with risk for CAH). Nine different junction sites result in nine different CYP21A1CYP21A2 chimeras, each of which will harbor CYP21A1 mutations (7).

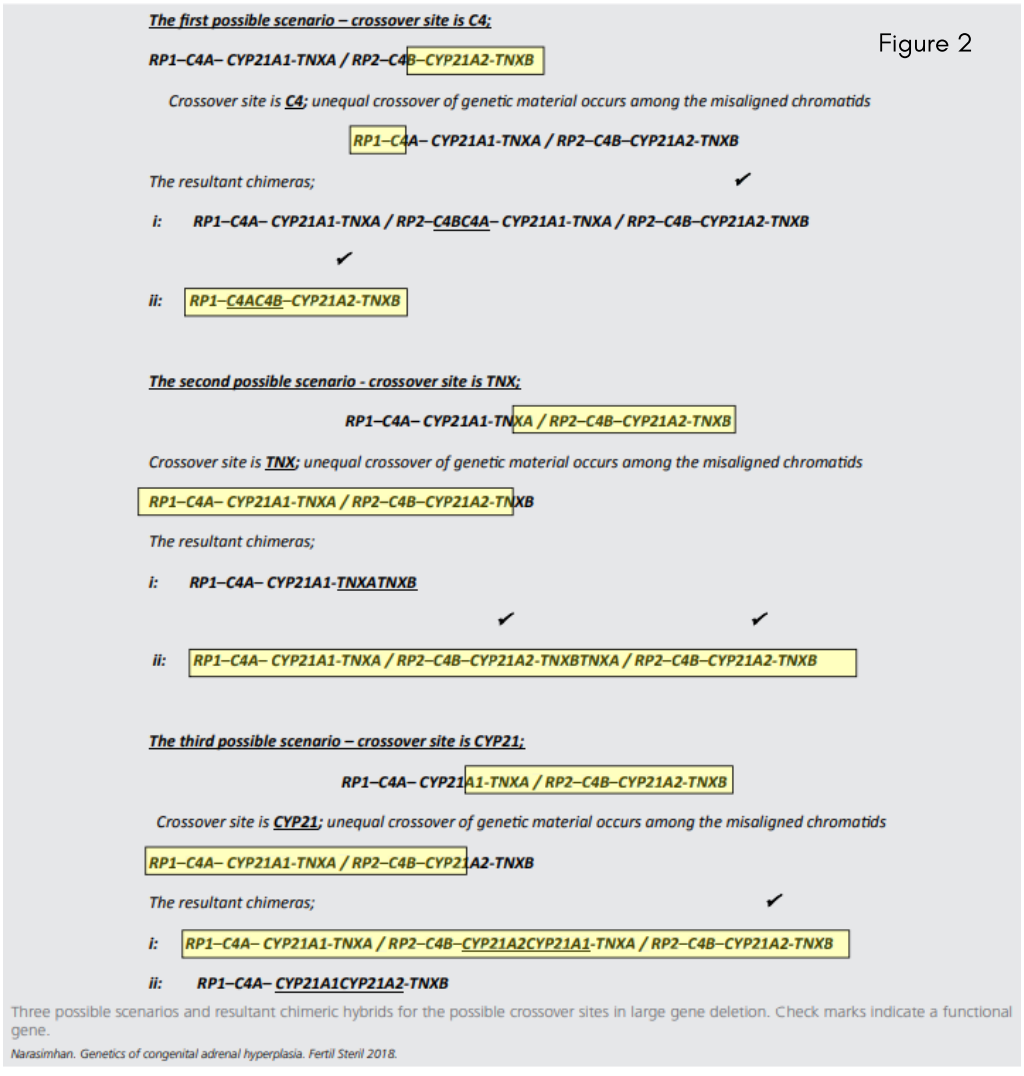


Figure 2

Three possible scenarios and resultant chimeric hybrids for the possible crossover sites in large gene deletion. Check marks indicate a functional gene.

Narasimhan. Genetics of congenital adrenal hyperplasia. Fertil Steril 2018.

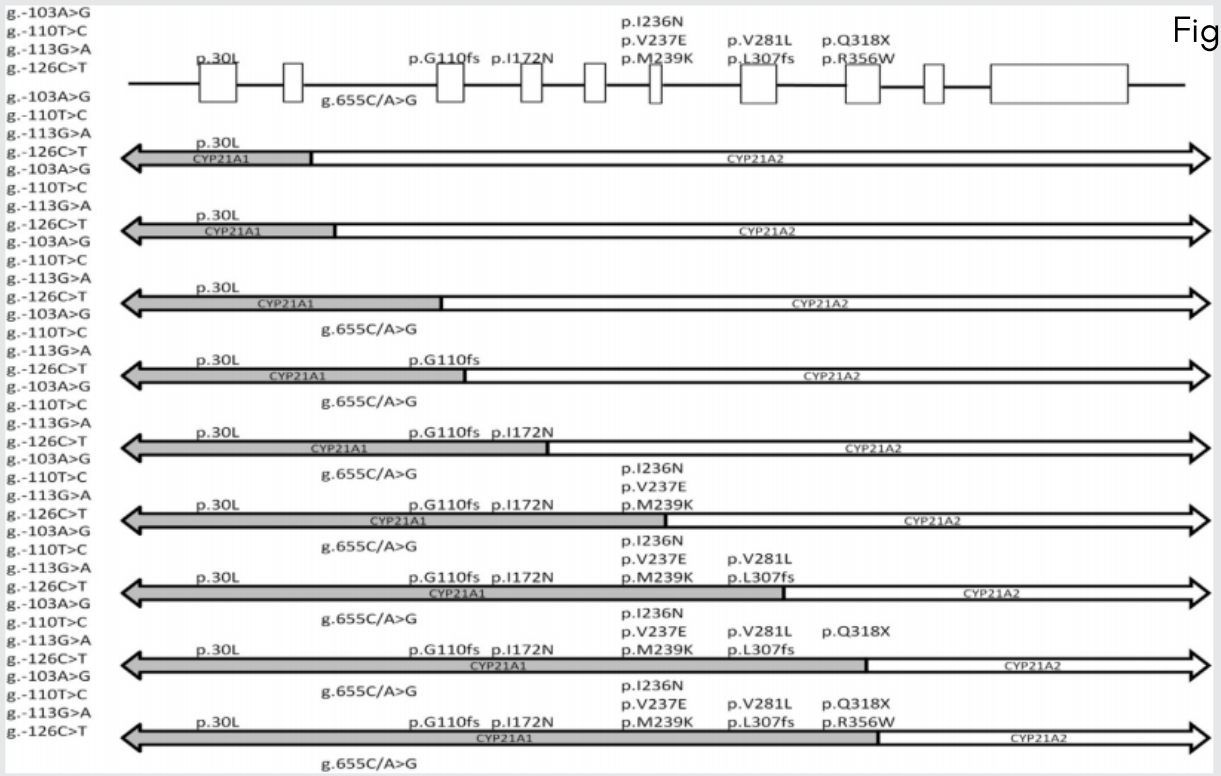
Figure 3 shows the nine possible CYP21A1CYP21A2 chimeras with the respective mutations. CYP21A1(pseudogene) and CYP21A2 are denoted by gray and white arrows, respectively.

GENOTYPE-PHENOTYPE CORRELATION IN CAH AND THE CLINICAL RELEVANCE

In addition to pseudogene-derived mutations, which are believed to account for more than 90% of mutations in the CYP21A2 gene, hundreds of other mutations associated with different disruptive effects have been reported. Of the pseudogene-derived mutations, promoter region mutations exon 1 (p.P30L) and exon 7 (p.V281L) are usually associated with nonclassical CAH. Exon 3 (p.G110fs), exon 4 (p.I172N), exon 6 cluster mutation (p.I236N) (p.V237E) and (p.M239K), exon 7 (p.L307fs), exon 8 (p.Q318X) and (p.R356W), and intron 2 G (g.655C/A>G) are associated with an expected clinical phenotype of classical CAH and female genital ambiguity (1, 6).

Variability in phenotype has been described with p.P30L, intron 2 G, and p.I172N mutations. A clinical phenotype of classical CAH has been associated with p.P30L in about 30% of cases; simple virilizing CAH has been associated with intron 2 G in 20% of cases; and salt-wasting CAH has been associated with p.I172N mutations in 25% of cases (7).

Figure 3



Nine different CYP21A1CYP21A2 chimeras with the respective mutations that result when the crossover site is CYP21.

Narasimhan. Genetics of congenital adrenal hyperplasia. Fertil Steril 2018.

The autosomal-recessive nature of inheritance is well established in CAH, with the allele harboring the less severely affected mutation determining the phenotype. For patients to manifest classical CAH, they have to possess two classical CAH mutations on each of the maternally and paternally inherited CAH allele. Patients who inherit a mutation known to be associated with nonclassical CAH and another mutation associated with classical CAH will be expected to manifest
nonclassical CAH and so on (1, 6, 7, 12).

The postnatal diagnosis of CAH is established on clinical grounds via biochemical testing and genetic confirmation. The risk of CAH in the fetus is 1 in 4 when the expectant couple are both carriers. Although amniotic fluid testing for biochemical markers has been used to diagnose a fetus with CAH, current diagnostic practices involve amniotic fluid/chorionic villous tissue sampling for CYP21A2 genotyping. Further management of an affected pregnancy, which is discussed in detail by Simpson et al. in this Views and Reviews section, is usually based on the genotype of the fetus. When couples who are carriers for CYP21A2 mutations already have an affected child (a proband), the clinical phenotype associated with their combination of mutations will be known. In the absence of a proband in the family, the counseling team relies solely on genetic data and established phenotypic correlations for prenatal diagnosis of CAH. This calls for an accurate correlation between the genotype and phenotype in CAH (7, 12).

An extensive genotype-phenotype correlation in 1,507 patients with CAH has been published recently by New et al. (6). Unfortunately, genotype-phenotype discordances exist, some of which are explained. An example of an unexplained genotype-phenotype discordance is from a report of a patient who was homozygous for the exon 7 (p.V281L) mutations and had a clearly expected phenotype of nonclassical CAH manifesting with clinical features consistent with salt-wasting CAH (1, 6).

Duplication Silencing a Mutation

The exon 8 mutation (p.Q318X) is known to be associated with a phenotype of salt-wasting CAH but is frequently associated with duplication in the CYP21A2 gene. The duplication results in an allele that carries an intact CYP21A2 gene and a mutated one (the disruptive effects of the p.Q318X mutation are hence muted). In 2013, Lekarev et al. reported a case of erroneous prenatal diagnosis of CAH that was finally explained after the duplication was discovered; this pregnancy was unnecessarily treated with dexamethasone to prevent falsely anticipated genital ambiguity in the fetus (13).

The Extent of the Deletion

The most commonly encountered CYP21A2, a 30 kb deletion, is known to be associated with classical CAH. An "attenuated form" of the deletion, which spares mutations downstream of the intron 2 splice site, is thought to be associated with less severe disease because the hybrid CYP21A1CYP21A2 chimera will only harbor the promotor region mutations (with secondary impairment of transcriptional activity) and the exon 1 mutation (associated with nonclassical CAH) (14,15).

Of note, deletions of CYP21A2 that extend into TNXB result in a "contiguous gene syndrome" consisting of classical CAH and Ehler-Danlos syndrome (8). Siblings with identical CYP21A2 mutations have shown phenotypic variability indicating the involvement of

other genes in the clinical spectrum of CAH (16).

In summary, the established genotype-phenotype correlation in CAH continues to display discordances. The diagnosis and treatment of patients with CAH must account for hormonal and clinical evidence in addition to genetic confirmation. Physicians providing anticipatory guidance during management of at-risk pregnancies and preconceptional counseling must always account for genotype-phenotype discordances in CAH.

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REFERENCES -

1. Haider S, Islam B, D'Atri V, Sgobba M, Poojari C, Sun L, et al. Structurephenotype correlations of human CYP21A2 mutations in congenital adrenal hyperplasia. Proc Nat Acad Sci U S A 2013;110:2605-10.
2. Khattab A, Haider S, Kumar A, Dhawan S, Alam D, Romero R, et al. Clinical, genetic, and structural basis of congenital adrenal hyperplasia due to 11beta-hydroxylase deficiency. Proc Nat Acad Sci U S A 2017;11:E1933-40.
3. Simard J, Rheaume E, Sanchez R, Laflamme N, de Launoit Y, Luu-The V, et al. Molecular basis of congenital adrenal hyperplasia due to 3 betahydroxysteroid dehydrogenase deficiency. Mol Endocrinol 1993;7:716-28.
4. Picado-Leonard J, Miller WL. Cloning and sequence of the human gene for P450c17 (steroid 17 alpha-hydroxylase/17,20 lyase): similarity with the gene for P450c21. DNA 1987;6:439-48.
5. Meimaridou E, Hughes CR, Kowalczyk J, Chan LF, Clark AJ, Metherell LA. ACTH resistance: genes and mechanisms. Endocr Dev 2013;24:57-66.
6. New MI, Abraham M, Gonzalez B, Dumic M, Razzaghy-Azar M, Chitayat D, et al. Genotype-phenotype correlation in 1,507 families with congenital adrenal hyperplasia owing to 21-hydroxylase deficiency. Proc Nat Acad Sci U S A 2013;110:2611-6.
7. New MI, Lekarev O, Mancenido D, Parsa A, Yuen T. Chapter 3A—Congenital adrenal hyperplasia owing to 21-hydroxylase deficiency. In: New MI, Lekarev O, Parsa A, Yuen TT, O'Malley BW, Hammer GD, editors. Genetic steroid disorders. San Diego: Academic Press; 2014:29-51.
8. Miller WL, Merke DP. Tenascin-X, congenital adrenal hyperplasia, and the CAH-X syndrome. Horm Res Paediatrics 2018;89:352-61.
9. White PC, Speiser PW. Congenital adrenal hyperplasia due to 21-hydroxylase deficiency. Endocr Rev 2000;21:245-91.
10. Tusie-Luna MT, Traktman P, White PC. Determination of functional effects of mutations in the steroid 21-hydroxylase gene (CYP21) using recombinant vaccinia virus. J Biol Chem 1990;265:20916-22.
11. Rafii S, Butler JM, Ding B-S. Angiocrine functions of organ-specific endothelial cells. Nature 2016;529:316.
12. New MI, Tong YK, Yuen T, Jiang P, Pina C, Chan KC, et al. Noninvasive prenatal diagnosis of congenital adrenal hyperplasia using cell-free fetal DNA in maternal plasma. J Clin Endocrinol Metab 2014;99:E1022-30.
13. Lekarev O, Tafuri K, Lane AH, Zhu G, Nakamoto JM, Buller-Burckle AM, et al. Erroneous prenatal diagnosis of congenital adrenal hyperplasia owing to a duplication of the CYP21A2 gene. J Perinatol 2013;33:76-8.
14. L'Allemand D, Tardy V, Gruters A, Schnabel D, Krude H, Morel Y. How a patient homozygous for a 30-kb deletion of the C4-CYP 21 genomic region can have a nonclassic form of 21-hydroxylase deficiency. J Clin Endocrinol Metab 2000;85:4562-7.
15. Concolino P, Costella A. Congenital adrenal hyperplasia (CAH) due to 21-hydroxylase deficiency: a comprehensive focus on 233 pathogenic variants of CYP21A2 gene. Mol Diag Ther 2018;22:261-80.
16. Khattab A, Yuen T, Al-Malki S, Yau M, Kazmi D, Sun L, et al. A rare CYP21A2 mutation in a congenital adrenal hyperplasia kindred displaying genotypephenotype nonconcordance. Ann N Y Acad Sci 2016;1364:5-10.

Neurocrine BIOSCIENCES

Neurocrine Biosciences Partners with the CAH Community to Develop a New Treatment Option for Classic CAH

by Eiry W. Roberts, M.D.

Neurocrine Biosciences is committed to developing a therapy for adults and children living with classic congenital adrenal hyperplasia (CAH). We recognize that science alone is not enough - that's why we're partnering with patients, caregivers and healthcare professionals in the CAH community to better understand this genetic disorder and the long-term experience of people who are living with this disease.

CAH is a complex and potentially life -threatening condition that is often difficult to manage with limited treatment options. Patients with CAH currently receive higher than replacement doses of glucocorticoids that, over the long-term, can lead to serious side effects, including bone loss, metabolic problems, and (in children) growth impairment. Furthermore, most patients are still unable to achieve hormonal balance.

We believe that patients with CAH deserve options for their care. Our team is focused on evaluating a study medication that may manage the high androgen levels that occur in CAH, while also allowing reduction in the amount of glucocorticoids that need to be taken every day.

Crinecerfont is an investigational, oral, non-steroidal corticotropin-releasing factor type 1 (CRF1) receptor antagonist we are developing for the potential treatment of classic CAH. Research suggests that lowering adrenocorticotropic hormone (ACTH) and androgen levels by blocking the CRF1 receptor may decrease the release of ACTH, which in turn decreases the production of adrenal steroids, including androgens. This could potentially reduce the doses of glucocorticoids that patients must take for their condition.

We have worked closely with the CAH community to develop our clinical program for crinecerfont, which includes studies in adults and adolescents. In June 2020, we reported the results of our Phase II study in adults with classic CAH. The data demonstrated that crinecerfont produced reductions in three disease hormone markers, including ACTH and the main adrenal androgen, androstenedione. In the study, crinecerfont was well tolerated with no serious adverse events reported related to crinecerfont.

Developing treatments for rare conditions like CAH, which affect relatively small populations, can be challenging, but we are fortunate to be partnering with CARES Foundation to raise awareness of our clinical program and encourage CAH patients to inquire about our clinical trials. In this second half of 2020, we have initiated a Phase III study of crinecerfont in adults with classic CAH. In addition, enrollment is proceeding in our Phase IIa study in adolescents with classic CAH.

The participation of the patient community in CAH clinical trials is critical to advancing the next generation of innovative treatments. If you are living with CAH or care for an adolescent with CAH, please visit these links to find out whether you or your loved one qualify to be a part of our clinical program: **www.cahtalyststudy.com, www.CAHlibratePediatricStudy.com**, and **www.clinicaltrials.gov.**

For more information about crinecerfont, visit **neurocrine.com**

Eiry W. Roberts, M.D., was appointed Chief Medical Officer in January 2018 and is responsible for all clinical development and medical affairs activities at Neurocrine. Dr. Roberts has over 25 years of research and development experience in the pharmaceutical industry across all phases of drug development from research through commercialization in multiple therapeutic areas, including neuroscience, inflammation, oncology and metabolic diseases.

The CAHtalyst clinical research study will evaluate the safety and efficacy of crinecerfont in lowering the high glucocorticoid doses that patients with classic congenital adrenal hyperplasia (CAH) often need to control high androgen levels. Neurocrine Biosciences is working with 65 centers throughout the world to enroll 165 patients in an 18-month study including a 6-month double-blind, placebo-controlled period followed by 12 months of open-label treatment. You may be eligible to participate in the CAHtalyst study if you are a least 18 years old, have a medically confirmed diagnosis of classic 21-hydroxylase deficiency CAH, are currently taking a glucocorticoid medication and are not pregnant or breastfeeding. For more information go to https://www.cahtalyststudy.com/

LIFE WITH CAH Study

Life with Congenital Adrenal Hyperplasia Study Group

Earlier in the year, we completed the online **Life with CAH Study.** This has been an exciting collaboration between the CARES' Centers of Excellence at Riley Hospital for Children at Indiana University Health (Indianapolis, IN), Children's Hospital Los Angeles and Keck School of Medicine, University of Southern California (Los Angeles, CA), Komansky Children's Hospital, New York Presbyterian Hospital, Weill Cornell Medicine (New York, NY) and Cohen Children's Medical Center of New York and Zucker School of Medicine at Hofstra/ Northwell (Lake Success, NY).

The goal of the Life with CAH Study was to answer several questions identified by people living with CAH as both important and needing more research. We anticipate a dozen important publications to be coming from this effort. Among others, we are looking at experiences with stress dose steroid use, finding out what worries people about CAH at different stages of life and how to talk about surgery with your daughter. We hope this research effort will help improve the care of people with CAH.

Thank you to the hundreds of individuals who participated, both men and women with CAH as well as parents!

The first paper has just been accepted for publication to the Journal of Pediatric Urology: "Majority of females with a life-long experience of CAH and parents do not consider females with CAH to be intersex." The study found that the majority of females with CAH (90%) and parents of females with CAH (96%) living in the United States believe CAH should be excluded from the intersex designation, and should be considered separately in legislation pertaining to childhood genital surgery.

- Konrad Szymanski, MD MPH, on behalf of the Life with Congenital Adrenal Hyperplasia Study Group

NEW TREATMENT ANNOUNCED!

Eton Pharmaceuticals announces FDA Approval of Orphan Drug **ALKINDI® SPRINKLE** (hydrocortisone) as replacement therapy in pediatric patients with adrenocortical insufficiency.

ALKINDI SPRINKLE is the first and only FDA-approved granular hydrocortisone formulation for the treatment of adrenocortical insufficiency specifically designed for use in children. "*The FDA approval of ALKINDI SPRINKLE is a breakthrough for patients and caregivers treating pediatric adrenocortical insufficiency. We are excited to offer an FDA-approved product that enables low dosing and administration of hydrocortisone to pediatric patients,*" said Sean Brynjelsen, CEO of Eton Pharmaceuticals. *"We look forward to making the product available to patients in the coming months."*

The FDA approval of ALKINDI SPRINKLE was supported by six clinical studies, including the first and only interventional Phase III study of oral hydrocortisone for Pediatric AI in neonates to children under eight years of age. Prior to the approval of ALKINDI SPRINKLE, oral hydrocortisone was only FDA-approved in tablet formulations of 5mg and stronger. Many pediatric patients require significantly lower doses and the flexibility of precision titration. ALKINDI SPRINKLE will be available in 0.5mg, 1mg, 2mg, and 5mg strengths, allowing clinicians greater flexibility to individualize dosing based on each patients' needs in accordance with the instructions for dosage and administration.

About Pediatric Adrenocortical Insufficiency

Pediatric adrenocortical Insufficiency (AI) is a rare disease characterized by an inability to synthesize and release cortisol, and sometimes aldosterone. This causes excessive androgens (abnormal sexual development in females, premature puberty, premature growth termination and short stature). The most common form of pediatric AI is Congenital Adrenal Hyperplasia (CAH), which is caused by a genetic defect. Patients with primary or central (secondary and tertiary) AI lack appropriate levels of cortisol in their system. Diminished cortisol in the system may result in deadly consequences like adrenal crisis. To survive, patients with AI must replace the missing cortisol daily. Eton estimates that pediatric AI effects between 5,000 and 11,000 children in the United States.

About ALKINDI SPRINKLE

ALKINDI SPRINKLE is an immediate -release oral hydrocortisone granule preparation that has been specifically designed to meet the dosing needs of pediatric patients with adrenocortical insufficiency. Prior to ALKINDI SPRINKLE's approval, parent caregivers had to cut or split higher strength hydrocortisone tablets to achieve the lower doses required for small children, which could result in inaccurate dosing. Taste-masking excipients that are acceptable for pediatric use eliminate the bitter taste of hydrocortisone. ALKINDI SPRINKLE has a shelf life of three years at ambient temperature and does not require refrigeration.

For more information, visit: https://alkindisprinkle.com/

spruceBIOSCIENCES

CAHMELIA 203 204

CARES Foundation is excited to share that the CAHmelia 203 clinical study is now open to screening adult patients (18+) with classic CAH due to 21-hydroxylase deficiency.

The CAHmelia trials are designed to evaluate tildacerfont, a new investigational non-steroidal oral medication for the treatment of classic CAH. Tildacerfont is being investigated to evaluate the efficacy and safety in normalizing adrenal hormones, improving clinical symptoms and reducing the burden of steroids in CAH management. To learn more, and/or to determine if you qualify for CAHmelia 203 clinical study, go to [CAHstudy.com.](CAHstudy.com)

CAHmelia Webinar

We are inviting classic CAH patients/parents to join the Spruce Biosciences team on a webinar on Tuesday, November 17, at 8pm EST/5pm PT to learn about the **CAHmelia** trials for individuals living with classic CAH. This event will largely benefit young adults with CAH.

The Spruce team will present an overview of the trials, the screening process and how to connect with the resource team that is in place to assist those individuals living with CAH with evaluation and enrollment. There will also be an opportunity to submit moderated questions via the webinar platform.

There is no charge to attend this informational webinar but registration is required.

Please email **Odaly@caresfoundation.org** if you would like to take part in this important informational session. **Must respond by November 16.**

MEDICATION SHORTAGE UPDATE

Throughout the year, CARES has kept the CAH community apprised of information regarding shortages of hydrocortisone. We often hear reports of patients having trouble finding medication and in many cases trouble with insurance not paying for their medication.

Here is the latest news from Pfizer regarding the availability of hydrocortisone: the 5 mg tablets are again in stock, and not backordered. So every pharmacy should have it, or at least be able to get it from their wholesalers. As a reminder, the amount produced is the regular amount, not a decreased amount, no decreased production. However, lately we have seen increased demand - partly because many of the generic companies have pulled out of the market, so if demand stays higher than normal, there could be spotty shortages or backorders in a few weeks. There may be brief backorders so you should probably not wait to fill your prescriptions now. There is no change in the availability of the other tablet sizes.

PLEASE CONTINUE TO LET US KNOW IF you experience a medication shortage situation. **Email Dina@caresfoundation.org** and tell her What medication? Where you live? and What pharmacy you use? **IF** you are denied coverage for you medication by your insurance company. **Please email Dina@caresfoundation.org** and tell her Which medication? Where you live? What pharmacy you use? and with whom you have medical/prescription insurance?

EDUCATION

Our first-ever **Virtual Patient Education Conference** will take place on November 14, 2020 and will include many medical experts speaking on many different topics pertaining to CAH. Sessions include: Stress Dosing in CAH, Surgical Considerations in CAH, How to Discuss CAH with your Doctor, Optimal Nutrition for CAH, CAH Care: Transitioning from Pediatric to Adult, Fertility & Pregnancy in Women wit CAH, Women with NCAH, Males with CAH, Women with CAH & Romantic Relationships, and Life with CAH Children. Noted CAH healthcare professionals will also offer attendees an opportunity to ask questions on different discussion topics during the Q&A Panel. There will also be sessions offered on Act-o-vial injection training. **IT'S NOT TOO LATE TO REGISTER! USE THIS LINK:** https://caresfoundation.z2systems.com/eventReg.jsp?event=1200&

DEADLINE TO REGISTER NOV. 11!

About Gene Therapy

ASGCT American Society of Gene + Cell Therapy

Vectors 101
Vectors are essentially vehicles designed to deliver therapeutic genetic material, such as a working gene, directly into a cell.

Gene therapy is a way to treat a specific disease by introducing, removing, or modifying genetic material —DNA or RNA—inside of a person's cells. One common way that researchers have found to accomplish this is by using a vector.

Using Viruses
Vectors are typically derived from viruses, because viruses have proven to be very efficient at finding their way into cells. In order to make vectors safe to use, all of the viral genes are removed,

Continued on pg. 13

Continued from pg. 16

Dr Andreas Schedl, *"Differentiation of stem cells into adrenal organoids*", 50 000 € (AFM)
Congenital adrenal hyperplasia is a devastating disease that is caused by defects in one of the genes required for hormone production. Correcting the defective gene within adrenal stem cells represents a potential cure that would ensure continuous supply of functioning steroidogenic cells throughout life.

We are developing strategies to differentiate stem cells into adrenal cells with the long-term goal to transplant them into patients. During the past funding period we have identified conditions that direct cells into early adrenal cells, but the efficiency is still relatively low. Here we will further fine-tune conditions and test out transplantation in a model system to provide a proof of principle that this approach may in the future be suitable for clinical applications.

Pr Gary Hammer, *"Transcriptional programs involved in ACTH-induced hyperplasia - Implication of the transcription factor Hhex in adrenal differentiation and response to chronic hormonal challenges.*", 125 000 €
The adrenal pathology in CAH results from a combination of unrestrained cellular proliferation and dysfunctional steroid production. However, the rules that govern the normal coupling of these processes are not understood. New technology has enabled us to uncover novel cell populations within the adrenal. We have determined unique gene signatures of these populations at a single-cell level. We are now in the process of defining the rules underlying proliferation and differentiation programs in normal homeostasis and disease. We have identified HHEX as a new down-regulated target of ACTH restricted to zona fasciculata. We propose that its prolonged ACTH-dependent modulation contributes to aberrant differentiation in CAH. Using single -cell methods, we will examine transcriptional changes in the adrenal after ACTH exposure. In parallel, the analysis of a mouse model of HHex deficiency will determine the contribution of HHEX to ACTH-regulated programs in health and disease. This combined approach will improve our knowledge of CAH and adrenal deficiency.

FUN-RAISING!

CAH VIRTUAL AWARENESS WALKS 2020

Thanks to Covid, ALL of our CAH Awareness Walks went virtual. We started with a Zoom Kick-Off on October 16 and then "walked" with our Teams, friends & families to the finish line on November 2nd. Fundraising pages were created and Walk Chairs encouraged their followers to donate to CARES and help raise awareness of CAH by creating their own fundraising pages and even MORE TEAMS! ***We appreciate your generous support!***

FAMILY FUNDRAISERS

THE JAMES PARTY

March 1, 2020 was the date of the 7th Annual James Party, held at the Coronado Cays Yacht Club in beautiful Coronado, CA and hosted by Sue Baker Shirey in honor of her son James, who passed away unexpectedly, at the age of 14 in 2009 of complications from CAH.

This special event featured cocktails, silent and live auctions, music, laughs and a fantastic meal. The James Party raised $20,000 for CARES.

To Sue Shirey and her family, we extend our heartfelt gratitude for you outstanding efforts. Congratulations on another successful event!

On January 19, 2020, longtime CARES supporter, co-chair of our 2020 Gala, and CAH patient, Erik Bogaard,

Continued on pg. 12

Host, Sue Shirey

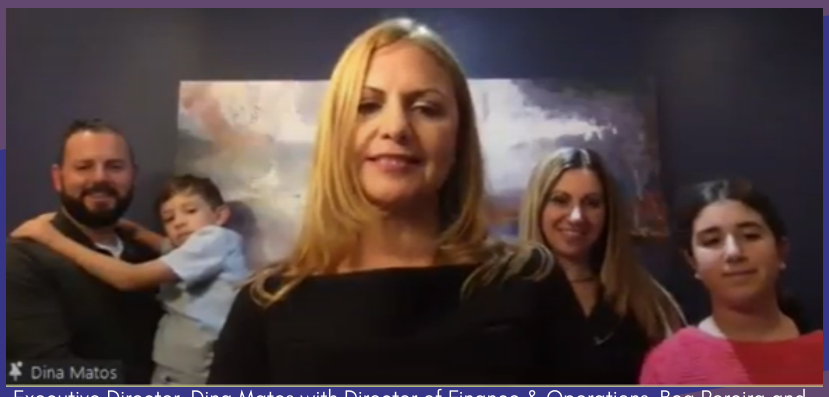
Board of Trustees Chair, Louise Fleming

Our FIRST-EVER VIRTUAL GALA

was a huge success, thanks to the Gala Committee chaired by Erik Bogaard and Ryan Hendler, our amazing host, Sue Shirey, our auctioneer, Ken Shirey and ALL of our dedicated CARES Community members! THANK YOU FOR YOUR SUPPORT!

The Gala was live-streamed via Zoom which allowed people from all over the country to participate. Viewers enjoyed musical entertainment, testimonials, a special 2020 CARES video, live and silent auctions. and more. Our silent auction was open before, during and after the live event as well.

Thanks to our production company, Jupiter Return, and to our DJ, Tatiana Alvarez for all of your hard work. And thanks to our vocal performers and dancers for sharing your talents with us: Anthony Paul, Yana Netreba, Brianna Nixon and Lara Bilgore.

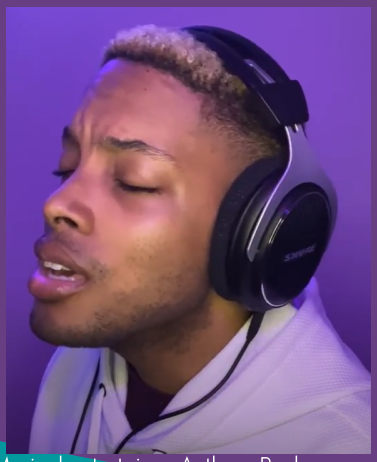


Executive Director, Dina Matos with Director of Finance & Operations, Bea Pereira and family

Auction Host, Ken Shirey

We would also like to take this opportunity to THANK our generous sponsors. Your support will undoubtedly help us continue our mission of improving the lives of families and individuals affected by CAH through proactively advancing research for a cure, educating the public and healthcare professionals about all forms of CAH, advocating for EMS protocols and patient rights, and providing support services and resources vital to the CAH community worldwide.

Anthony Paul, Yana Netreba and Brianna Nixon



Musical entertainer, Anthony Paul

Vocal performer, Lara Bilgore

Gala Co-Chair, Ryan Hendler & Family

Testimonials by Hema Mehra, Lesley Holroyd, Kaye Colello and Alexandra Dubois

Continued from pg. 9

hosted a special event at his home to raise awareness of CAH and funds for CARES. Erik invited his friends, co-workers and family for a taco dinner, tequila drinks and relaxation in their beautiful, California backyard oasis. Erik spoke about his life as a CAH patient and invited his guests to donate to CARES as the only nonprofit solely dedicated to this rare disorder.

THANK YOU to Erik, the Bogaard family, and all of their guests for raising over $3,000 for CARES!

BAGS & BREWS

Nicole Bono & family hosted this uniquely fun event, **BAGS & BREWS FOR CAH,** on February 9, 2020 at the Old Ox Brewery in Ashburn, VA. Family and friends gathered to play a little corn hole, drink some craft beer, win prizes and play games, all in support of CAH and CARES. CAH parent, Nicole, whose son has SWCAH, enlisted the help of her local community service club, Willowsford Cares for this successful event. ***Thanks to the Bono Family, Willowsford Cares and sponsors Wegmans, Rubbino's Pizzeria and Old Ox Brewery. and all of the people who came out in support of this event!***

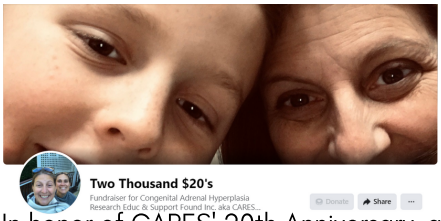
HAMILTON FAMILY RARE DISEASE DAY FUNDRAISER

To celebrate Rare Disease Day 2020, the Hamilton family, Megan, Eric & Avery, decided upon a raffle fundraiser wherein their friends and family bought $10 entries. A random winner was chosen and the winner received the grand prize of a basket of small shop goodies, donated by some of the family's favorite online stores run by moms. These shops were located all over the country, and some items were personalized to the person who won. ***THANK YOU Hamiltons for your support!***

A SPECIAL THANK YOU

TO all of our community members who hosted Facebook fundraisers in honor of their birthdays! Together, over $4,000 was raised for CARES Foundation. Here is a easy-to-follow guide if you would like to host your own Facebook fundraiser! https://rb.gy/cchdmz

KATHERINE'S 2000-20'S FACEBOOK FUNDRAISER



In honor of CARES' 20th Anniversary, and to raise awareness of CAH, Board of Trustees member and CAH parent, Katherine Fowler, hosted a fundraiser on Rare Disease Day wherein she asked all of her friends, family and colleagues to donate $20 to CARES Foundation. This clever idea raised over $2,000 for CARES! ***We appreciate your efforts, Katherine, and your dedication to CARES!***

CAPTAIN JACK'S QUEST FOR A CURE SAVE-THE-DATE GOLF TOURNAMENT

Due to Covid, the 3rd Annual Quest for a Cure Golf Tournament had to be cancelled. FORTUNATELY, fingers crossed, the 3rd Annual event will now take place on **May 10, 2021** at Pinehills Golf Club in Plymouth, MA. Thank you to everyone who has already supported this event! We look forward to seeing Captain Jack on the links soon. Stay tuned for registration information. ***Special thanks to the Porters!***

OTHER WAYS TO SUPPORT CARES

This is a very simple way to make an impact. If you're already an Amazon shopper then you know how easy it is to shop on their website and with shipping bargains like Prime, the convenience is unbeatable. So now, take one extra step and instead of going to Amazon.com, go to www.smile.amazon.com and designate CARES Foundation (type in as: Congenital Adrenal Hyperplasia Research, Advocacy, etc.) as your charity. Everything else is the same. Amazon will donate a portion or your purchase to CARES!

Continued from pg. 8

and the vector is modified to deliver only therapeutic genes. The choice of which viruses to use as vectors is based on three criteria:

- How well researchers understand the virus
- How well the virus can target certain cell types
- How safe the virus is to use

Vectors make use of the shell of the virus, also known as the capsid, to help transport working genes to the target cell. Think of vectors like envelopes being used to deliver a specific message. The envelope allows the message to be delivered, while the message inside provides new instructions to the cell on how to function properly. It might sound backward to use a virus to treat a disease, but the use of vectors is backed by years of research and has been shown to be safe, which is always a top priority.

Gene therapy using viral vectors does more than just treat symptoms. Vectors, with the genetic information they carry, can directly target the cause of a disease and change the way a cell functions. In addition, they typically only need to be administered once and are commonly used for rare inherited diseases that have few to no other treatment options available.

Adeno-Associated Viral (AAV) Vectors

Adeno-associated viral vectors, also known as AAVs, are typically used to deliver smaller DNA packages or genes. The size capacity of this vector may be a factor to determine which rare diseases it can target. They're known to be safe and efficient when used for *in vivo* gene therapy approaches. *In vivo* therapy involves injecting a gene therapy into specific parts of the body so that new genetic instructions can be delivered directly to the cells within the body.

AAVs are usually **non-integrating.** That means the DNA they carry doesn't typically insert itself into the cell's genome. So, if the vector is taken up by a cell that divides, the therapeutic gene won't be copied with each cell division and may be lost over time, thereby diluting the treatment effect. Because of this, AAVs are commonly used to target non-dividing cells, such as cells in the liver, nervous system, eyes, and skeletal muscles. AAVs can persist in patients for a prolonged period of time—possibly even a lifetime.

Innate immunity is one limitation of AAVs since many people may have had prior exposure to AAVs through natural infections. This means that pre-existing antibodies can disqualify anywhere from 30 to 70 percent of patients from clinical trial participation depending on the type of AAV being used. For these patients, their immune system may attack or destroy the vector before it can deliver its therapeutic package, rendering it useless. In addition, patients will often be limited to a single administration of therapy because they may develop antibodies following the first administration. Testing for innate immunity is becoming more widespread and is used as an exclusion criteria for clinical trial eligibility. For now, scientists are working on a variety of strategies to help combat this challenge such as creating synthetic capsids that would not be attacked by the immune system or by utilizing an enzyme that can split through the antibodies in the short term. These solutions come from knowing there is a short window of time (hours) where the vector is injected and then travels to the target cell and once the vector makes it inside the cell it is protected from antibodies.

Adenoviral Vectors

In some ways, adenoviral vectors are similar to AAV vectors. For instance, they're most often used to deliver DNA packages into non-dividing cells. However, adenoviral vectors are larger and capable of delivering genetic packages almost eight times the size of AAVs. Adenoviral vectors can cause **strong immune responses**, which result in potentially harmful inflammation throughout the body and decreased effectiveness of the therapy. In recent years, scientists have worked to develop adenoviral vectors that result in milder immune responses in order to deliver larger packages with less risk.

Lentiviral and Retroviral Vectors

Lentiviral and retroviral vectors can carry larger genetic packages of RNA, which is converted into DNA. During this process, the vectors **integrate** into the genome of the target cell, unlike AAVs and adenoviral vectors.

The ability to integrate into the cell genome makes lentiviral and retroviral vectors best suited for dividing cells, which are targets of an ex vivo treatment approach. For example, these vectors are used to target T cells, which are a type of immune cell, and stem cells, which are special cells that can develop into many cell types. In contrast to *in vivo* treatments, *ex vivo* treatment of cells occurs outside the body. Cells are removed from the body and are cultured on plates allowing them to replicate and expand. Then these cells are treated with vectors and modified with new genetic instructions, such as a working gene. The modified cells are then returned to the body. After that, the treated cells begin to divide and generate new cells. Thanks to integration, the new genetic material is copied into all the new cells and continues to function beyond the original cell.

Other Limitations

Gene therapy using viral vectors carries a lot of potential, but is not without some risk. These examples are are in addition to limitations that have been discussed above including innate immunity and strong immune responses.

Off-target effects are when tissues other than the main target tissue may be affected after administration. Vectors that insert their genetic package into the host genome can potentially integrate at an incorrect location of the genome and cause unintended consequences. In order to maintain as much control over the process as possible, researchers have developed targeting techniques. In addition, they have the ability to monitor the vector's long-term effects in patients at the insertion site.

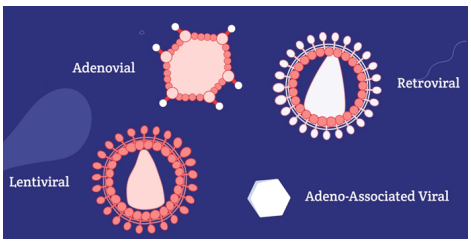
Manufacturing is another challenge that is being addressed by professionals in the field. Creating a very large quantity of safe viral vectors requires time, effort, and resources. The complexities of the process add to manufacturing costs and makes it hard to effectively streamline production. Researchers will continue working towards more efficient production methods as more gene therapies are researched and approved for use.

Non-Viral Vectors

Researchers are also developing more non-viral vectors to address (or eliminate) these limitations. Non-viral vectors are cheaper to manufacture than their viral counterparts. They can potentially deliver larger genetic

packages, allow for repeated dosing, and make quality control easier. Non-viral vectors also have the benefit of a lowered chance of triggering adverse immune responses.

While non-viral vectors hold a lot of promise, scientists simply have less experience with them. Many of the non-viral mechanisms are developing rapidly but challenges still remain, such as carrying capacity and ability to target specific organs or tissues. For now, they can't be used for in vivo approaches that are common with AAVs and adenoviral vectors.



Gene Therapy and Oncology
The approach to gene therapy is very different when it comes to oncology and cancer treatment. Current vectors cannot treat 100% of cells, so gene addition or specific gene targeting strategies, which are methods used for rare diseases such as adding a working gene, simply aren't as effective for cancer treatment. However, there are strategies that use gene therapy to treat cancer by enhancing the immune response to cancer cells. These methods vary greatly from rare disease treatment, in which a working gene sits next to a faulty gene. One way to treat cancer is to provide dividing immune cells with new genetic instructions that can turn them into cells that recognize and kill cancer cells. Another approach is to use vectors that can only multiply rapidly in tumor cells. From there, the vectors with specific instructions to kill those cancer cells are able to do so.

EDUCATIONAL VIDEOS AVAILABLE

Educational videos addressing Adrenal Crisis and Stress Dosing are available for purchase in our online CARES Shop and available for viewing on our website. These videos have proven to be essential tools in educating caretakers, school personnel, babysitters and even emergency department staff.

THE DOCTOR IS IN

Dr. Karen Su
CARES
Medical
Director

Guide to Medications and How They Work

Glucocorticoids

As a class, glucocorticoids are similar to the adrenal hormone cortisol, which is deficient in patients with CAH and other forms of adrenal insufficiency. They also lower adrenal androgen production, which is increased in CAH. There are several different oral glucocorticoids commonly used for regular chronic replacement of cortisol.

- ***Hydrocortisone*** (Cortef®): structurally identical to cortisol, it is considered to be the most physiologic of the pharmacological glucocorticoids. It has both glucocorticoid and mineralocorticoid (see below) activity. With the exception of cortisone, it is the least potent of the available glucocorticoids, and is the shortest-acting (given 2-3 times/day). Compounded liquid suspensions of hydrocortisone are unreliable and should not be used.
- ***Cortisone acetate:*** slightly less potent than hydrocortisone, it must be converted to active cortisol in the body using an enzyme called 11ß-hydroxysteroid dehydrogenase type I.
- ***Prednisone/Prednisolone:*** 4-5 times as potent as hydrocortisone and longer-acting (given 2x/day). Considered to be more growth suppressive than hydrocortisone even at equivalent glucocorticoid doses, so usually not recommended in growing children.
- ***Dexamethasone:*** 40-80 times as potent as hydrocortisone and very long-acting (given once a day). Not generally used in growing children because difficult to titrate at very small doses and tends to suppress growth.

Mineralocorticoids

Mineralocorticoids are similar to aldosterone, which is deficient in patients with salt-wasting CAH. They act on the mineralocorticoid receptor in the kidneys to reabsorb sodium and excrete potassium.

- ***Fludrocortisone:*** acts on the mineralocorticoid receptor to replace aldosterone; also has some glucocorticoid activity; comes as 0.1 mg tablets.
- ***Hydrocortisone:*** acts on the mineralocorticoid receptor also, but much higher doses are needed (40 mg of hydrocortisone is roughly equivalent to 0.1 mg of fludrocortisone)

Androgen receptor blocker

- ***Spironolactone:*** blocks the androgen receptor, so it prevents any androgens that are circulating in the blood from causing symptoms (such as acne, excess facial/body hair, or signs of early puberty). When the androgens are very high, though, higher doses may be required to be effective. Unfortunately, spironolactone also blocks the aldosterone receptor, so at high doses it can cause salt-wasting even in non-salt-wasters.

Oral contraceptive pill (OCP)

Oral contraceptive pills regulate menstrual cycles and can lower ovarian androgen production. The estrogen component increases sex hormone binding globulin, so more testosterone is bound and there is less free testosterone circulating (thereby reducing symptoms). While OCPs alone do not substantially reduce adrenal androgens in CAH, they can reduce some of the bioavailable androgens and are useful for individuals with concomitant polycystic ovarian syndrome

NEED ANSWERS? ASK THE EXPERT!

CARES has a special feature on their website for you to get answers to CAH questions from our Medical Director, Dr. Karen Su via email. We now also feature "Pregúntale al Experto en Español" con el Dr. Alejandro Díaz. ("Ask the Expert" in Spanish). VISIT OUR WEBSITE TO SUBMIT YOUR QUESTIONS.
https://caresfoundation.org/faqs/ask-expert/

https://caresfoundation.org/pregunta-al-experto-en-espanol/

ADVOCACY

Preserve Access to Surgery

IT'S TIME TO ACT TO PRESERVE THE RIGHTS OF PATIENTS TO HAVE ACCESS TO ALL TREATMENT OPTIONS AND THE RIGHTS OF PARENTS TO MAKE DECISIONS ON BEHALF OF THEIR CHILDREN.

Over the past few years, we have been sounding the alarm about the real possibility of a complete ban on surgery for girls with classic CAH who have anatomic differences in their external genitalia. That reality may be closer than ever. There are several legislative challenges aimed at banning physicians from performing surgical procedures on any child's genitalia in infancy or early childhood. In addition to proposed legislation, some institutions have given in to the demands of anti-surgery activists and have already made the decision to either put a moratorium on or ban surgery altogether. These institutions include Lurie Hospital for Children in Chicago and Boston Children's Hospital. These decisions are clearly not made with the best interest of the child in mind.

Those making the decisions are not hearing from CAH patients because many in our community have remained silent. The repercussions on continuing that silence are huge. We fear that a complete ban on surgery for girls with CAH in the United States may become a reality very soon if patients and parents don't speak up now!

CARES understands that adult patients who are pleased with their surgery often do not want to speak out because they are doing well and want to keep their surgery private. For them, it was an issue that was addressed and is behind them. Parents whose children had surgery as infants or at a young age may feel the same way. However, we ask you to think about CAH patients who are being born now and in the future. What will their lives be like without an option for surgery? What will happen to the prepubertal girls who will need additional procedures? They will be left with no options. Even if they are willing and able to give consent, there will not be any surgeons with the expertise to perform those surgeries. Future generations of classic CAH females will have to live with the physical and emotional toll that atypical genitalia may take on them.

For those parents who have opted to wait until their children are older to decide whether or not to proceed with surgery, your children will not be afforded the expertise and skill of a doctor to perform these surgeries when your child does require them. Think about this.

Let's be clear, we are not advocating for or against surgery. We understand that it is a very individual decision that should be made between expert medical providers in conjunction with parents and patients, whenever possible. Like every parental decision, these decisions are made with the best interest of the child in mind given all the information available to them.

If you care about preserving access to all forms of treatment for CAH, we need to hear from you! We need you to write letters, participate in legislative meetings, and yes, speak to the media. We remain committed to working on behalf of our patients so that they will have the best quality of life possible from new medications and treatments to surgical options, but we cannot do it alone! **To add your voice to this fight, please contact Dina@caresfoundation.org.**

The future of CAH treatment and parental rights is at stake. Time is running out to protect our patients!

VISIT YOUR EMS PROVIDER

REMEMBER: Visiting your local EMS provider is one of the easiest and most productive acts of advocacy in which YOU can participate. Please, take the time today to visit your local firehouse or EMS station. Schools, churches, clubs, etc. are also great places to visit.

EMERGENCY REMINDERS:
Visit your local EMS near your home, child's school and/or your workplace BEFORE an emergency occurs.

IT IS YOUR RESPONSIBILITY to make sure that your local EMS officials are prepared to help you or your child in case of an emergency!

Bring local protocols (if available, see our website), emergency instructions + the Medication Safety Alert: EMS Protocols for Adrenal Crisis.
Have EMS flag your address or phone number.
BEFORE calling 9-1-1, inject Solu-Cortef® **THEN call and say** you need paramedics/ALS to come because you have a person with adrenal insufficiency who is in adrenal crisis. When paramedics arrive, have Solu-Cortef® and letter from the endocrinologist available

ALWAYS WEAR MEDICAL I.D.

Medical ID should include: Adrenal Insufficient/Steroid Dependent - Administer Solu-Cortef® with your appropriate dosage.

CARES SUPPORT
We're here for you!

Support for patients and families can be life-altering. We are constantly expanding and improving our support offerings in order to best serve our community. We have traditional one-on-one over the phone support; secret Facebook groups geared toward specific groups; and support group calls with experts available to answer questions.

This is a unique opportunity for patients and parents/caregivers to gather valuable information.

We are excited about our new support group leaders and all they have to offer our community:

Mark Kennedy: ID + Men with SWCAH
Lauren Kulp: PA + Teens/Young Adults
Jenny Lua: Northern CA, Kids with SWCAH
Rebecca Mendel: MI, IL, Teens/Young Adults
Cara Parker: ID, Kids with SWCAH

Please visit the support page on our website for more resources: https://caresfoundation.org/physician-referrals/support-groups/

CAH AROUND THE WORLD

2020 IFCAH PROJECT GRANTS

IFCAH is a private fund, aimed to promote research on Congenital Adrenal Hyperplasia (CAH). In 2020, it launcheds its tenth call for proposals, in association with ESPE. A total amount of 350.000€ is associated to this program. Participation was open worldwide and will, if possible, include teams based in Europe. **The goal of the program is to increase knowledge on pathophysiology of CAH and the projects could be directly or indirectly targeted on CAH and adrenal insufficiency which also included research on adrenal development, differentiation and homeostasis. THE FOLLOWING PROPOSALS WERE CHOSEN:**

Dr Hedi Claahsen, Dr Antonius Herwaarden, "*The risk for developing clinical signs of cortisol deficiency in CAH and acquired adrenal insufficiency - what makes the difference?*"
75 000 €
Primary adrenal insufficiency (PAI) is a serious condition as patients miss the stress hormone cortisol. In childhood this is mostly caused by congenital adrenal insufficiency (CAH). In adulthood the most common cause is autoimmune disease (Addison's Disease, AD). In general, these patients are at risk to develop a life-threatening Addisonian crisis. Therefore, treatment with cortisol including stress dosing during illness is an important goal. There is an increasing number of reports of CAH patients who decide to stop cortisol treatment surprisingly without serious complaints. This is not reported in patients with AD. The mechanism of how some untreated CAH patients can survive with obviously a lack of cortisol is unknown. In our project we want to study the special situation of untreated CAH patients in more detail and want to compare these patients with patients with AD. We want to know if these patients develop complaints of Addisonian crisis or other complications. Furthermore, we want to find out which factors play a role in the protective mechanisms of CAH that differ from patients with AD. We hypothesize that other adrenal products which are markers of CAH may protect some CAH patients from signs of cortisol deficiency but we do not know if these markers are also sufficient to prevent Addisonian crisis. Furthermore, differences in the free fraction of cortisol, the active part of cortisol, may protect patients form clinical relevant complaints.

Dr Alaa El Ghoneimi, "*New standardized method for objective short and long term functional and morphological evaluation of operated CAH genitalia in children and adolescent: The EvaSurg study*"
50 000 €
Early feminizing genitoplasty for CAH females with virilized genitalia is still debated, in particular when clitoroplasty is performed, because of concerns about secondary vaginal introitus stenosis and clitoral neurovascular bundles injury. Nevertheless, this surgery lacks objective evaluation before first sexual intercourse in the literature. This study aims at evaluating clitoral sensitivity after genitoplasty with or without clitoroplasty, before first sexual intercourse, in 2 paediatric expert centers in Paris. Neurological testing of the clitoris will rely on both a specific reflex loop called clitorocavernosus reflex, quantified by electromyogram, and a sensitivity testing with clinical response to touch and vibration. Patients with clitoroplasty will be compared to non-operated CAH (genitoplasty without clitoroplasty or no genitoplasty at all). This study will provide a simple, objective and reproducible method to evaluate the results of genital surgery for virilized CAH patients. Patients and their families will be aware of the consequences of the surgery and in case of unfavorable results the surgical techniques should be reconsidered.

Dr Gerard Ruiz Babot, "*Generation of human steroid-producing organoids: a new approach towards a treatment for CAH (Renewal)*", 100 000 € (AFM IFCAH)
Adrenal glands control essential bodily functions through production of hormones. People unable to make hormones suffer from adrenal insufficiency, a life-threatening condition. Stem cells can generate all cell types in the body, including adrenal cells. This project aims to produce cells in the laboratory that can produce hormones to treat patients with adrenal insufficiency. However, once introduced into humans, cells generated in the laboratory can be recognized and destroyed by the patient immune system. To avoid that, cells will be protected using small medical devices that should allow them to survive, produce hormones and control patient´s bodily functions.

Continued on pg. 9

WELCOME ABOARD

We would like to extend a warm welcome to the newest members of our Board of Trustees, Lesley Holroyd, R.N., Maria Maebius, Esq., Brian Stair, and Valentina Tudor.

Lesley Holroyd, R.N.

Lesley has been a nurse since 1978, and has worked in many different areas of medicine. She came to the States in 1991 from the UK where she was in a midwifery nursing program. She intended to complete the program in the U.S., but worked post partum instead at University Hospital of Cleveland. Her nursing work includes many training and evaluator positions as well. Currently, Lesley is the Nurse Audit Coordinator at HMS, Irving, TX. Her job is very diverse and can be very fluid. She works with a team of other RN's but she has her our own territories and RN's to supervise.

Lesley has classical CAH. She was born in Chichester, Sussex UK. She has a younger sister and 3 brothers. Her youngest brother also has classical CAH. She married Alan in 1984, and he was raising two kids, a girl of 13 & a boy of 14. They moved to the states in 1991. She and Alan now have 4 adult grandkids and 3 young great grandkids. Lesley also supports CARES by annually hosting the Florida CAH Awareness Walk.

Maria Maebius, Esq.

Maria Maebius is an intellectual property lawyer that acts as an advisor for the newly formed venture capital company, Linden Lake Ventures LLC. Prior to that, she was a patent attorney for the law firm, Seyfarth Shaw LLC, where she focused on the procurement and analysis of a wide variety of biotechnological and chemical inventions. Maria has been practicing law since 1998 when she graduated from George Washington University Law School and prior to that, she was a Patent Examiner at the United States Patent and Trademark Office. She graduated from The Ohio State University with a Bachelor of Science in Biology and a concentration in Genetics.

Maria is an active volunteer in Fairfax County, where she currently serves as a Court-Appointed Special Advocate (CASA) advocating for abused or neglected children placed under Court protection. She is a mother of four daughters, the youngest of which has congenital adrenal hyperplasia.

Brian Stair

Brian Stair is the owner and director of two companies in the antique conservation and decorative arts field. Both companies, Stair's Incurable Collector, and Oxford Restoration, LLC, are located in New York City. Brian is married to Virginia Stair, and they have two children, Elizabeth and John, who was diagnosed with Salt-wasting CAH at 5 days old. Brian's career began in his teens, following four generations of Stairs in the antique trade. He apprenticed at Sotheby's Restoration in various departments learning and practicing restoration techniques in many field. Brian worked together with his family to maintain Sotheby's Restoration for 13 years. In 2002, Brian established Oxford Restoration by purchasing remnants of the restoration department at Sotheby's. Brian and his staff of artisans and conservators provide a range of skilled services for antiques, decorative works of art, paneled rooms, libraries, and yachts. Oxford Restoration provides services to high end private clientele, museums, corporate collections, and specialized government contracts. The Stair family actively supports CARES Foundation and their mission.

Valentina Tudor

Valentina is currently Owner and Patent researcher at Patent Fusion LLC where she does patent and literature research for various technologies as pertaining to new inventions. Valentina has an impressive resume that includes highly-skilled positions in major companies. She is a licensed realtor and tax accountant as well as holding a B.A. in Economics from The Academy of Economical Studies in Bucarest, Romania.

Valentina lives in Maryland with her husband Valentin and four children. Her daughter, Anna, has CAH.

COMPREHENSIVE CARE CENTERS FOR CAH

CARES is proud to announce the opening of **FOUR NEW COMPREHENSIVE CARE CENTERS!**

Rutgers-Robert Wood Johnson Medical School (RWJMS), Child Health Center of New Jersey (CHINJ)
New Brunswick, New Jersey - LEVEL 2
Co-Medical Directors: Ian Marshall, M.D., Ahmed Khattab, M.D.,MSC

UT Southwestern Children's Medical Center Dallas, Dallas, Texas - LEVEL 1
Medical Director: Perrin C. White, M.D.Associate Medical Director: Grace M. Tannin, M.D.

Seattle Children's Hospital and University of Washington Medical Center, Seattle, WA - LEVEL 1
Medical Director: Patricia Y. Fechner, M.D., FAAP, FACE
Co-Surgical Directors: Mark Cain, M.D., FAAP, and Margarett Shnorhavorian, M.D. MPH,FAAP,FACS

Cook Children's Health Care System,
Fort Worth, TX - LEVEL 2
Medical Director: Paul Thornton, M.D.,BCh, MRCPI, DCh

Comprehensive Care Centers are designated as either Level 1 (surgical included) or Level 2 (non-surgical).

These newly designated Centers of Excellence join New York Presbyterian/Weill Cornell Medical Center, Manhattan, NY (Level 1); CHLA/University of California/Keck School of Medicine in Los Angeles, CA (Level 1); Cohen Children's Medical Center/Northwell Health, Long Island, New York (Level 2); Riley Hospital for Children/ Indiana University Health - Indianapolis IN (Level 1).

tidbits

Dr. Richard J. Auchus is Recipient of the Outstanding Clinical Investigator Award from the Endocrine Society

Congratulations to Dr. Richard J. Auchus, MD, PhD, a distinguished member of CARES' Scientific & Medical Advisory Board and expert in CAH cares, for winning the James A. Shayman and Andrea S. Kevrick Professor in Translational Medicine, on his receipt of the Outstanding Clinical Investigator Award from the Endocrine Society. This annual award honors an internationally recognized clinical investigator who has contributed significantly to understanding the pathogenesis and therapy of endocrine and metabolic diseases. Dr. Auchus is a professor of internal medicine and pharmacology at the University of Michigan in Ann Arbor, Mich., and the world's foremost authority on steroid-related diseases. His pioneering science has transformed fundamental principles of steroid biosynthesis, and his clinical investigation has repeatedly changed clinical practice for androgen synthesis, endocrine hypertension, and hypercortisolism.

Professor Richard Ross receives International Honor from Endocrine Society

Professor Richard Ross, an esteemed member of CARES' Scientific & Medical Advisory Board, and a founding Director of Diurnal and Chief Scientific Officer, has been recognized by the Endocrine Society's 2021 Laureate Awards for Outstanding Innovation.
Established in 1944, the Endocrine Society's Laureate Awards recognizes the highest achievements in the endocrinology field, including ground -breaking research and innovations in clinical care. The Outstanding Innovation Award recognizes endocrinologists who have demonstrated innovation and entrepreneurship to further endocrine research or practice in support of the field of endocrinology, patients, and society at large.

Professor Ross has been awarded this honor for his research on optimizing endocrine replacement therapy that has focused on replacement of cortisol in patients with adrenal insufficiency (AI) and congenital adrenal hyperplasia (CAH).

HELP US KEEP OUR DATABASE UP TO DATE

At CARES, our goal is to make life easier, safer, and healthier for our CAH community. **THE MORE INFORMATION WE HAVE, THE MORE WE CAN DO OUR JOB: HELP YOU!**

Please make sure that we have up to date contact information for you! It is especially crucial that you have a current email address on file, for we send our most important messages regarding research, like surveys, studies, and information on clinical trials. Email us at contact@caresfoundation.org with updates!

VISIT THE CARES SHOP FOR GREAT HOLIDAY GIFTS!

In our online store, you will find great gift ideas for that special CAH someone, as well as tools to make living with CAH a little bit easier.

THE OFFICIAL CARES FOUNDATION MUG

The Perfect Holiday Gift

Beautiful 17 oz. ceramic mug with CARES logo, website and signature heart! Use at home or at the office - a conversation starter for CAH awareness!

CARES Magnet

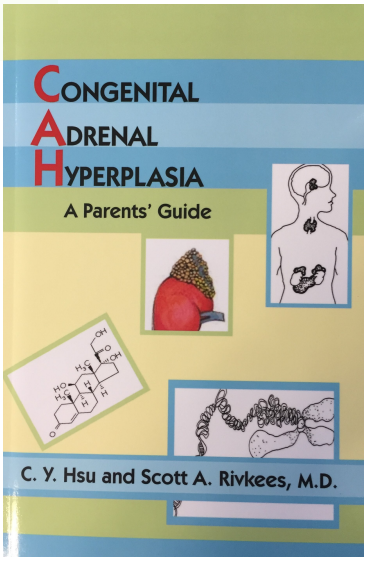
CARES heart shaped magnet. Spread awareness of CAH by placing this nicely-sized heart magnet on your vehicle. 6"x6"

BUZZY Pain Management Device

Buzzy is a palm-sized device combining cold and vibration that when placed between the brain and the pain, decreases sharp pains. His wings are icy cold, and his tummy vibrates when you touch his head. This confuses your body's nerves to block sharp feelings, just like rubbing a bumped elbow helps stop the hurt, or cool running water soothes a burn. Buzzy is ideal for blood draws, vaccinations, flu shots, dental procedures and more.

CARES Foundation CAH Awareness Pin

Wear this fashionable, lapel pin to help RAISE AWARENESS of CAH. This silver pin is tie-tack style and works on any garment in any location. Measures roughly 1.25"x.75"



Congenital Adrenal Hyperplasia: A Parents' Guide takes a nuts-and-bolts look at CAH- what this condition is, how it is inherited, and how it is treated and monitored. This new book on CAH written for a lay audience will be welcomed by all patients, parents, caregivers, and healthcare professionals.

By C.Y. Hsu and Scott A. Rivkees, M.D.

EMERGENCY RESPONSE KITS - Perfect for school, camp, clubs, sports, and leaving with the baby sitter! Clear, plastic, water-resistant bags just the right size for your Emergency Response Kit. Emergency wallet card and Emergency Instructions brochure are included. Purchase our package of 3 kits and have extra for all your needs - keep one in a purse, backpack, at Grandma's, etc. Colors may vary from picture.

CARES "Pass the Salt" T-Shirt

We think you'll enjoy this creative way to spread awareness of CAH! Wear this fun, CARES tee around & you will surely be asked by at least one person, "What is CAH?"

CARES Connections

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CELEBRATING OUR LEGACY
CARES20
20 YEARS IGNITING THE FUTURE

Please remember that CARES Foundation newsletters have "gone green" and are now only available electronically. Please make sure we have your most current email address and contact information to ensure that you continue receiving newsletters and other important information from CARES. Send your updated information to Odaly Roche at Odaly@caresfoundation.org.

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YEAR-END GIVING 2020

2020 has been a tough year for all of us. It has been incredibly tough on CARES because we were limited in our ability to fundraise. We hope that you will find it in your hearts to GIVE GENEROUSLY to our Foundation this year. We need your support now more than ever. Remember, your generosity matters!