Genetic Causes in Adrenal or Ovarian Hyperandrogenism in the Reproductive Years
Bals-Pratsch M, Seifert B, Ortmann O

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Hyperandrogenism

The accumulation of hirsutism within families and balding in male family members suggests a joint genetic cause. Hirsutism, acne and loss of hair are clinical signs of hyperandrogenism in the reproductive years. These bodily symptoms also are described as androgenisation, which is to be distinguished from virilization with clitoral hypertrophy up to the point of disorders of sex development (DSD). A hypertrichosis on the other hand is not androgen-dependent but rather ethnically conditioned.

Hyperandrogenism affects not only skin and hair, but also leads to abnormal menstrual cycles and infertility as well as disorders in the metabolism of carbohydrates and lipids. Like hirsutism and balding, polycystic ovaries, insulin resistance and obesity also appear more frequently within affected families. Metabolic disorders are likely the common cause for abnormal menstrual cycles and hyperandrogenism. A raised sensitivity of target cells as well as increased or reduced local activity of enzyme systems in the target cells can cause hyperandrogenism.

Androgens are mainly produced in the adrenal glands and in the ovaries as well as in fatty tissue. The most important androgens are testosterone and DHEAS. The localization of androgen-producing tumors is signaled by DHEAS (Fig. 1) for adrenal tumors and by testosterone for ovarian tumors. Suspection of a tumor exists if values are > 800 μg/dl for DHEAS and > 200 ng/dl for testosterone. In patients with androgenisation and hyperandrogenism with suspicion of neoplasms, imaging diagnostics of the adrenal glands and ovaries and, if indicated, of the pituitary gland are obligatory as well as diagnostics for internal metabolic disturbances.

Keywords: PCOS, androgenisation, virilization, CAH, candidate genes, functional genetic polymorphisms, CYP21

Figure 1. Clinical work-up of hyperandrogenism

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Congenital Adrenal Hyperplasia (CAH)

Inherited disorders of adrenal steroidogenesis result from a deficiency in one of the five enzymatic steps necessary for normal cortisol synthesis (Fig. 2). Precursors of cortisol and aldosterone accumulate and DHEAS and testosterone production increase. The most common gene mutation CYP21 on chromosome 6p21.3 causes deficiency of 21-hydroxylase and accounts for 95% of CAH cases. The incidence in newborns is 1:5,000–15,000. The precursor 17-OHP progesterone and androgen productions increase and cortisol and aldosterone biosynthesis are limited. 11β-hydroxylase deficiency is seldom and caused by CYP11B2 mutation (5% of CAH cases). The gene is located on chromosome 8q24.3 and the incidence of the gene mutation in newborns is 1:100,000. The precursor desoxycorticosterone (DOC) is accumulated, thus affected patients suffer from hypertension. Other gene mutations in the adrenal steroidogenesis such as the 3β-HSD-II-gene mutation on chromosome 1p13.1 with deficiency of 3β-hydroxy-steroid-dehydrogenase [1] and accumulation of 17-OH-pregnenolone are rare (<1% of CAH cases).

The virilizing characteristic of classic CAH (with salt loss or simply virilization) is the most common cause of disorders of sex development. This diagnosis is made by pediatric endocrinologists based on symptoms mostly in newborn or infant stages. Nowadays elevated 17-OHP is detected regularly within the newborn screening in Germany and other Western countries. Prompt treatment with glucocorticoids in simple virilization CAH (ca 25%) and also mineralocorticoids in CAH with salt loss (ca 75%) has to be initiated to avoid life-threatening events. The non-classic CAH (late-onset CAH) is mostly asymptomatic beginning at puberty because these patients do not have genital abnormalities. Instead, these patients are mainly seen first by gynecologists because of menstrual disorders like secondary amenorrhea or oligomenorrhea, hirsutism and acne. In adrenal hyperandrogenism with increased DHEAS, high 17-OHP values in the follicular phase of the cycle indicate CYP21 mutations. 17-OHP values do not represent any reliable discriminating factors even in combination with the adrenocorticotropic hormone (ACTH) test, unless the test results are generated in a highly specialized endocrine laboratory. Genetic counseling with molecular genetic diagnosis is mandatory in confirming the diagnostic of CAH. Patients with CAH should be regularly seen and treated with hydrocortisone by gynecologists and internists specialized in endocrinology [2].

CAH and the Desire to Have Children

CAH is a monogenic disorder with a frequency of 1:50 in heterozygous mutation carriers in central Europe. The expected ratio of homozygous affected, heterozygous or homozygous normal children in mutation carrier families according to the Mendelian rules of inheritance is 1:2:1. CAH homozygous females and males with a heterozygous partner even face a risk of 50% for affected children. To improve fertility in CAH females with menstrual disorders the hydrocortisone substitution regimen should be changed to three to four single doses including a dose at 3 a.m. [3].

Genetic counseling should be offered to all couples at risk before getting pregnant. The possibility of prenatal dexamethasone (DEX) treatment as an experimental strategy to prevent unwanted virilization in affected female embryos should be discussed with pediatricians and gynecologists experienced in endocrinology and prenatal medicine. Treatment with DEX 20 μg/kg bodyweight in three divided doses based on prepregnancy weight (maximum 1.5 mg daily) is to be started at the time of diagnosing a pregnancy. DEX crosses the placenta from the mother to the embryo, suppresses ACTH secretion and prevents exaggerated adrenal androgen produc-
tion and thus fetal hyperandrogenism. If treatment is started as late as the ninth week of pregnancy, virilization of the affected female fetuses has already occurred (Fig. 3). Thus DEX treatment should be started in all pregnancies at risk, although seven of eight fetuses are treated without reason at least for a short term [4]. It can be stopped in male or unaffected female fetuses after karyotyping and DNA analysis by chorionic villus sampling (CVS) at 9–11 weeks of gestation or amniocentesis at 15–16 weeks of gestation (Fig. 4). Although it is undisputable today that DEX obviates the need for traumatizing genital surgery in affected females, potentially harmful effects on cardiovascular, metabolic and neuroendocrine disorders in adult life cannot be excluded [5]. Recently long-term negative effects have been reported on verbal working memory and on certain aspects of self-perception even in short-term treated, CAH-unaffected children [6].

Thus, parents should be thoroughly informed about the potential risks and uncertainties as well as the benefits of the controversial aspects of prenatal treatment with DEX. It is important that all cases of prenatal treatment are reported to a CAH study center regarding the safety and future use of the treatment. In Germany, the “Arbeitsgemeinschaft Pädiatrische Endokrinologie” (APE), a pediatric endocrinology association, has been collecting data centrally on the prenatal CAH therapy since 1990 at the University Children’s Medical Center of Erlangen (e-mail: Helmuth-Guenther.Doerr@uk-erlangen.de).

Prenatal CAH therapy in Germany still requires optimization. Some of the affected families are not adequately advised and diagnosed regarding endocrinology and genetics. Because interdisciplinary specialized pregnancy guidance is often missing, frequently initiation of DEX treatment is too late or with an inadequate dose of DEX or without treatment observation. Reporting to a central registration office only takes place partly (Download registration form: http://www.repromedizin.de/files/downloads/aktueller-arztfragebogen-ags.pdf).

**Polycystic Ovary Syndrome (PCOS)**

Functional hyperandrogenism often accompanies the sonographic image of polycystic ovaries (Fig. 5). The cardinal clinical symptoms are acne, hirsutism and an abnormal menstrual cycle. Stein and Leventhal [7] were the first to describe this syndrome. According to Geisthövel et al [8] patients with polycystic ovaries can be divided into three groups: “ovarian form”, “adrenal form” or “metabolic syndrome”.

This complex grouping division, which corresponds to a category-parameter-cluster including a functional sonographic ovary score, has so far not been able to prevail. The classification of the American Association of Reproductive Medicine (ASRM) and the European Society of Human Reproduction and Embryology (ESHRE) [9] is simple to use in clinical routine. PCOS, however, can only be diagnosed according to the current consensus from ASRM and ESHRE if at least two of the three PCOS criteria are fulfilled (ultrasound, hyperandrogenism, and anovulation or a cycle > 35 days [Fig. 1]). According to the ASRM/ESHRE consensus, other causes of hyperandrogenism, such as classic or non-classic CAH or Cushing’s syndrome, are exclusion criteria for PCOS.
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Candidate Genes

For many years, there has been a search for candidate genes for PCOS. In accordance with common clinical symptoms and findings like obesity, resistance to insulin, disorders in metabolizing lipids, hyperandrogenism, anovulation and tendency to miscarriage, uncountable genes in correlation with these symptoms were examined (Fig. 6). Research particularly concentrates on genes in the regulation of insulin, the maturation of follicles and androgen secretion and effect [10]. The results are up to now inconsistent and contradictory because the areas of research are based on different definitions of PCOS as well as on a small number of cases [11].

A potential candidate gene is the insulin gene, which influences the secretion and effect of insulin. The promoter of the insulin gene determines its expression. A VNTR (variable number of tandem repeats) polymorphism exists here. The number of repeats influences the expression of the insulin gene. Most women carry class-I alleles with an average of 40 repeats or class-III alleles with a mean of 157 repeats. An association between the existence of class-III alleles of the insulin gene and PCOS is probable. This would explain the risk for hyperinsulinism and type-II diabetes in PCOS patients [12].

A further candidate gene is the insulin-like growth factor (IGF). The homozygotic mutation of the IGF2 gene with two G alleles of the Apa1 variant is associated with PCOS [13]. The existence of the G allele possibly causes a raised IGF2 expression and secretion in the liver. IGF2 stimulates the production of androgens in the ovaries and adrenal glands and thus possibly explains an aspect of the pathomechanism in PCOS. On the other hand, our data showed no significant difference for the genome as well as for the allele distribution in the IGF2 gene among 219 PCOS patients and 152 healthy subjects [14].

CYP11a gene codes the cytochrome 450scc as the key enzyme for the androgen biosynthesis and metabolism. It is localized on chromosome 15. While Gharani et al. [15] found an association between the 4R gene type polymorphism in the CYP11a gene and hyperandrogenism in PCOS patients, San Millán et al. [16] could not prove a correlation.

The examination of 37 candidate genes in 150 PCOS families showed an association with PCOS only for the follistatin gene [17]. As opposed to activin, follistatin inhibits follicular growth, increases ovarian androgen production, suppresses the endogenous FSH level and inhibits the release of insulin. These effects are characteristic of PCOS. Up to now, this data could not be confirmed [18].

In the meantime, with the D19S884 allele 8 (A8) within the intron 55 of fibrillin 3 (FBN3) gene on chromosome 19p13.2, a possible PCOS candidate gene has been identified by a workgroup from Chicago [19]. In this examination of 412 PCOS families, the D19S884 polymorphism was associated with resistance to insulin and a defective β-cell function of the pancreas.

From a clinical perspective, not only the pathogenesis of the PCOS is of significance but also the treatment options, particularly in infertility. The interaction between FSH and its receptor plays a key role in ovarian stimulation with gonadotropins. Polymorphisms in FSH receptor genes regarding the ovarian response were examined by several workgroups.

Looking at the genotype of the FSH receptor gene polymorphism p.N680S, patients with a slight or increased ovarian response to FSH stimulation can be identified before the beginning of the stimulation cycle [20]. Withdrawal from treatment and severe ovarian hyperstimulation syndrome therefore can possibly be avoided in the future.

The years to come will be exciting because genetic diagnostics will have increasing clinical significance in the clarification of PCOS, resulting in improved treatment strategies for internal medicine, endocrinology and reproductive medicine.
## Practical Aspects

The most common cause of hyperandrogenism in the reproductive years is PCOS. For several years research has concentrated on identifying potential candidate genes for PCOS without a breakthrough yet. Although PCOS is frequent, rare cases of endocrine neoplasms and late onset CAH have to be distinguished from PCOS. Patients at risk of giving birth to CAH homozygous female fetuses should be offered prenatal dexamethasone treatment to prevent virilization in affected female embryos.

### References:


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