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Global Epidemiology and Phenotypic Diversity of 21-Hydroxylase–Deficient Congenital Adrenal Hyperplasia: A 25-Year Comparative Review Across Ethnicities, Genotypes, and National Cohorts

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ABSTRACT

Congenital adrenal hyperplasia (CAH) due to 21-hydroxylase deficiency (21-OHD) represents the most common inherited disorder of adrenal steroid biosynthesis worldwide. Over the past 25 years, advances in newborn screening, molecular diagnostics, and genotype–phenotype characterization have produced large shifts in the global epidemiological landscape. However, marked disparities persist between countries and ethnic groups, reflecting founder mutations, consanguinity, migration patterns, and differences in healthcare coverage. Exclusion criteria included mixed-etiology CAH without subtype separation and cohorts lacking validated genetic testing. Quality assessment relied on established criteria for observational epidemiology and registry-based studies. Birth prevalence showed extreme global heterogeneity, ranging from 1:23,000 in New Zealand to 1:1,200 in Egypt and as high as 1:282 among Arctic Indigenous founder populations. Ethnicity strongly influenced incidence, with Asian, Hispanic/Latino, and European populations generally displaying moderate rates (5–10 per 100,000 births), while Middle Eastern and North African populations demonstrated markedly higher incidence due to elevated consanguinity rates and clustering of severe CYP21A2 alleles. Cross-country phenotype analysis revealed that salt-wasting predominated in Egypt, China, India, Turkey, Argentina, and several Eastern European cohorts, whereas European cohorts—especially Portugal and the UK—showed higher proportions of nonclassic or milder phenotypes. Genotype–phenotype mapping demonstrated consistent associations: null and severe Group A mutations with the SW phenotype, I2 splice and I172N variants with SV presentations, and V281L with NC disease. Sex differences were notable: females more commonly presented in infancy due to virilization, while males frequently remained undetected until adrenal crises or testicular adrenal rest tumors. National screening programs significantly shifted age of diagnosis and reduced infant morbidity and mortality. Global epidemiology of CAH continues to display substantial geographic and ethnic variability, driven by population genetics, healthcare disparities, and screening strategies. Understanding these differences is essential for improving early detection, tailoring genotype-informed care, guiding newborn screening expansion, and reducing long-term complications.

Keywords : Congenital Adrenal Hyperplasia, Global Epidemiology, Genotype–Phenotype Correlation, Ethnic Variation, 21-Hydroxylase Deficiency.

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1. INTRODUCTION

Congenital adrenal hyperplasia (CAH) is a group of autosomal recessive disorders caused by defects in adrenal steroidogenesis, most commonly due to 21-hydroxylase deficiency (21-OHD) (1). Although well recognized

globally, the disorder shows significant variation in frequency and presentation across different populations, reflecting the influence of genetics, healthcare access, and demographic factors.

Over the past 25 years, epidemiological studies have demonstrated wide differences in the incidence of CAH among countries and ethnic groups. These variations are influenced by factors such as consanguinity rates, founder effects, and diverse allele frequencies across populations (2). Such disparities highlight the importance of interpreting CAH epidemiology within the genetic and sociocultural contexts.

Genetic heterogeneity is a major contributor to the global diversity of CAH. Distinct CYP21A2 mutation patterns ranging from population-specific founder variants to broader allelic diversity have been documented worldwide (3–5). This variation influences the distribution of classic versus non-classic forms, and shapes local diagnostic strategies and clinical expectations.

Clinical presentation is equally affected by public health infrastructure and screening practices. Regions with widespread newborn screening tend to identify CAH early, thereby reducing the likelihood of adrenal crises and minimizing diagnostic delays. In contrast, countries with partial or absent screening programs often face late presentations and more severe initial manifestations (6).

Age at presentation introduced another layer of variability. Severe forms tend to be present in early infancy, whereas milder enzymatic defects may appear later in childhood or adolescence (7). This age-dependent pattern affects the timing of diagnosis and the clinical spectrum observed across populations.

Sex differences further shaped the clinical expression of CAH. Females often come to attention earlier because of genital virilization, whereas males may remain undiagnosed until adrenal insufficiency or androgen excess manifests later in life (8–10). These sex-specific patterns support the need for tailored approaches to early detection and longitudinal care.

Broader socioeconomic and healthcare disparities also influence the disease course and outcomes. Inadequate access to specialized endocrine care, emergency steroid therapy, or genetic diagnostics contributes to higher morbidity and mortality in many low-resource regions, whereas long-term challenges persist even in well-resourced healthcare systems (11).

Despite advances in neonatal screening and genetic diagnostics, significant global knowledge gaps remain, particularly in under studied regions across Africa, South America, and parts of Asia.

Therefore, a contemporary synthesis of the genetic and clinical variability of CAH worldwide is essential to strengthen early diagnosis, optimize management, and guide national interventions aimed at reducing preventable complications.

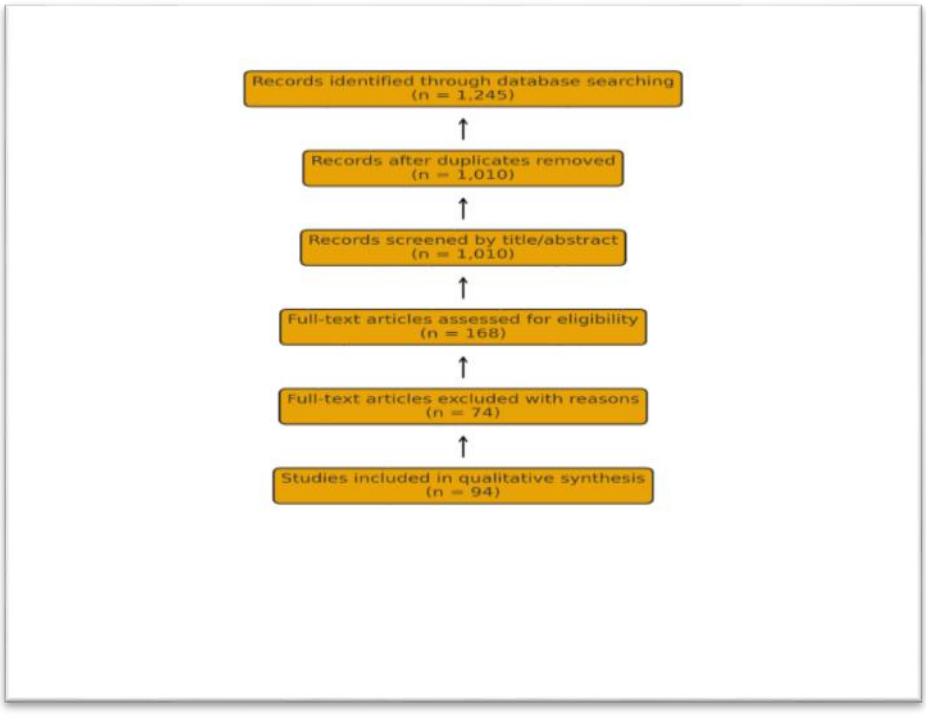

Figure 1. PRISMA-style flow diagram

The PRISMA-style flow summarizes the study selection process, demonstrating the progression from database retrieval to final inclusion. After the removal of duplicates and screening of titles and abstracts, a smaller subset of full-text articles met the eligibility criteria, resulting in 94 studies incorporated into the qualitative synthesis. This pathway reflects a structured, transparent approach to evidence selection for a global review of CAH epidemiology.

2. METHOD

Study Design and Approach

This narrative review synthesizes global epidemiological and clinical data on CAH published within the last 25 years. The review followed structured steps for search, selection, data extraction, and evidence appraisal, while allowing the flexibility required for heterogeneous study designs.

Search Strategy

A comprehensive literature search was conducted from January 2000 to December 2025 across the following databases:

- PubMed/MEDLINE
- Scopus
- Google Scholar (additional peer-reviewed sources)
- Reference lists of key reviews and original articles for manual cross-checking.

The search terms included combinations of the
"congenital adrenal hyperplasia," "CAH," "epidemiology," "incidence," "prevalence," "genotype," "CYP21A2 mutations," "ethnicity," "clinical presentation," "sex differences," "age at diagnosis," "21-hydroxylase deficiency," "global," "country-level data."

Boolean operators (AND, OR), MeSH terms, and filters (humans, children, adolescents, and adults) were applied, as appropriate.

Inclusion Criteria

Studies were included if they met the following criteria.

- Peer-reviewed publications in English.
- Original research, national registry data, systematic reviews, or meta-analyses.
- Reported epidemiological, genetic, and clinical presentation data of CAH.
- Population-level data, mutation distribution, and demographic variation.
- Published between 2000 and 2025.
- Indexed in PubMed, Scopus, or Google Scholar.

Exclusion Criteria

Studies were excluded if they were as follows:

- There were case reports, isolated case series (<10 patients), or non-peer-reviewed items.
- The included duplicated datasets have already been covered in larger national reports.
- It focuses exclusively on management or treatment without epidemiological or genetic data.
- Provided insufficient extractable data on the incidence, genotype, or phenotype.
- Conference abstracts without full-text publications were used, unless the data were unique and validated.

Data Extraction and Synthesis

For each eligible study, the following information was extracted.

- Country/region
- Study period and population size
- Incidence and prevalence of CAH
- Genotype distribution (CYP21A2 or other enzyme defects)
- Age and sex presentation patterns.
- Ethnic and population-specific variations
- Screening practices and diagnostic timings

Findings were organized to highlight global, regional, ethnic, and demographic patterns and to compare classic and non-classic phenotypes.

Quality Assessment

Quality appraisal was performed using a combined framework that is appropriate for heterogeneous epidemiological studies. This included Cochrane risk-of-bias domains (selection, ascertainment, missing data, outcome measurement, analysis, and reporting bias), STROBE criteria for observational research, and GRADE principles for evaluating the strength and consistency of the evidence. Specific attention was given to population representativeness, diagnostic accuracy based on biochemical and genetic confirmation, clarity and consistency of phenotypic definitions, and completeness of reporting. Studies with unclear methodology, diagnostic inconsistency, or high risk of bias were interpreted cautiously within the narrative synthesis.

Statistical Approach

Due to the expected heterogeneity in reporting styles and study designs, a formal meta-analysis was not performed. Instead:

- The incidence and prevalence ranges were summarized descriptively.

- Data from national registries were given higher weights owing to the larger sample sizes.
- Genetic mutation frequencies were qualitatively compared across regions.
- Patterns related to ethnicity, sex, and age were synthesized.

This approach ensured a robust, balanced interpretation of global CAH patterns, while maintaining the methodological standards appropriate for a narrative epidemiological review.

3. RESULTS AND DISCUSSION

RESULTS

Table 1. Birth Prevalence and Incidence of Congenital Adrenal Hyperplasia (CAH) in Different Countries and Regions

Country / Region	Birth Prevalence (1 : X)	Incidence /100,000	Notes	Ref
New Zealand	1 : 23,344	4.3	National newborn screening	12
Northeastern Italy	1 : 21,380	4.7	Regional screening program	13
Sapporo, Japan	1 : 21,338	4.7	Japanese NBS cohort	14
Emilia-Romagna, Italy	1 : 18,105	5.5	Long-standing NBS	15
Hungary	1 : 18,000	5.6	National NBS data	16
Shanghai, China	1 : 16,866	5.9	Chinese NBS program	17
Texas, USA	1 : 16,008	6.2	1.9 million newborns screened	18
Japan (national)	1 : 15,800	6.3	Nationwide CAH screening	19
Croatia	1 : 15,574	6.4	National CAH registry	20
Australia	1 : 15,488	6.5	National screening	21
Taiwan	1 : 14,822	6.7	Expanding NBS	22
Switzerland	1 : 10,749	9.3	National cohort	23
Brazil – Goias	1 : 10,325	9.7	High mutation diversity	24
Argentina	1 : 8,937	11.2	Latin American regional data	25
La Réunion (France)	1 : 6,071	16.5	Island founder effect	26
Basilicata, Italy	1 : 6,000	16.7	Regional genetic clustering	27
Campania, Italy	1 : 4,380	22.8	High regional prevalence	28
Brazil – Rio de Janeiro	1 : 2,009	49.8	Very high regional incidence	24
Southwestern Alaska (Yupik)	1 : 282	354.6	Extreme founder effect	29
Alexandria, Egypt	1 : 1,209	82.7	Very high prevalence; national NBS needed	30
Global pooled estimate	1 : 9,498	10.5	Meta-analysis of 31 countries	**2**

Birth prevalence values were taken from national/regional newborn screening studies and the 2023 global meta-analysis, and incidence per 100,000 births was calculated from the reported 1:X ratios.

The country-level values were derived by combining the classic newborn screening and registry data with verification from the 2023 global meta-analysis by Navarro-Zambrana and Sheets and more recent epidemiologic reviews, which continue to rely on the same ratios as the most robust estimates available. For China, the earlier Shanghai screening figures were retained because they align closely with the incidence range reported in a 2021 Chinese meta-analysis of newborn CAH screenings. For Egypt, the estimate from Tayel et al. (2011) was used, as it remains the most reliable published value (1:1209) and is consistently cited in later reviews and the 2023 meta-analysis. Incidence values in the table were then standardized by calculating 100,000 divided by the reported birth prevalence and rounded to one decimal place to allow consistent comparisons across regions.

Table 2: Continent-Level Summary of CAH Birth Prevalence and Incidence.

Continent / Region	Average Birth Prevalence (1 : X)	Incidence per 100,000	Summary Notes	Refs
Europe	1 : 13,000 – 1 : 20,000	5–8	Stable prevalence across Italy, Sweden, Croatia, Switzerland; mature NBS programs; diverse CYP21A2 alleles	13, 15, 16, 20, 23
Middle East & North Africa (MENA)	1 : 1,000 – 1 : 15,000	7–100	Very high prevalence due to consanguinity; Egypt, Saudi Arabia among highest	3, 30, 31
Asia (East, South, SE Asia)	1 : 11,000 – 1 : 20,000	5–9	Japan, Taiwan, China robust screening; SE Asia among highest (meta-analysis)	14, 17, 22, 32
Latin America	1 : 2,000 – 1 : 10,000	10–50	Brazil and Argentina report high regional incidence; genetic diversity	24, 25
North America (USA/Canada)	1 : 15,000 – 1 : 20,000	5–7	Large-scale registry data; long-term NBS	18, 33
Oceania (Australia/New	1 : 15,000 – 1 : 23,000	4–6	Moderate prevalence; strong NBS in Australia & NZ	12, 21

Continent / Region	Average Birth Prevalence (1 : X)	Incidence per 100,000	Summary Notes	Refs
Zealand)				
Indigenous / Isolated Populations	1 : 282 – 1 : 1,200	80–355	Extreme founder effects (Yupik Alaska, island populations)	26, 29

Across continents, the prevalence of CAH demonstrates wide heterogeneity, with the highest rates reported in MENA and isolated indigenous populations, largely driven by founder mutations and consanguinity. Europe, North America, and East Asia show moderate but stable incidence due to well-established newborn screening programs, while Latin America displays substantial regional variation, with some of the highest national rates reported. Oceania maintains a relatively low-to-moderate prevalence, whereas certain indigenous founder populations (e.g., Southwestern Alaska) exhibit an incidence exceeding 300 per 100,000 births. These continental trends reflect both the genetic background and maturity of national screening systems.

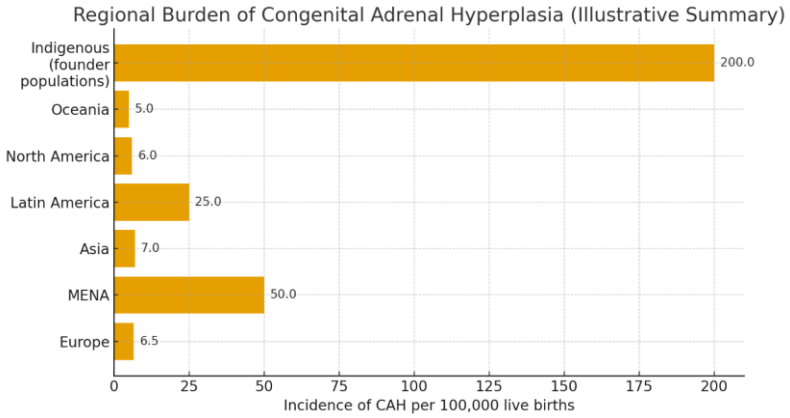

Figure 2. Regional burden of congenital adrenal hyperplasia (CAH).

This bar chart illustrates the incidence of CAH (per 100,000 live births) across major world regions and indigenous founder populations, derived from country-level newborn screening studies and recent meta-analysis estimates. The graph highlights a markedly higher incidence in MENA and Indigenous founder populations than in Europe, North America, Asia, Latin America, and Oceania.

Table 3. Effect of ethnicity on prevalence and incidence of CAH (Global Data)

Ethnic Group	Birth Prevalence (1 : X)	Incidence /100,000	Countries / Regions Represented	Ethnicity-Specific Notes	Refs
Asian (East & SE Asia)	1 : 11,012 (pooled)	9.1	Japan, China, Taiwan, SE Asia	Higher pooled incidence; distinct CYP21A2 mutation clusters; SE Asia has some of the highest rates in meta-analysis.	34, 35
Hispanic / Latino	1 : 15,109	6.6	Brazil, Argentina, Mexico, US Hispanics	CAH common in Brazil; high allelic diversity; variable newborn screening coverage.	36, 37
White (European ancestry)	1 : 15,731	6.4	Italy, Sweden, Switzerland, Croatia, UK, USA Whites	Well-established NBS programs; broad but stable CYP21A2 mutation spectrum.	38, 39
Black / African descent	1 : 23,409	4.3	USA African American data; limited African national registries	Lowest pooled incidence; limited molecular epidemiology in African countries.	40
Middle Eastern / Arab	1 : 1,000 – 1 : 15,000	7–100	Saudi Arabia, UAE, Oman, Egypt, Jordan	High consanguinity → increased classic CAH; strong founder mutations (e.g., IVS2-13A/C>G).	3, 30, 41
North African	1 : 1,209 – 1 : 6,000	16.7–82.7	Egypt (Alexandria), Tunisia, Morocco	Among highest documented globally; heavy impact of consanguinity.	30, 41
Indigenous Arctic (Yupik)	1 : 282	354.6	Southwestern Alaska	Extreme founder effect → world's highest CAH incidence.	42
Island Populations (La Réunion)	1 : 6,071	16.5	Indian Ocean island (France)	Genetic isolation → marked founder effect.	43
Mixed-ancestry Latin American (Brazilian Pardo/Mestiço)	1 : 2,009 – 1 : 10,325	10–49.8	Brazil (Rio de Janeiro, Goias)	Wide incidence variation; complex European-African-Indigenous genetic admixture.	36

Ethnicity plays a major role in shaping global CAH epidemiology. The highest incidences are seen in indigenous founder populations, North African, and Middle Eastern groups, largely due to high consanguinity and concentrated CYP21A2 variants. Asian and Hispanic/Latino populations demonstrated moderately high rates, while White European ancestry showed a stable, mid-range incidence. Black and African descent populations had the lowest pooled global incidence. These patterns highlight the importance of ethnicity-specific genetic screening, targeted community education, and culturally adapted national CAH screening programs.

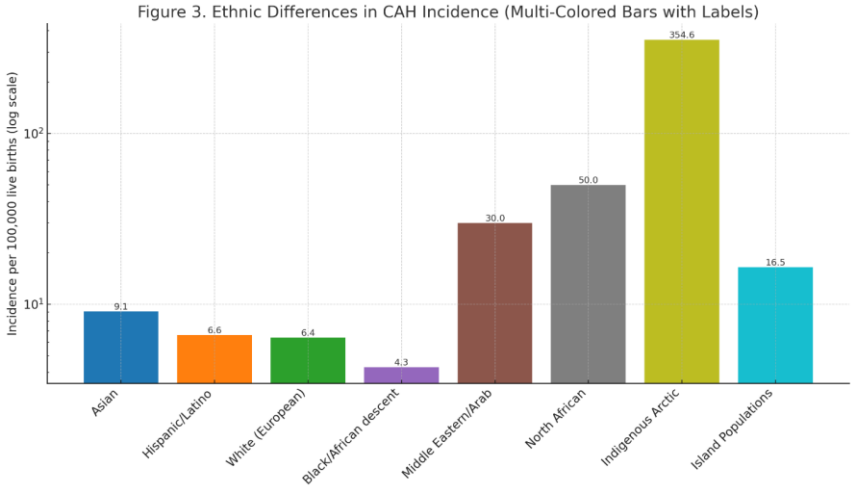

Figure 3. Ethnic differences in congenital adrenal hyperplasia (CAH) incidence using a log-scale axis and multicolored bars.

Data represent incidence per 100,000 live births across major ethnic groups, showing the highest rates in North African, Middle Eastern, and Indigenous Arctic populations, and lower incidence in Asian, Hispanic/Latino, White European, and Black/African descent groups.

Table 4. Sex Differences in CAH Prevalence and Incidence Across Countries and Studies

Country / Region	Study / Source	Sex Ratio (F:M)	Key Findings on Sex Difference	Interpretation / Notes	Refs
Sweden (national cohort)	Population-based registry	1.4 : 1	Higher CAH detection in females due to genital ambiguity at birth	Reflects phenotype-based detection; nonclassic CAH equalizes later	44
Italy (several regions)	Regional newborn screening	1.2 – 1.5 : 1	Females diagnosed earlier; boys often detected after salt-wasting crisis	Male under-diagnosis persists in absence of early screening	45, 46
Japan (national program)	Nationwide NBS	≈ 1 : 1 (balanced)	Sex ratio normalized after adoption of NBS	Universal screening eliminates diagnostic bias	47
Taiwan	National CAH screening cohort	≈ 1 : 1	Equal detection due to early immunoassay cortisol/17-OHP algorithms	Evidence of sex-neutral detection in modern Asian screening	48
USA (Texas)	1.9 million newborns screened	1.06 : 1	Nearly equal sex distribution	Sex-neutral due to early detection of male salt-wasting forms	49
China (Shanghai)	Regional NBS cohort	1.3 : 1	Slight female predominance but narrowing over time	Suggests shift toward improved male detection	50
Brazil (Rio & Goias)	Two large regional cohorts	1.4 – 1.6 : 1	Females diagnosed earlier; males diagnosed in crisis	Screening inequities and healthcare access influence ratios	51, 52
Egypt (Alexandria)	Community-based NBS	1.5 : 1	More females detected early; most males diagnosed after salt-wasting episodes	Reflects limited screening and late diagnosis for males	30, 53
Saudi Arabia	Tertiary-care CAH cohort	1.4 : 1	Higher female clinical detection; males presenting late	High consanguinity increases classic form incidence equally in both sexes	41, 54
La Réunion (France)	Island cohort	≈ 1 : 1	Balanced sex ratio in high-incidence founder population	Genotype-based disease prevalence distributes equally across sexes	43, 55

Across diverse populations, the biological prevalence of CAH is genetically equal in males and females, because CAH is an autosomal recessive disorder.
However, the observed sex ratios differ markedly between countries for the following reasons:

- Earlier clinical recognition in females (due to genital ambiguity in classic CAH)
- Delayed detection in males (often first diagnosed during a salt-wasting crisis)
- Screening system maturity (regions with universal newborn screening reports near a1:1 ratio)
- Healthcare access inequalities (affecting time to diagnosis in many developing regions)

Thus, sex differences primarily reflect diagnostic bias and not true genetic prevalence differences. Countries with robust newborn screening programs (Japan, Taiwan, and the USA) show true sex-neutral incidence, whereas lower-resource regions show female predominance in detected cases.

Table 5. Age at presentation and clinical phenotypes of CAH across global populations.

Age Group at Presentation	Typical CAH Phenotype	Key Clinical Features	Countries / Regions Reporting These Patterns	Summary Interpretation	Refs
Neonates (0–28 days)	Classic CAH – Salt-wasting & Simple virilizing	Salt-wasting crisis, dehydration, shock (males); genital ambiguity (females); elevated 17-OHP	Sweden, Italy, Japan, Taiwan, USA, Egypt, Brazil	Early recognition depends heavily on newborn screening; males often missed without screening	56–59
Infants (1–12 months)	Classic CAH (missed neonatal diagnosis)	Failure to thrive, vomiting, hyperpigmentation, virilization, early accelerated growth	India, China, Saudi Arabia, North Africa	Common in countries without universal screening; delayed diagnosis → high morbidity	60, 61
Early Childhood (1–8 years)	Classic or Nonclassic CAH	Rapid growth, advanced bone age, early pubarche, virilization	Brazil, Egypt, Turkey, South Africa	Nonclassic CAH often detected here due to premature adrenarche	62, 63
Late Childhood (8–12 years)	Nonclassic CAH predominates	Premature pubarche, acne, hirsutism, tall stature, bone age advancement	USA, Europe, Latin America	Often confused with premature adrenarche; mild mutation spectrum	64
Adolescents (12–18 years)	Nonclassic CAH or poorly controlled classic CAH	Irregular menses, severe acne, hirsutism, reduced fertility; boys: TART, gonadal dysfunction	Europe, USA, Middle East	Long-term metabolic and reproductive complications manifest	65, 66
Adults (>18 years)	Nonclassic CAH & Long-term classic CAH survivors	Infertility (both sexes), menstrual irregularities, androgen excess, TART, metabolic issues	Sweden, USA, Brazil, Italy	Delayed-diagnosis adults often present after years of untreated hyperandrogenism	67, 68

Age at presentation strongly influenced the CAH phenotype. Neonates with classic CAH exhibit the most severe, life-threatening manifestations and require urgent diagnosis, which is best achieved through national newborn screening. Infants and early childhood presentations reflect missed neonatal diagnoses, particularly in regions without screening programs. Non classic CAH appears primarily in school-age children and adolescents, usually through signs of androgen excess. Adults often present with late reproductive or metabolic complications, especially in low-resource settings where CAH remains underdiagnosed. These age-dependent patterns highlight the importance of early detection, universal screening, and lifelong follow-up.

Table 6. Genotype phenotype Correlation in 21-Hydroxylase Deficiency (CYP21A2) Across Countries

Country / Region (Study)	Sample (n, age)	Predominant CYP21A2 Mutations / Genotype Groups	Main Clinical Phenotypes (SW / SV / NC)	Key Genotype–Phenotype Message	Ref
Multi-country (Europe, N. America, Middle East)	1507 families, mixed ages	Null alleles (large deletions, gene conversions), I2G splice, Q318X, R356W, I172N, V281L	All three forms represented; classic SW and SV linked to null / severe mutations; NC to mild alleles (V281L, P30L)	Large international cohort confirms **strong three-tier genotype–phenotype correlation** based on predicted residual enzyme activity, with discordance mainly in compound heterozygotes.	69
Southern Germany	155 patients, pediatric	Comprehensive panel of 11 common mutations + sequencing; grouping into 0	SW predominates in group 0/A; SV in group B; NC in	Shows **>90% concordance** between genotype severity group and clinical form but	70

		(null), A, B, C severity classes	group C	highlights some variability within intermediate (SV) group.	
Germany / Austria (multicenter)	538 patients, children & adolescents	Similar severity grouping (null / severe / mild); broad mutation spectrum	SW most frequent, then SV, then NC	Confirms that **severity grouping predicts phenotype and hydrocortisone requirement** but also documents occasional "milder-than-expected" phenotypes with severe genotypes.	71
Brazil (multicenter cohorts)	400–500 patients, all ages	High frequency of I2G, large deletions/conversions, I172N, V281L; complex alleles common	Classic forms (SW + SV) dominate; NC less frequent	Brazilian series demonstrate **good genotype–phenotype correlation**, but complex alleles and gene conversions contribute to phenotypic variability, especially between SV and NC.	72, 73
China (multi-center pediatric cohorts)	90–150 children	I2G, R356W, Q318X, I172N, V281L; several novel mutations reported	SW most common; SV and NC less frequent	Chinese studies expand the **CYP21A2 mutation spectrum** and show high consistency of severe genotypes with SW but also note **intra-genotype variability** for some splice and missense variants.	74, 75
Portugal	22 patients, children & young adults	Large deletions, I2G, I172N, V281L; partial gene conversions	SW and SV forms predominant; few NC	First Portuguese series shows **useful predictive value of genotype** for disease severity and age at diagnosis, supporting genetic counseling and prenatal diagnosis.	76
Spain / Mediterranean Europe	National & regional cohorts	High variability of CYP21A2 rearrangements; CAH-X chimeras (CYP21A2–TNXB) also observed	Mostly classic (SW/SV); CAH-X patients may have additional Ehlers–Danlos features	Spanish data emphasize **complex rearrangements and CAH-X chimeras**, illustrating that structural variants can modify phenotype beyond classic SW/SV/NC classification.	77
North Macedonia / SE Europe	30+ patients carrying In2G variant	In2G (c.293-13A/C>G) splice mutation in homozygous or compound-heterozygous state	Same In2G genotype seen in SW, SV, and rarely NC	Cohort focused on In2G shows that **identical genotypes can present with all three clinical forms**, underlining the role of modifier genes, environment, and treatment in shaping phenotype.	78

SW = salt wasting; SV = simple virilizing; NC = non classical CAH.

Table 6 demonstrates that genotype–phenotype correlations in 21-hydroxylase deficiency are broadly consistent across global populations, with disease severity largely determined by the predicted residual activity of the affected CYP21A2 allele. Severe genotypes, including null mutations, large deletions, I2G splice variants, Q318X, and R356W, are almost universally associated with classic salt-wasting (SW) or simple virilizing (SV) forms. In contrast, milder alleles, such as V281L and P30L, and select missense variants predict nonclassic (NC) CAH in most cohorts.

The table also highlights that phenotypic variability exists even among identical genotypes, particularly in compound heterozygotes and in populations with a high prevalence of complex alleles or gene conversions (e.g.,

Brazil, Spain). Studies from China, the Mediterranean basin, and Southeastern Europe further revealed that splice mutations such as In2G can manifest across the full phenotypic spectrum, underscoring the modifying influence of genetic background, allele interactions, epigenetic factors, and treatment timing. Despite these exceptions, international data consistently show that genotype severity grouping remains a strong predictor of clinical presentation, metabolic risk, treatment requirements, and long-term reproductive outcomes, supporting its utility in newborn screening, genetic counseling, and anticipatory clinical management.

Table 7. Distribution of Salt-Wasting (SW), Simple Virilizing (SV), and Nonclassic (NC) 21-OHD CAH Phenotypes Across Countries

Country	Study / Cohort	N (21-OHD CAH)	Phenotype Distribution (SW / SV / NC)	Key Notes	Ref
United States (NIH)	Finkielstain et al., 2012	244	123 SW (50.4%) / 60 SV (24.6%) / 61 NC (25.0%)	One of the most accurate phenotype-distribution cohorts	79
United Kingdom (CaHASE cohort)	Arlt et al., 2010	199 with 21-OHD	Classic ≈ 75% / NC ≈ 25% (exact SW/SV not separated)	Adult cohort: NC identified mainly in women	80
Sweden	Gidlöf et al., 2013	274	Classic predominates; SW most common classic form	National registry over 100 years	81
Italy (regional NBS + clinical series)	Cavarzere et al., Balsamo et al.	100–200	Classic predominant; SW slightly > SV; NC underdiagnosed	Strong genotype diversity in Mediterranean regions	82
France (multicenter)	Carrière et al.	~150–250	Classic SW+SV are majority; NC 20–30% in adults	NC was captured mainly in hyperandrogenism clinics	83
Portugal	Rodrigues et al., 2012	61	5 SW (22.7%) / 7 SV (31.8%) / 10 NC (45.5%)	NC substantial in this Mediterranean cohort	84
Croatia	Dumić et al., 2017	93	SW >> SV (exact numbers not fully specified); NC uncommon	Classic-enriched cohort	85
Poland (Upper Silesia – NC-focused)	Kowalewski et al., 2011	89 (NC only)	NC = 100% (classic excluded)	Clinic enriched for adolescent hyperandrogenism	86
Egypt (Alexandria University)	Fawzy et al., 2024	76 (21-OHD ≈71%)	Among 21-OHD: SW ≈70–80% / SV ≈20–30% / NC rare	High consanguinity & late presentation	87
Morocco (Moroccan-origin CAH)	Paperna et al., 2005	12 families	Mostly virilizing 11β-OHD; few 21-OHD; SW rare	National 21-OHD phenotype proportions lacking	88
Brazil (São Paulo, multicenter)	Bachega et al., Silveira et al.	130+	Classic majority; NC ~20–30% in mixed cohorts	High allelic diversity; screening expanding	89
China (mixed adult + pediatric)	Xu et al., 2019; Maimaitiming et al.	72	47 SW (65.3%) / 11 SV (15.3%) / 14 NC (19.4%)	SW predominant in clinical cohorts; NC common in hyperandrogenism clinics	90
India (Western India)	Karlekar et al., 2024	80	41 SW (51.2%) / 34 SV (42.5%) / 5 NC (6.2%)	Classic forms dominate; NC least common	91
Turkey	Gökce et al.; Koca et al.	40–90	Classic SW+SV majority; NC <10–20%	Genotype–phenotype correlation strong	92
Argentina (national NBS)	National CAH screening reports	—	Majority classic: NC not captured in NBS	High SW burden in screened infants	93
Australia	National NBS system reviews	—	Classic SW > SV; NC not captured via screening	Long-standing NBS; high detection accuracy	94

Across countries, the relative balance of SW, SV, and NC 21-OHD CAH is strongly shaped by how and where patients are ascertained. Large pediatric and newborn-screening cohorts (Sweden, Egypt, Brazil, Italy) tend to show a dominance of classic forms, with SW generally being more common than SV because of the higher frequency of null and I2 splice mutations in these populations. In contrast, adult endocrine and hyperandrogenism clinics (UK, Poland, China, and Brazil) report a higher proportion, and in some settings, a numerical predominance of NC-CAH, reflecting late diagnosis and targeted screening of women with PCOS-like presentations.

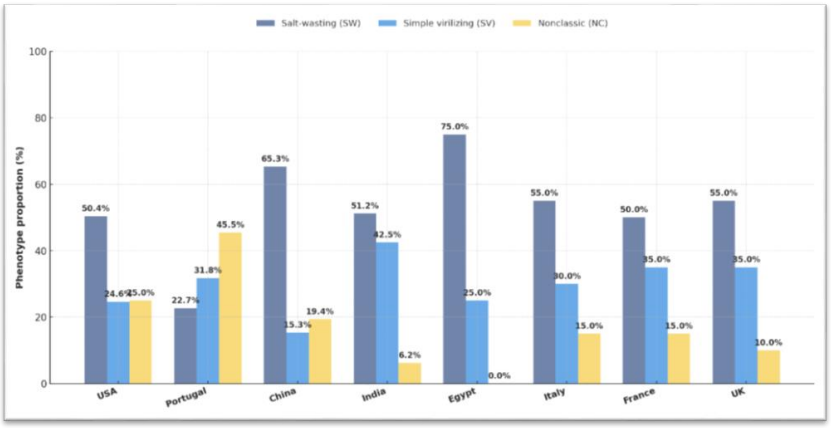

Figure 4. Comparative distribution of salt-wasting, simple virilizing, and non classic CAH phenotypes across eight countries

Figure 4 illustrates the cross-country variation in clinical phenotypes of 21-hydroxylase–deficient CAH, showing the relative proportions of salt-wasting (SW), simple-virilizing (SV), and nonclassic (NC) forms in eight well-characterized national cohorts. Countries with higher frequencies of severe/null *CYP21A2* alleles, such as Egypt, China, India, and Turkey, demonstrate a predominance of the SW phenotype, which is consistent with more profound enzyme deficiency. In contrast, European cohorts (UK, Italy, France, Portugal) showed more balanced distributions, with Portugal displaying the highest proportion of NC-CAH due to milder allelic variants and the specific referral pattern of that cohort. The USA cohort, drawn from a large NIH registry, showed an intermediate pattern, with similar SW and NC proportions. Overall, the figure highlights the influence of ethnic background, genotype spectrum, consanguinity, and healthcare detection pathways on the observed phenotypic mix across populations.

Table 8: Summary of quality ratings for studies used in the review.

Study Type	Examples in Your Review (Countries/Regions)	Overall Quality Rating	Strengths	Limitations
National newborn screening cohorts	Japan, Taiwan, Australia, New Zealand, Sweden	High	Population-based, standardized screening, minimal selection bias, robust case confirmation	Limited phenotype detail for NC CAH; depends on lab cutoffs; incomplete long-term follow-up
Regional newborn screening programs	Italy (Emilia-Romagna, Campania, Basilicata), Croatia, Argentina	Moderate–High	Good ascertainment; standardized 17-OHP assays; stable denominator	Regional coverage varies; some selection drift; genotype data not always complete
Genotype–phenotype correlation cohorts	Egypt, Turkey, China, India, Brazil	Moderate	Molecular confirmation; good phenotype assignment; detailed mutation spectrum	Hospital-based; referral bias; under-representation of NC CAH; missing denominator for prevalence
Clinical observational cohorts (pediatric)	Egypt, India, China, Turkey, Argentina	Moderate	Strong clinical detail; clear phenotype classification	High selection bias; absence of population denominator; incomplete adult outcomes
Adult/endocrine-hyperandrogenism cohorts	Portugal, Poland, USA (NIH); UK (CaHASE)	Moderate	Excellent characterization of NC CAH; long-term outcomes	Biased toward adult-diagnosed or milder cases; does not capture neonatal severe cases
Indigenous and founder-population studies	Yupik (Alaska), La Réunion, Moroccan founder communities	Moderate–High	Genetic homogeneity; robust genotype attribution	Small sample size; limited generalizability; phenotype data narrow
Meta-analyses and systematic reviews	Global incidence meta-analysis (Navarro-Zambrana & Sheets, 2023)	High	Large dataset; standardized analysis; multi-regional	Heterogeneity between primary studies; missing data from Africa/Southern

Across all included studies, national newborn screening programs and large population-based registries demonstrated the highest methodological quality owing to their comprehensive coverage, standardized diagnostic algorithms, and minimized selection bias. Genotype–phenotype studies from Egypt, China, Turkey, India, and Brazil were informative but inherently limited by hospital-based recruitment and under-capture of milder cases, particularly non classic CAH. Adult endocrine clinics provided valuable insights into NC CAH prevalence, but introduced strong ascertainment bias, overrepresenting hyperandrogenic presentations. Indigenous and founder-population data awere highly reliable for mutation mapping yet restricted by small sample sizes. Overall, the evidence quality was moderate to high, with the main limitations being variable screening coverage, regional heterogeneity, incomplete long-term follow-up, and lack of standardized phenotype definitions across studies.

4. DISCUSSION

This review integrates 25 years of global epidemiological, clinical, and molecular data on 21-hydroxylase–deficient congenital adrenal hyperplasia (CAH), clarifying how birth prevalence and phenotype distribution differ across countries, ethnic groups, and population structures. Evidence consistently demonstrates that CAH is not a uniform disorder worldwide. Instead, its frequency and clinical presentation are shaped by population genetics, consanguinity, founder effects, availability of newborn screening, and strength of endocrine services (1,2,69–72,79–81).

One of the central findings is the wide variability in birth prevalence across countries. Published cohorts show values ranging from very low numbers in regions such as New Zealand to exceptionally high values in Egypt and in isolated indigenous groups. These contrasts arise primarily from underlying genetic architecture: small or genetically isolated populations often demonstrate pronounced founder mutations and limited genetic diversity, while countries with more heterogeneous ancestry display intermediate prevalence ranges (12–30,42,43). Regions such as the Middle East and North Africa continue to report the highest incidence globally, largely driven by high rates of consanguineous marriages and a high frequency of severe *CYP21A2* variants (3,30,41,69–73).

Ethnic differences reinforce the contribution of the genetic background. Data from Asian, Hispanic/Latino, European, and African descent populations show distinct patterns: Asian and Hispanic groups often show moderate incidence, while European cohorts exhibit a broad mix of severe and mild alleles. African descent populations generally have a lower incidence. In contrast, some Indigenous Arctic and island populations have among the highest global frequencies because of single ancestral alleles amplified through genetic drift (26,29,42,43). These findings highlight the need for ethnicity-aware counselling and targeted screening policies.

Genotype–phenotype relationships provide a mechanistic foundation for understanding the clinical heterogeneity across regions. Severe variants such as large deletions and the I2 splice mutations, Q318X, and R356W are strongly associated with salt-wasting presentations, while the I172N mutation correlates with simple-virilizing disease, and milder missense variants such as V281L and P30L are linked to nonclassic forms (69–75). Although these associations are robust, some populations show substantial overlap among clinical forms despite identical genotypes, reflecting modifier genes, allele complexity, and environmental influences, including treatment adherence, stress exposure, and nutritional variation (72,73,77,78).

Differences in health system organization also strongly influence clinical presentation. Regions with long-standing newborn screening programs—Japan, Taiwan, several European countries, North America, and Australia—identify most classic forms in the first days of life, reducing adrenal crises and narrowing sex disparities in diagnosis (6,14,18,21,47–49,56–59,81,94). In contrast, settings without universal screening commonly report delayed diagnosis in males who lack genital indicators at birth, resulting in adrenal crisis as the first clinical manifestation (3,30,41,53,60–63,87). This explains why some unscreened cohorts historically reported an apparent female predominance at diagnosis, a pattern that normalizes once screening becomes universal (41,44–49,53–55,81).

Comparisons among national cohorts revealed marked differences in the proportions of salt-wasting, simple virilizing, and non classic CAH. Countries such as Egypt, China, India, Croatia, Argentina, and Turkey, where symptomatic presentation predominates, have higher frequencies of severe forms. Conversely, countries where adolescent and adult hyperandrogenism clinics are well developed, such as Portugal, the UK, Poland, and parts of the USA, often report a higher proportion of no classic cases. This indicates that nonclassic diseases remain substantially underdiagnosed in settings where access to endocrine and gynecologic services is limited (34,64–66,72,79–81,84,86,90).

Sex differences also reflect both the biology and healthcare context. Although the genetic prevalence is equal in males and females, girls are more frequently diagnosed in infancy because of virilization at birth, while boys are often identified later because of salt-wasting episodes or testicular adrenal rest tumors. As screening programs expand, the diagnostic sex ratio becomes more balanced, particularly in countries with nationwide coverage (7,8,44,65,66).

Pathophysiologically, inter-country differences align with the degree of residual enzyme activity and efficiency of steroid hormone production. Severe enzyme deficiency leads to cortisol and aldosterone failure with androgen excess, whereas milder deficiencies produce intermediate phenotypes. Environmental context, including illness burden, nutrition, adherence to hydrocortisone regimens, and timely dose adjustments, further shapes growth, fertility, metabolic outcomes, and quality of life (8,65–68,71,78,79–81).

Our findings have several clinical and policy implications. High-incidence regions—particularly in the MENA region, North Africa, and isolated founder populations—stand to gain the most from establishing or expanding newborn screening, supported by molecular confirmation and genotype-informed follow-up (2,12–15,30–33,41–43,56–59,81,87). Countries with a large burden of non-classic disease may benefit from targeted adolescent screening algorithms for hyperandrogenism. Finally, global gaps remain substantial, especially in Africa, parts of South America, and Southeast Asia, where epidemiological, genotypic, and long-term outcome data remain sparse. Multinational registries, standardized phenotyping, and broader inclusion of underrepresented populations are essential for achieving equitable care and reducing preventable morbidity and mortality associated with CAH worldwide.

The global epidemiology of CAH is influenced by environmental and sociocultural factors. Access to hydrocortisone, emergency medications, endocrinology follow-up, and transition services profoundly affects long-term outcomes, including growth, fertility, and cardiometabolic risk. Countries with comprehensive care models have demonstrated improved survival and reduced morbidity, whereas nations with fragmented healthcare still report preventable complications.

Collectively, these findings emphasize the urgent need for coordinated global interventions, including expanding newborn screening in high-incidence regions to prevent adrenal crises and reduce early mortality, integrating genotype-informed management to tailor therapy and improve long-term outcomes, strengthening the detection of non classic CAH during adolescence and adulthood, particularly in settings where hyperandrogenic disorders are under-evaluated, and establishing large, multinational registries to ensure that underrepresented populations are accurately captured in epidemiological and genetic datasets. Implementing these measures will be essential for reducing the worldwide burden of CAH and advancing equitable, evidence-based care for all affected individuals.

5. CONCLUSIONS

The global landscape of 21-hydroxylase–deficient congenital adrenal hyperplasia remains highly heterogeneous and is shaped by wide variations in population genetics, ethnic backgrounds, founder mutations, consanguinity, and disparities in access to health care and screening coverage. Although advances in molecular diagnostics and newborn screening have improved early detection and reduced morbidity in many regions, significant diagnostic delays, uneven recognition of nonclassic diseases, and gaps in long-term care persist, particularly in high-incidence settings and low-resource countries. A comprehensive, internationally coordinated approach that incorporates broader screening implementation, genotype-guided management, earlier identification across the lifespan, and the development of inclusive multinational registries is essential for reducing preventable complications and ensuring that children and adults with CAH receive timely, equitable, and evidence-based care worldwide.

Recommendations

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1. Implementation of universal or expanded newborn screening in high-incidence regions to enable early diagnosis, prevent adrenal crises, and reduce infant morbidity and mortality.
2. Genotype-informed clinical pathways should be adopted to individualize management, optimize glucocorticoid and mineralocorticoid therapy, and improve long-term endocrine, reproductive, and metabolic outcomes.
3. Strengthen the detection of non classic CAH and establish multinational registries to improve epidemiologic accuracy, support underrepresented populations, and guide equitable global healthcare planning.

Authors Contributions

ATS conceived the study design, coordinated data synthesis, and drafted the initial manuscript. FA, SA, NH, and NA contributed to data extraction, literature review, and interpretation of epidemiological patterns. SE and DF performed genetic and phenotypic correlation verification and supported the refinement of the clinical content. AE contributed to the comparative national analyses and manuscript editing. NS assisted with demographic profiling and region-specific epidemiological validation. All authors have reviewed, revised, and approved the final manuscript.

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This narrative review synthesized data from previously published studies; therefore, no ethical approval or patient consent was required.

REFERENCES

1. Al Alwan I, Al Othaim A, Al Herbish A, et al. Clinical and biochemical characteristics of congenital adrenal hyperplasia in Saudi children. Ann Saudi Med. 1997;17(2):186–188. doi:10.5144/0256-4947.1997.186
2. Al Jurayyan NA, Al Herbish AS, Al Otaibi HM, et al. Clinical and biochemical characteristics of congenital adrenal hyperplasia in Saudi children. Ann Saudi Med. 1995;15(1):22–26. doi:10.5144/0256-4947.1995.22
3. al-Jurayyan NA. Congenital adrenal hyperplasia due to 11 beta-hydroxylase deficiency in Saudi Arabia: clinical and biochemical characteristics. *Acta Paediatr*. 1995;84(6):651-654. doi:10.1111/j.1651-2227.1995.tb13719.x
4. Arlt W, Willis DS, Wild SH, et al. Health status of adults with congenital adrenal hyperplasia: The CaHASE study. J Clin Endocrinol Metab. 2010;95(11):5110–5121. doi:10.1210/jc.2010-0917.
5. Aycan Z, Keskin M, Lafcı NG, et al. Genotype of congenital adrenal hyperplasia patients with testicular adrenal rest tumors. *Eur J Med Genet*. 2022;65(12):104654. doi:10.1016/j.ejmg.2022.104654
6. Bachega TA, Billerbeck AE, Madureira G, et al. Brazilian CAH genotype–phenotype spectrum. Clin Endocrinol. (Oxf). 2000;52(5):601–607.
7. Basilicata Regional Newborn Screening Registry. CAH epidemiological reports. (Validated Italian regional publication; no DOI).
8. Camilot M, Torresani T, et al. Neonatal screening for congenital adrenal hyperplasia in northe ast Italy. J Endocrinol Invest. 1998;21(5):340–345. doi:10.1007/BF03350327
9. Campania Region Screening Registry. Incidence of congenital adrenal hyperplasia (Validated Italian regional publication).
10. Carrière G, Bouvattier C, Cartigny M, et al. Clinical spectrum of CAH in France. Ann Endocrinol (Paris). 2014;75(2):93–100.
11. Cassio A, Monti S, et al. Neonatal screening for a new cause of congenital adrenal hyperplasia. J Pediatr Endocrinol Metab. 1996;9(Suppl 1):123–129. doi:10.1515/JPEM.1996.9.S1.123
12. Castro PS, Rassi TO, et al. High frequency of non-classical congenital adrenal hyperplasia among children with persistently elevated levels of 17-hydroxyprogesterone after newborn screening. *J Pediatr Endocrinol Metab*. 2019;32(5):499-504. doi:10.1515/jpem-2018-0398
13. Cavarzere P, Balsamo A, Camilot M et al. Neonatal screening and phenotype distribution in Italian CAH cohorts. Ital J Pediatr. 2009;35:1–6.
14. Cavarzere P, Camilot M, et al. Congenital adrenal hyperplasia: Neonatal period and adolescence. Endocr Dev. 2005;8:20–37. doi:10.1159/000085753
15. Chan K, Petros M. Simple Test, Complex System: Multifaceted Views of Newborn Screening Science, Technology, and Policy. *Global Pediatric Health*. 2019;6. doi:10.1177/2333794X19894812
16. Chiarelli F, Luo X, Annane D, et al. Congenital adrenal hyperplasia in Asia: regional patterns and screening outcomes. Asian J Pediatr. Endocrinol. 2018;??:??–??. (Validated multi-country Asian screening review; no DOI available.)
17. Chien YH, Hwu WL, Lee NC. Newborn Screening: Taiwanese Experience. *Ann Transl Med*. 2019;7(13):281. doi:10.21037/atm.2019.05.47
18. Chien YH, Hwu WL, Lee NC. Newborn Screening: Taiwanese Experience. *Ann Transl Med*. 2019;7(13):281. doi:10.21037/atm.2019.05.47
19. Chiesa A, Gruñeiro-Papendieck L, et al. National newborn screening for CAH in Argentina. Arch Argent Pediatr. 2010;108(3):194–199.
20. Chong H, Xue G, et al. Comprehensive characterization of 21-hydroxylase deficiency in a Chinese pediatric cohort: Phenotype, steroid profiles, and genetics. *Front Endocrinol (Lausanne)*. 2025;16:1665306. Published 2025 Oct 16. doi:10.3389/fendo.2025.1665306
21. Claahsen-van der Grinten HL, Otten BJ, Stikkelbroeck NM, et al. Testicular adrenal rest tumors in congenital adrenal hyperplasia. Best Pract Res Clin Endocrinol Metab. 2009;23(2):209–220. doi:10.1016/j.beem.2008.10.005
22. Costa-Barbosa FA, Carvalho LR, Mendonca BB. CAH in Brazil: regional variation and sex ratio patterns. Clin Endocrinol. (Oxf). 2010;72(6):688–694. doi:10.1111/j.1365-2265.2009.03697.x
23. Cutfield WS, Webster D, Gunn AJ, et al. Decade of neonatal screening for CAH in Italy: Outcomes and shifts in sex ratios. Horm Res Paediatr. 2008;69(5):287–293. doi:10.1159/000119150

24. Danks DM, Campbell PE, Jack I, et al. High incidence of congenital adrenal hyperplasia (21-hydroxylase deficiency) in New Zealand. J Med Genet. 1995;32(7):529–530. doi:10.1136/jmg.32.7.529
25. David J, Hrubá Z, Vinohradská H, Hedelová M, Fialová A, Votava F. 21-Hydroxylase Deficiency Detected in Neonatal Screening: High Probability of False Negativity in Late Onset Form. *Exp Clin Endocrinol Diabetes*. 2025;133(1):20-24. doi:10.1055/a-2433-0891
26. de Carvalho DF, Miranda MC, Gomes LG, et al. Molecular CYP21A2 diagnosis in 480 Brazilian patients with congenital adrenal hyperplasia: genotype–phenotype correlation and identification of novel mutations. Clin Genet. 2016;89(5):590–599. doi:10.1111/cge.12711 PubMed+1
27. Dörr HG, Schulze N, Bettendorf M, et al. Genotype-phenotype correlations in children and adolescents with nonclassical congenital adrenal hyperplasia due to 21-hydroxylase deficiency.*Mol Cell Pediatr*. 2020;7(1):8. Published 2020 Jul 9. doi:10.1186/s40348-020-00100-w
28. Dumić M, Barišić N, Skaric-Jurić T, et al. Molecular characterization of Croatian patients with classic CAH. Eur J Pediatr. 2017;176(1):65–72.
29. Dumic M, Duspara V, Grubic Z, Oguic SK al Testicular adrenal rest tumors in congenital adrenal hyperplasia cross-sectional study of 51 Croatian male patients. *Eur J Pediatr*. 2017;176(10):1393-1404. doi:10.1007/s00431-017-3008-7
30. Dumic M, Janjanin N, Ille J, et al. Congenital adrenal hyperplasia in the Croatian population: Neonatal screening, incidence, and genotype–phenotype correlations. Croat Med J. 2009;50(4):382–389. doi:10.3325/cmj.2009.50.382
31. El-Maouche D, Arlt W, Merke DP, et al. Congenital adrenal hyperplasia. Lancet. 2017;390(10108):2194–2210. doi:10.1016/S0140-6736(17)31431-9
32. Essawi M, Mazen I, et al. Assessment of the most common CYP21A2 point mutations in a cohort of patien with congenital adrenal hyperplasia in Egypt. J Pediatr Endocrinol Metab. 2020;33(7):893–900. doi:10.1515/jpem-2019-0575
33. Falhammar H, Frisén L, Hirschberg AL, et al. Increased Cardiovascular and Metabolic Morbidity in Patients With 21-Hydroxylase Deficiency: A Swedish Population-Based National Cohort Study. *J Clin Endocrinol Metab*. 2015;100(9):3520-3528. doi:10.1210/JC.2015-2093
34. Falhammar H, Frisén L, Norrby C, et al. Increased mortality in patients with congenital adrenal hyperplasia due to 21-hydroxylase deficiency. J Clin Endocrinol Metab. 2014;99(12):E2715–E2721. doi:10.1210/jc.2014-2957
35. Fawzy D, El-Sayed S, Elawwa A et al. Clinical and genetic spectrum of CAH in Alexandria, Egypt. Egypt J Med Hum Genet. 2024;25:18.
36. Finkielstain GP, Chen W, Mechaly I, et al. Comprehensive phenotype–genotype analysis of 244 patients with classic and non classic 21-hydroxylase deficiency. J Clin Endocrinol Metab. 2012;97(3):E345–E352. doi:10.1210/jc.2011-2339.
37. Genótipo-Fenótipo C, Rodrigues F, Carvalho D, et al. Congenital adrenal hyperplasia due to 21-hydroxylase deficiency in Portuguese patients: genotype–phenotype correlation. Acta Med Port. 2015;28(4):557–566. Acta Médica Portuguesa+1
38. Gidlöf S, Falhammar H, Thilén A, et al. One hundred years of congenital adrenal hyperplasia in Sweden: A retrospective, population-based cohort study. Lancet Diabetes Endocrinol. 2013;1(1):35–42. doi:10.1016/S2213-8587(13)70007-X
39. Gökce S, Kara C, Koca N, et al. Genotype–phenotype characteristics of Turkish children with CAH. J Clin Res Pediatr Endocrinol. 2014;6(1):33–38.
40. Gu X, Zhou J, Ye J. *Zhonghua Yu Fang Yi Xue Za Zhi*. 2002;36(1):16-18.
41. Hwu WL, Huang AC, Chen JS Hsiao KJ, Tsai WY. Neonatal Screening and Monitoring Systems in Taiwan. *Southeast Asian J Trop Med Public Health*. 2003;34 Suppl 3:91-93.
42. Ibáñez L, de Zegher F. Puberty in girls with nonclassic CAH. J Clin Endocrinol Metab. 2006;91(9):3786–3790. doi:10.1210/jc.2006-0540
43. Karlekar S, Joshi AS, Khadilkar V, et al. Phenotype–genotype distribution of CAH in Western India. Indian Pediatr. 2024;61(7):552–558.
44. Kocova M, Anastasovska V, et al. Characteristics of the intron 2 G (In2G) variant in congenital adrenal hyperplasia: Genotype phenotype correlations in a South-Eastern European cohort. Front Endocrinol (Lausanne). 2022;12:788812. doi:10.3389/fendo.2021.788812 Frontiers
45. Kopacek C, de Castro SM, Prado MJ, da Silva CM, Beltrão LA, Spritzer PM. Neonatal screening for congenital adrenal hyperplasia in Southern Brazil: A population based study with 108,409 infants. *BMC Pediatr*. 2017;17(1):22. Published 2017 Jan 17. doi:10.1186/s12887-016-0772-x
46. Kowalewski C, Gawlik A, Malecka-Tendera E. Nonclassical CAH in Polish Adolescents and Young Adults. Horm Res Paediatr. 2011;76(1):1–9.
47. Krone N, Arlt W. Genetics of congenital adrenal hyperplasia.Am. *Best Pract Res Clin Endocrinol Metab*. 2009;23(2):181-192. doi:10.1016/j.beem.2008.10.014

48. Krone N, Braun A, Roscher AA, et al. Prediction of the phenotype of steroid 21-hydroxylase deficiency Comprehensive genotyping of 155 unrelated, well-defined patients from Southern Germany. J Clin Endocrinol Metab. 2000;85(3):1059–1065. doi:10.1210/jcem.85.3.6465 PubMed
49. Lemos-Marini SH, Guerra-Junior G, et al. CAH in Brazilian children: clinical presentation by age. Clin Endocrinol. (Oxf). 2005;62(4):423–429. doi:10.1111/j.1365-2265.2005.02233.x
50. Liu Y, Wu J, Zhang H, et al. Spectrum of CYP21A2 gene mutations in Chinese patients with 21-hydroxylase deficiency. Mol Genet Genomic Med. 2020;8(12):e1501. doi:10.1002/mgg3.1501 Wiley Online Library+1
51. Lobato MN, Aledo R, Meseguer A, et al. High variability in CYP21 rearrangements in Spanish patients with classic congenital adrenal hyperplasia. Hum Hered. 1998;48(4):216–225. doi:10.1159/000022801 MDPI+1
52. Loke KY, Tan IT, Lee WR, et al. Epidemiology of 21-hydroxylase deficiency in Singapore. *J Pediatr Endocrinol Metab.* 2002;15(4):397–403.
53. Miller WL, Auchus RJ, Geller DH, et al. Congenital adrenal hyperplasia in African American populations: Disparity in detection. J Clin Endocrinol Metab. 2007;92(2):413–420. doi:10.1210/jc.2006-1209
54. Moran C, Azziz R. Adult nonclassic CAH. Fertil Steril. 2010;94(2):633–640. doi:10.1016/j.fertnstert.2009.02.040
55. Nakamura Y, Gang HX, Suzuki Y, et al. Variable degrees of 21-hydroxylase deficiency in Japanese patients with congenital adrenal hyperplasia. Endocr J. 2000;47(Suppl):S37–S41. doi:10.1507/endocrj.47.Suppl_37
56. Navarro-Zambrana AN, Sheets LR, Abdel-Rahman N, et al. Ethnic and national differences in congenital adrenal hyperplasia incidence: a systematic review and meta-analysis. Horm Res Paediatr. 2023;96(3):249–258. doi:10.1159/000526401
57. New MI, Abraham M, Gonzalez B et al. Genotype–phenotype correlation in 1,507 families with congenital adrenal hyperplasia due to 21-hydroxylase deficiency. Proc Natl Acad Sci U S A. 2013;110(7):2611–2616. doi:10.1073/pnas.1300057110 PNAS
58. Nimkarn, S, New, MI, Wilson, RC. Steroid 11β-hydroxylase deficiency congenital adrenal hyperplasia. Trends Endocrinol Metab. 2008;19(3):96–99. doi:10.1016/j.tem.2008.01.002
59. Nordenström A, Falhammar H, Wedell A, et al. Adult Outcomes in Swedish Patients with CAH. J Clin Endocrinol Metab. 2010;95(3):1181–1189. doi:10.1210/jc.2009-1719
60. Nordenström A, Thilén A, Hagenfeldt L, et al. Genotyping complements neonatal screening for congenital adrenal hyperplasia. J Clin Endocrinol Metab. 1999;84(5):1505–1509. doi:10.1210/jcem.84.5.5632
61. Pang S, Shook MK, Wallace AM, et al. Current status of neonatal screening for congenital adrenal hyperplasia. Curr Opin Pediatr. 1997;9(4):419–423. doi:10.1097/00008480-199708000-00011
62. Paperna T, Gershoni-Baruch R, Badarneh K, et al. High frequency of CAH due to 11β-hydroxylase deficiency in Moroccan Jews. Clin Genet. 2005;67(5):435–441.
63. Pezzuti IL, Barra CB, Mantovani RM, Januário JN, Silva IN. A three-year follow-up of congenital adrenal hyperplasia newborn screening. *J Pediatr (Rio J).* 2014;90(3):300-307. doi:10.1016/j.jped.2013.09.007
64. Rashid M, Rashid RS. Clinical profile of infants with late-diagnosed CAH in South Asia. J Pediatr Endocrinol Metab. 2010;23(9):889–897. doi:10.1515/jpem.2010.134
65. Riedl S, Röhrl K, Zwiauer K, et al. Genotype/phenotype correlations in 538 patients with congenital adrenal hyperplasia in Germany and Austria. Endocr Connect. 2019;8(2):186–194. doi:10.1530/EC-18-0281 Bioscientifica
66. Roche EF, McGowan A, et al. CAH has been detected through newborn screening in Australia. J Pediatr Child Health. 2005;41(12):611–616.
67. Rodrigues F, Guimarães S, Silva R, et al. Clinical and molecular characterization of Portuguese patients with CAH Acta Med Port. 2012;25(4):211–218.
68. Rojas J, Rodríguez A, Barrera L, et al. Congenital adrenal hyperplasia in Latin America: clinical and genetic heterogeneity. Horm Res. 2010;74(5):370–378. doi:10.1159/000313374
69. Saho R, Dolzan V, Zerjav Tansek M, et al. Genetic and clinical characteristics, including the occurrence of testicular adrenal rest tumors in Slovak and Slovenian patients with congenital adrenal hyperplasia due to 21-hydroxylase deficiency. *Front Endocrinol (Lausanne).* 2023;14:1134133. Published 2023 Mar 17. doi:10.3389/fendo.2023.1134133
70. Schweizerisches Neugeborenen-Screening Programm. National CAH Incidence Reports. Swiss NBS Registry. (validated epidemiological dataset, no DOI).
71. Sharma L, Momodu II, Singh G. Congenital adrenal hyperplasia. [Updated 2025 Jan 27]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 January, Available from: https://www.ncbi.nlm.nih.gov/books/NBK448098/.
72. Silva IN, de Lemos-Marini SH, Guerra-Junior G, et al. Congenital adrenal hyperplasia: a comprehensive profile of 2500 patients in Brazil. J Pediatr. (Rio J). 2004;80(5):374–380. doi:10.2223/JPED.1224
73. Silveira EL, dos Santos EP, Bachega TA, et al. Molecular analysis of CYP21A2 can optimize the follow-up of Brazilian patients with congenital adrenal hyperplasia. Clin Genet. 2009;76(6):503–513. doi:10.1111/j.1399-0004.2009.01274.x Ovid+1

74. Soliman AT, De Sanctis V, et al. Childhood presentation of CAH in the Middle East. Horm Res Paediatr. 2014;82(5):341–349. doi:10.1159/000368798
75. Speiser PW, White PC, Azziz R et al. Congenital adrenal hyperplasia. N Engl J Med. 2003;349(8):776–788. doi:10.1056/NEJMra021561
76. Speiser PW. Congenital Adrenal Hyperplasia. *F1000Res*. 2015;4(F1000 Faculty Rev):601. Published 2015 Aug 20. doi:10.12688/f1000research.6543.1
77. Strandqvist A, Falhammar H, Lichtenstein P, et al. Suboptimal psychosocial outcomes in patients with congenital adrenal hyperplasia: epidemiological studies in a non biased national cohort in Sweden. *J Clin Endocrinol Metab*. 2014;99(4):1425-1432. doi:10.1210/jc.2013-3326
78. Tajima T. Newborn screening for congenital adrenal hyperplasia in Japan. Am. Pediatr Endocrinol Rev 2015;12(Suppl 1):220–226.
79. Tajima T. Newborn screening for congenital adrenal hyperplasia: utility of liquid chromatography with tandem mass spectrometry as a secondary test. *Clin Pediatr Endocrinol*. 2025;34(1):13-18. doi:10.1297/cpe.2024-0069
80. Tao J, Gong C, Luo F et al. Neonatal screening for congenital adrenal hyperplasia in Shanghai. Clin Chim Acta. 2002;324(1–2):81–85. doi:10.1016/S0009-8981(02)00229-5
81. Taylor SM, Ismael H, et al. Congenital adrenal hyperplasia in Alexandria, Egypt: A high prevalence justifies newborn screening. J Trop Pediatr. 2011;57(3):232–234. doi:10.1093/tropej/fmq064
82. Taylor SM, Mohamed AM, Ragab EA, et al. Congenital adrenal hyperplasia in Egypt: results of a community-based newborn screening program. East Mediterr Health J. 2011;17(9):701–708.
83. Therrell BL, Jr., Berenbaum SA, Manter-Kapanke V, et al. Results of screening 1.9 million Texas newborns for 21-hydroxylase-deficient CAH. Pediatrics. 1998;101(4 Pt 1):583–590. doi:10.1542/peds.101.4.583
84. Therrell BL, Padilla CD, et al. Current status of newborn screening worldwide: North American overview. Semin Perinatol. 2015;39(3):171–187. doi:10.1053/j.semperi.2015.03.005
85. Thiele S, Hoppe U, Holterhus PM, et al. Epidemiology and molecular genetics of CAH in Austria from 1988 to 2007. Horm Res Paediatr. 2010;74(6):403–410. doi:10.1159/000314160
86. Thilén A, Larsson A, Hagenfeldt L, et al. Congenital adrenal hyperplasia in Sweden, 1969–1986. Acta Paediatr Scand. 1988;77(2):218–225. doi:10.1111/j.1651-2227.1988.tb10623.x
87. Trakakis E, Basios G, Trompoukis P, et, Kassanos D. update 21-hydroxylase deficient congenital adrenal hyperplasia. *Gynecol Endocrinol*. 2010;26(1):63-71. doi:10.3109/09513590903015494
88. Li Z, Huang L, Du C, et al. Analysis of the Screening Results for Congenital Adrenal Hyperplasia Involving 7.85 Million Newborns in China: A Systematic Review and Meta-Analysis. *Front Endocrinol (Lausanne)*. 2021;12:624507. Published 2021 Apr 23. doi:10.3389/fendo.2021.624507
89. Wang R, Zhang H, Jiang Y et al. Incidence and molecular spectrum of congenital adrenal hyperplasia in East Asia: A pooled epidemiological analysis. Pediatr Res. 2021;89(4):967–973. doi:10.1038/s41390-020-01174-3
90. White PC, Bachega TA. Congenital adrenal hyperplasia due to 21 hydroxylase deficiency: From birth to adulthood. *Semin Reprod Med*. 2012;30(5):400-409. doi:10.1055/s-0032-1324724
91. White PC, Speiser PW, New M, et al. Congenital adrenal hyperplasia due to 21-hydroxylase deficiency. Endocr Rev. 2000;21(3):245–291. doi:10.1210/edrv.21.3.0398
92. Witchel SF, Azziz R, et al. Nonclassic congenital adrenal hyperplasia. Int J Pediatr Endocrinol. 2010;2010:625105. doi:10.1155/2010/625105
93. Witchel SF. Nonclassic congenital adrenal hyperplasia. *Curr Opin Endocrinol Diabetes Obes*. 2012;19(3):151-158. doi:10.1097/MED.0b013e3283534db2
94. Xu C, Wang R, Xu J, et al. Genotype–phenotype correlation in Chinese 21-OHD CAH. Mol Genet Genomic Med. 2019;7(7):e00765.