Fertility in patients with nonclassical congenital adrenal hyperplasia

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Nonclassical congenital adrenal hyperplasia (NC-CAH) is by far a subtler and milder enzymatic defect to the classical form of the disease. A nuanced understanding of NC-CAH will lead to increased detection of the disorder in those initially misdiagnosed as having polycystic ovary syndrome, will assist in the detection of pregnancies at risk for severe genetic steroid disorders, and will facilitate appropriate ovulation induction and reduction in the hyperandrogenic symptoms which are a cornerstone of the disease. We describe the history of the disease as well as elucidate the pathophysiology, diagnosis, and treatment of the disorder. (Fertil Steril® 2019;111: 13–20. ©2018 by American Society for Reproductive Medicine.)

Key Words: Adrenal steroid disorder, congenital adrenal hyperplasia, 21-hydroxylase, NC-CAH, 17-OHP

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We begin this discussion of nonclassical congenital adrenal hyperplasia (NC-CAH) with a story of a historic family in whom consanguinity may have played a role in their infertility. Congenital adrenal hyperplasia (CAH) is an autosomal recessive disorder that occurs more frequently in consanguineous families. The great historian Salo Wittmayer Baron, in his study of the Old Testament and the teachings of Jewish history, revealed that an ancient pedigree demonstrated consanguinity (Fig. 1). Sarah, Abraham's wife, was also his niece, the daughter of his dead younger brother, Haran. Sarah was infertile and did not bear Abraham a son until she was 99 years old. One can only speculate whether they may have had nonclassical steroid 21-hydroxylase deficiency, but nonclassical steroid 21-hydroxylase deficiency is well known to be associated with impaired fertility, and consanguinity is frequently observed in families with this deficiency.

In 1957, Decourt et al. (1) presented one of the first reports of a mild form of adrenal steroid 21-hydroxylase deficiency. It was not until 1979 that Rosenwaks et al. (2) first described its autosomal recessive pattern of inheritance, which they initially called an attenuated form of congenital virilizing adrenal hyperplasia. Subsequent cases were later confirmed by Birnbaum and Rose (3), who referred to the disorder as partial adrenocortical hydroxylase deficiency syndrome.

In contrast to classical CAH, this milder form of CAH is associated with partial retention of 21-hydroxylase enzyme activity: salt wasting is not encountered, anatomic changes are not evident at birth, and biochemical findings are less pronounced. The disorder is characterized in adolescent and adult females by hyperandrogenemia, oligo-ovulation, and infertility (Fig. 2). Affected males, on the other hand, do not generally exhibit symptoms, except in rare cases of testicular adrenal rest tumors, which are associated with classical disease (4). In 1986, Dewailly et al. (5) characterized the various clinical phenotypes and HLA genotypes for the condition. Although varying clinical severities of CAH had always been observed, it was not until 2006 that the seminal work by New (6) described the specific hormonal and genetic criteria for the diagnosis and gene map for CAH (Figs. 3–5).

In this context, it is worthwhile to describe the discovery by New of the first nonclassical case of CAH. New was taking care of a young man who had classical simple virilizing CAH and was definitively genotyped to have simple virilizing CAH. Then because New was interested in seeing which mutations came from which parent, she genotyped the parents. When she received the hormone results from the father, she was surprised to find that he was hormonally affected. His genetics revealed that

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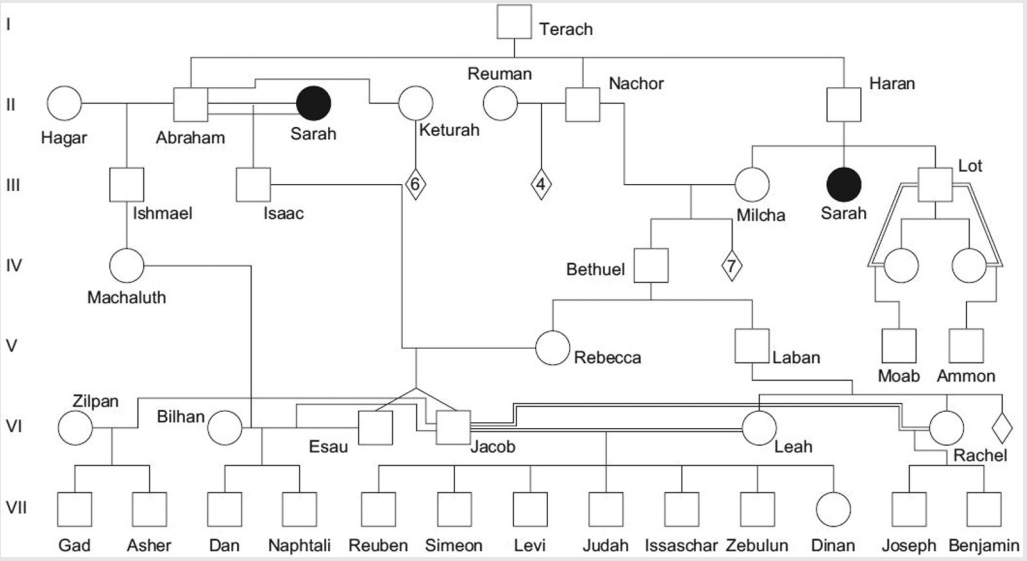
FIGURE 1



Pedigree of Abraham and Sarah based on the Old Testament of the bible. (Adapted from Figure 1.1 in New MI. Chapter 1: Introduction. In: New MI, Yuen TT, Parsa A, Lekarev O, eds. Genetic steroid disorders. New York: Elsevier, 2014.)

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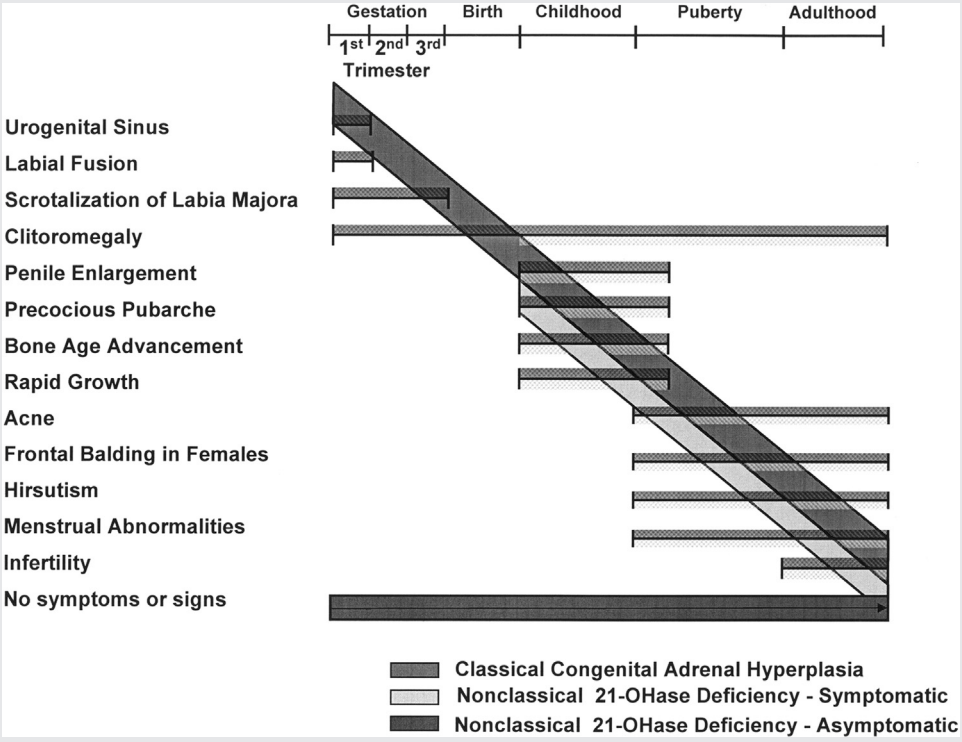
he was a compound heterozygote, having a severe and a mild mutation (Ex7/Ex4, Ex6). He passed his severe mutation to his son, who then received a second severe mutation from his mother, thus resulting in the classical simple virilizing CAH. The father then suggested that his own sister may also have this nonclassical form of CAH because she did not have menstrual periods and struggled with infertility. On genotyping his sister, she was indeed found to

FIGURE 2



Clinical spectrum of classical and nonclassical 21-hydroxylase deficiency (21-OHD). (Figure 2 from New MI. Extensive clinical experience: nonclassical 21-hydroxylase deficiency. J Clin Endo Metab 2006;91:4205-14.)

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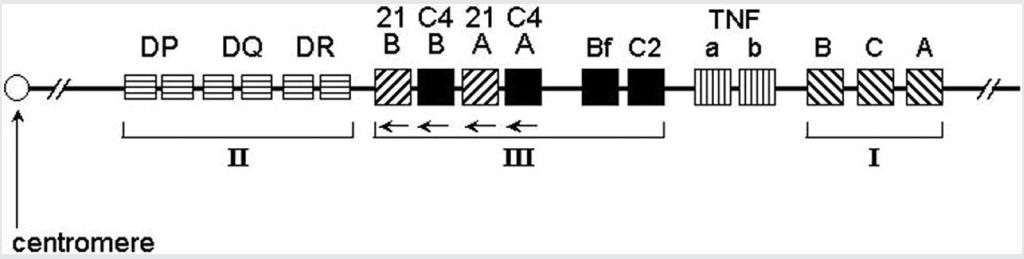
FIGURE 3



HLA region of chromosome 6p. The active gene is 21B, and the pseudogene is 21A. (Figure 6 from New MI. Extensive clinical experience: nonclassical 21-hydroxylase deficiency. J Clin Endo Metab 2006;91:4205-14.)

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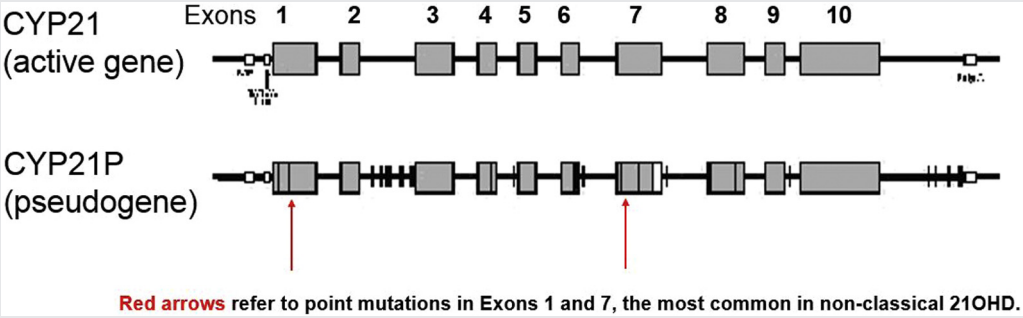
be a compound heterozygote like her brother, the very first patient diagnosed with nonclassical 21-hydroxylase deficiency.

NC-CAH is one of the most common autosomal recessive disorders, and the most common genetic steroid disorder. Estimating the exact prevalence of NC-CAH is challenging, however, given that newborn screening does not reveal an elevated 17-OH progesterone (17-OHP), and genital ambiguity is not observed in either male or female newborns. The prevalence of this disorder in early childhood has thus likely been grossly underestimated. Typically, the disorder manifests later in life but can sometimes be evident in childhood, presenting as premature pubarche, acne, and accelerated bone age. Moreover, diagnosis in adults is often obscured by the overlapping of symptoms with polycystic ovary syndrome (PCOS). Indeed, the prevalence of NC-CAH has been estimated in certain populations to be as high as 1 in 27 (7). The genotypes of nonclassical 21-hydroxylase deficiency are ethnic specific, with the highest prevalence observed in Ashkenazi Jews (Fig. 6, Table 1).

Diagnosis of NC-CAH is frequently made by reproductive endocrinologists, as infertility is a frequent presenting symptom; in 13% of NC-CAH cases, infertility is the symptom precipitating evaluation and diagnosis (8). In women for whom the diagnosis is suspected, a morning 17-OHP level can be assessed in the follicular phase (care should be taken to avoid assessment in the luteal phase, during which levels may be transiently elevated due to progesterone production). All patients presenting with a PCOS-like phenotype should be screened before a diagnosis of PCOS is made, given the significant phenotypic overlap of these two conditions. A morning follicular phase 17-OHP level of >200 ng/dL strongly suggests the diagnosis, which can then be confirmed via a high-dose corticotropin stimulation test, with measurement of 17-OHP levels at baseline and 60 minutes after adrenocorticotropic hormone administration (9). A corresponding 17-OHP nomogram has been published that allows the clinician to subsequently categorize the patient's diagnosis according to the elicited hormone data (Fig. 7) (10).

For patients in whom the diagnosis of NC-CAH is made based on dynamic hormone testing, sequencing of the 21-hydroxylase gene can determine the mutation present and help to clarify the risks to a potential fetus of an NC-CAH affected individual based on the known severity of the mutation (Fig. 8). Male partners of affected female patients should similarly have sequencing of the 21-hydroxylase gene performed so as to determine the risk to offspring. Dynamic hormone testing of the male partner is less useful in this scenario.

FIGURE 4



The two homologs: CYP21A2 (the active gene) and CYP21A1P (the pseudogene). Mutations associated with nonclassical 21-hydroxylase deficiency (NC21OHD) are indicated with black squares (exons 1, 7, 8, and 10). (Figure 2 adapted from New MI. Extensive clinical experience: nonclassical 21-hydroxylase deficiency. J Clin Endo Metab 2006;91:4205-14.)

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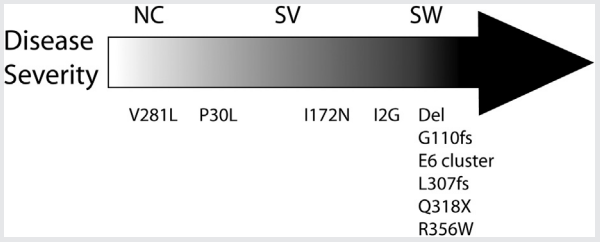
FIGURE 5



Spectrum of disease severity correlated with CYP21A2 mutations. (Figure 3a.8 from New MI. Chapter 3A. In: New MI, Yuen TT, Parsa A, Lekarev O, eds. Genetic steroid disorders. New York: Elsevier, 2014.)

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TABLE 1

Ethnic-specific genotype frequencies (%) of nonclassical 21-hydroxylase deficiency (NC21OHD) probands.

Ethnic group	n	Exon 7/ Exon 7	Exon 7/ Intron 2	Deletion/ Exon 7	Other
Ashkenazi Jews	140	50	18	18	14
African Americans	4	25	0	0	75
Hispanics	33	24	27	21	28
Italian Americans	48	17	19	15	49
Non-Jewish Caucasians	92	17	16	7	60
Total	317	31	18	15	36

Table 1 from New MI. Extensive clinical experience: nonclassical 21-hydroxylase deficiency. J Clin Endo Metab 2006;91:4205-14.

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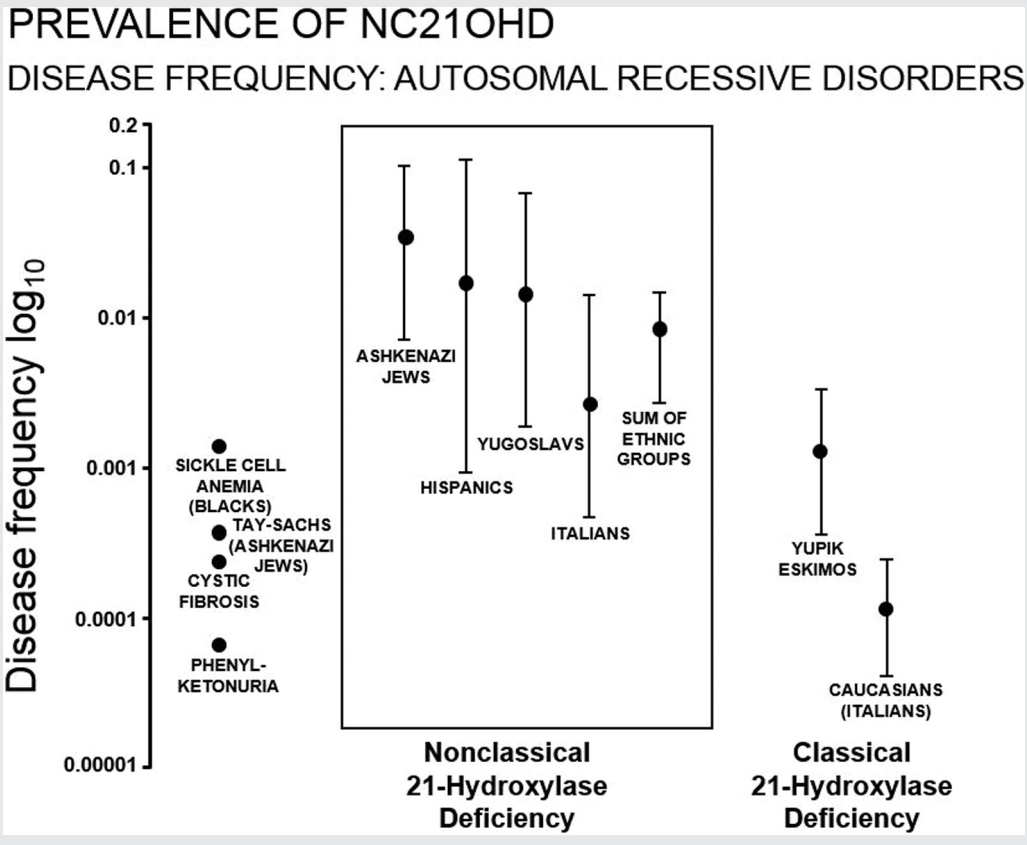
The projected probability for an NC-CAH mother to have a female infant affected with classical CAH is 1 in 720 (11, 12). Such couples are thus at a significantly higher risk of having an infant with classical CAH than the general population (~1:16,000-1:20,000 live births) (13). Moreover, these patients should be counseled that there is a roughly 1 in 32 chance of conceiving a fetus with the same disorder (14). These statistics may be underestimated, however, given the propensity toward intermarriage within certain populations in which carrier frequencies are enriched. In a specific study examining the offspring of women with NC-CAH, 4 out of 162 live-born infants (2.5%) were diagnosed with classical disease (15). In fetuses that are determined to be at risk, cell-free fetal DNA testing can now aid in noninvasive prenatal diagnosis (16). Such early noninvasive diagnosis can aid in ruling out females at risk for ambiguous genitalia, thus obviating the use of experimental treatment with dexamethasone to suppress fetal androgen production.

The pathophysiology of NC-CAH, in terms of the exact mechanisms by which elevated androgen production impairs ovulation, remains complex and somewhat poorly

FIGURE 6



Disease frequencies in different ethnic groups. (Figure 8 from New MI. Extensive clinical experience: nonclassical 21-hydroxylase deficiency. J Clin Endo Metab 2006;91:4205-14.)

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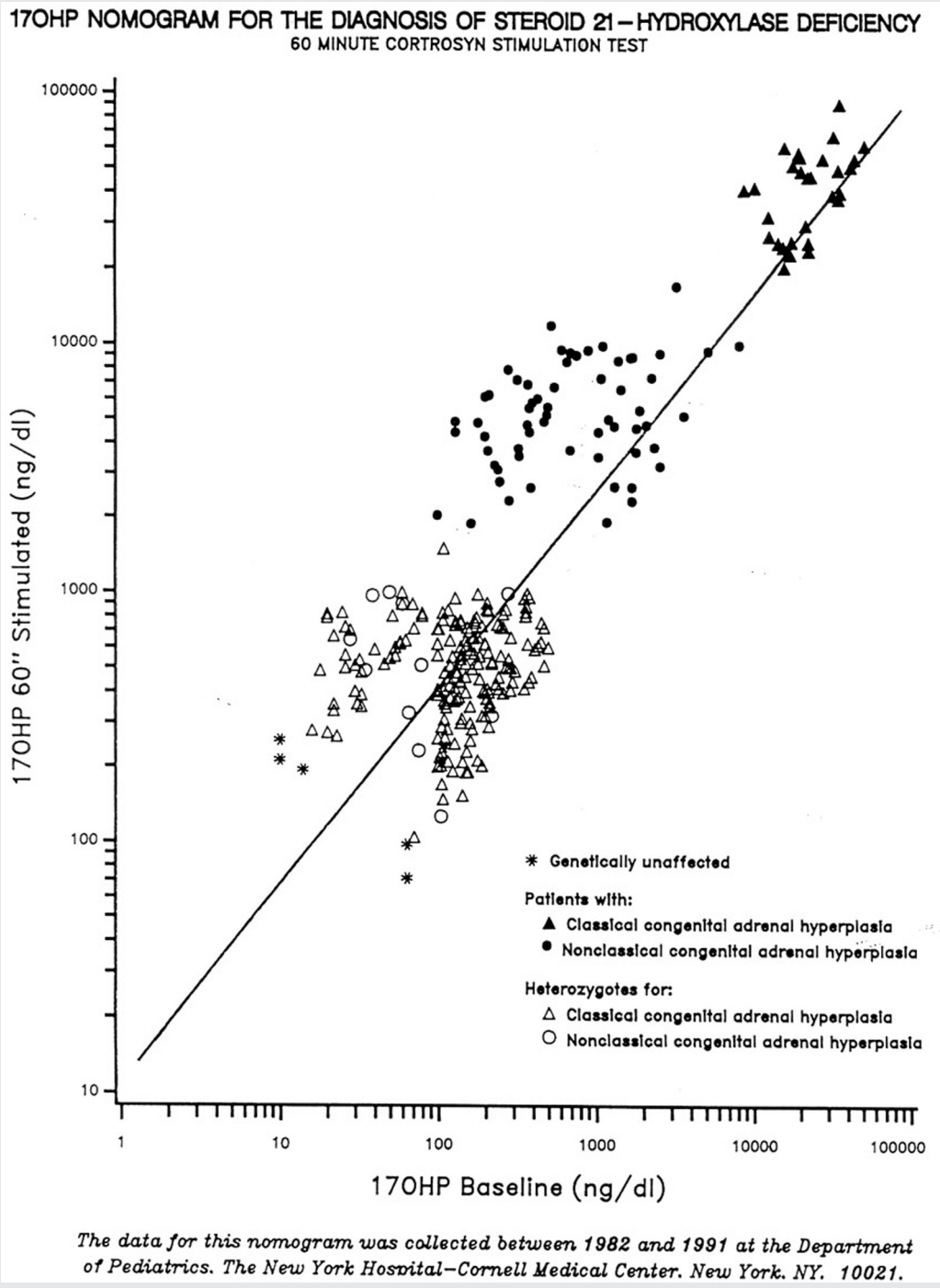
FIGURE 7



Nomogram regulating baseline to adrenocorticotropic hormone (ACTH) stimulation serum concentrations of 17-OHP. The scales are logarithmic. A regression line for all data points is shown (5). (Figure 2 adapted from New MI, et al. Genotyping steroid 21-hydroxylase deficiency: hormonal reference data. J Clin Endocrinol Metab 1983;57:320-6.)

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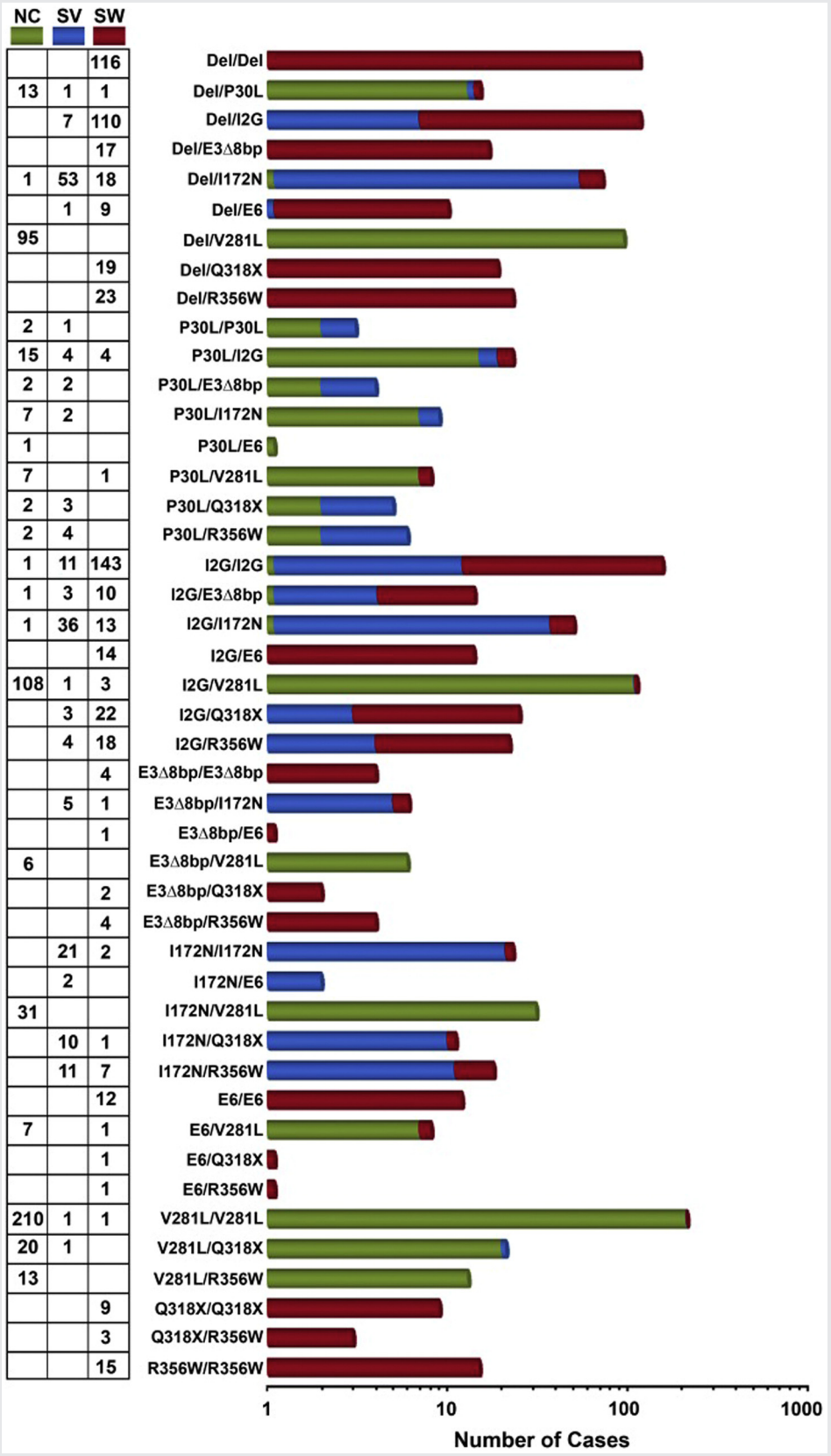
understood (17). While it was initially presumed that hyperandrogenemia leads to excess estrogen via peripheral aromatization, subsequent lines of inquiry have focused on the direct effects of elevated androgens on the gonadotropin-releasing hormone (GnRH) pulse generator itself (18). Treatment with steroids in CAH patients leads to normalization of luteinizing hormone (LH) levels and LH responsiveness to GnRH pulses, underscoring this mechanism (19). On the other hand, direct treatment of PCOS patients with androgens fails to alter basal LH secretion, although high-dose androgens slightly reduced follicle-stimulating hormone concentration in women

FIGURE 8



Frequency of *CYP21A2* genotypes in 1,507 congenital adrenal hyperplasia (CAH) patients. The number of CAH patients with each of the CYP21A2 genotypes is shown (7). Green, NC; blue, SV; red, SW. (Figure 3 from New MI, et al. Genotype-phenotype correlation in 1,507 families with congenital adrenal hyperplasia owing 21-hydroxylase deficiency. Proc Natl Academy Science 2013;110:2611-6.)

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with PCOS (20). Thus, the exact mechanism by which elevated androgens affect the hypothalamus and pituitary remains somewhat obscure.

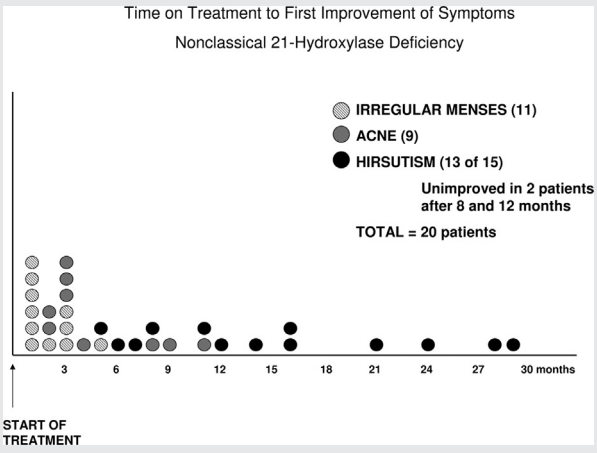
The elevated androgens encountered in NC-CAH also exhibit complex effects on the ovary itself. Elevated adrenal androgens have been demonstrated to inhibit granulosa cell aromatase activity in vitro, but direct administration of androgens leads to thickening of the ovarian capsule, an overall increase in the size of the ovary, and an expansion in the number of preantral follicles (21, 22). Given the colocalization of androgen receptor and follicle-stimulating hormone receptor mRNA in granulosa cells, it is not surprising that androgens are complex modulators of ovarian steroidogenesis with varying effects modulated by the extent and duration of androgen exposure (23).

Although patients affected with classical disease routinely require treatment with exogenous steroids, many individuals with NC-CAH will conceive with little or no intervention. Patients with classical disease routinely have significant anovulation and progesterone elevation in the follicular phase, as opposed to NC-CAH patients in whom oligo-ovulation is more common and progesterone elevation in the follicular phase is rarely encountered. In a longitudinal study of 95 patients with NC-CAH, 57.2% conceived without specific hormone treatments (24). This subset of patients had particularly mild phenotypes; patients exhibiting more pronounced hyperandrogenic symptoms are more likely to require treatment with glucocorticoids, but this intervention alone is typically sufficient to elicit ovulation. This type of successful treatment with low-dose glucocorticoids was first reported by Rosenwaks et al. in 1979 (2).

In a later study of 20 affected patients undergoing treatment for infertility, only 1 required additional treatment beyond glucocorticoids (25). Glucocorticoids can also be used for acne and hirsutism, albeit requiring much longer duration for symptom resolution (Fig. 9). For patients who are either poor candidates for glucocorticoids or in whom adverse reactions are noted, clomiphene citrate or aromatase inhibitors such as letrozole are often enough to induce ovulation (26). For the most refractory patients, oral ovulation induction agents or judiciously dosed injectable gonadotropins can be superimposed on low-dose glucocorticoid treatment, with a careful eye toward avoiding multifollicular recruitment and ensuing multiple gestations.

Nonclassical CAH is by far a subtler and milder enzymatic defect to the classical form of the disease. A nuanced understanding of NC-CAH will lead to increased detection of the disorder in those initially misdiagnosed as having PCOS, will assist in the detection of pregnancies at risk for severe genetic steroid disorders, and will facilitate appropriate ovulation induction and reduction in the hyperandrogenic symptoms that are a cornerstone of the disease.

FIGURE 9



Reversibility of symptoms in patients with nonclassical 21-hydroxylase deficiency (NC21OHD, n = 20). Preliminary data indicate that irregular menses and acne can be reversed with glucocorticoids within 3 months, whereas hirsutism requires nearly 30 months (4). (Figure 11 from New MI. Extensive clinical experience: nonclassical 21-hydroxylase deficiency. J Clin Endo Metab 2006;91:4205-14.)

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