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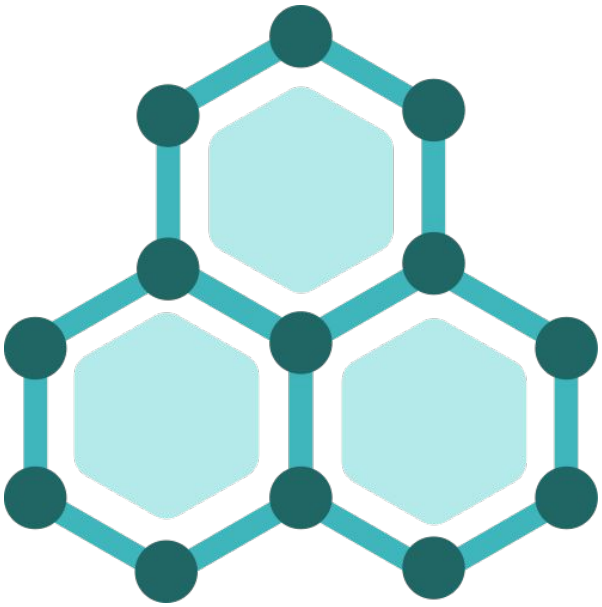
CAH & Testicular Feminization Syndrome

Reproductive Block



Objectives

- ***Adrenal steroidogenesis***
- ***Congenital adrenal hyperplasia syndrome:***
  - *Types*
  - *Biochemical characteristics*
  - *Clinical manifestations*
- ***Testicular feminization syndrome***

This Lecture was presented by:
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Editing File

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- Main Text
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- Dr's Notes
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Adrenal glands

comprise 3 separate hormone systems:

1. **Zona glomerulosa:** Secretes aldosterone.
2. **Zona fasciculata & reticularis:** Secrete cortisol & the adrenal androgens.
3. **Adrenal medulla:** Secretes catecholamines (mainly epinephrine).

Glucocorticoids: Steroids with cortisol-like activity
Potent metabolic regulators and immunosuppressants

Mineralocorticoids: Steroids with aldosterone-like activity
Promote renal sodium reabsorption

Hermaphroditism or Intersex

Definition

A person who has neither standard male or standard female anatomy, Discrepancy between type of gonads and the external genitalia

Types:

- True hermaphrodite (ovary plus testis)
  Depend on gonads
- Female pseudohermaphrodite (FPH, only ovary)
  gonad is clear (ovary) but external genitalia are either virilized or ambiguous.
- Male pseudohermaphrodite (MPH, only testis)
  gonad is clear (testes) but external genitalia are either female or ambiguous.

Steroidogenesis and Congenital adrenal hyperplasia syndrome

MCQ

- It is the result of an inherited enzyme defect in steroid biosynthesis.
- The adrenals::
  - **Cannot secrete cortisol** → absent negative feedback to the pituitary → ACTH continues to drive steroid biosynthesis → **adrenal hyperplasia and accumulation of cortisol precursors** (depending on which enzyme is lacking).
  - **Cannot secrete aldosterone** → electrolyte disturbances:
    - **Hyponatremia** (Low Na+)
    - **Hyperkalemia** (High K+)
- The condition might be fatal unless diagnosed early.

Types of CAH Syndromes

Dr Note: All of the types are important ! Types are Arranged by occurrence frequency (most common to least)

- **21 a-Hydroxylase deficiency** most common
- **11 b-Hydroxylase deficiency**
- 17 a-Hydroxylase deficiency
- 3 b-Hydroxysteroid dehydrogenase deficiency least common

21 a-Hydroxylase deficiency

General Info

★ The most common type of CAH (90%).
★ Autosomal recessive condition.

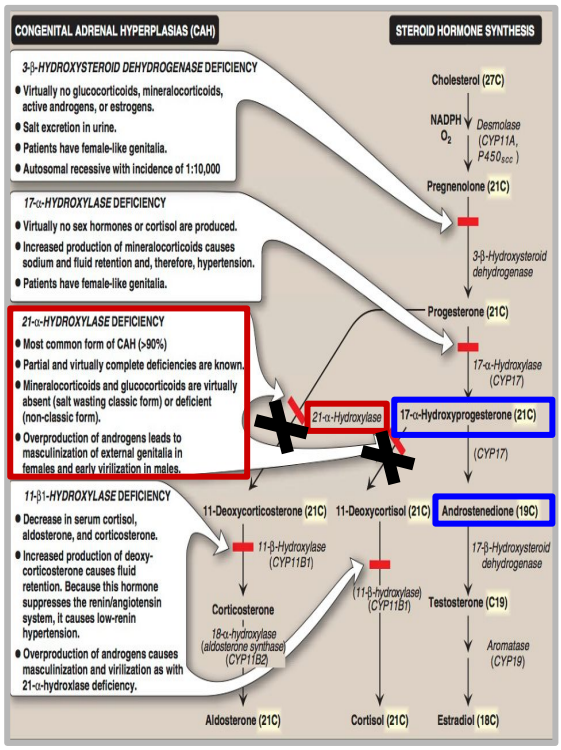
Patho-genesis

- Impaired synthesis of both cortisol & aldosterone.
- ↓ [cortisol]→ ↑ACTH secretion → Adrenal gland hyperplasia.
- **Accumulated 17-α-hydroxyprogesterone are diverted to the biosynthesis of sex hormones →signs of androgen excess:**
  - Ambiguous genitalia in newborn girls (**FPH**). Ovaries are present .
  - Rapid postnatal growth in both sexes.
- **Severe cases: mineralocorticoid deficiency** (complete) → salt & H2O loss → hypovolemia/hypotension & **shock** → **neonatal adrenal crisis.**

Note: Late presentation (adult life) is possible in less severe cases.

Clinical picture

1. **Complete enzyme defect** [1]→ ↑ stimulation of adrenal androgen production → **virilization/masculinization** in baby girls & **precocious puberty** in boys.
2. **Partial enzyme defect** [2]→ late onset form → menstrual irregularity & hirsutism in young females. Misdiagnosed with PCOS

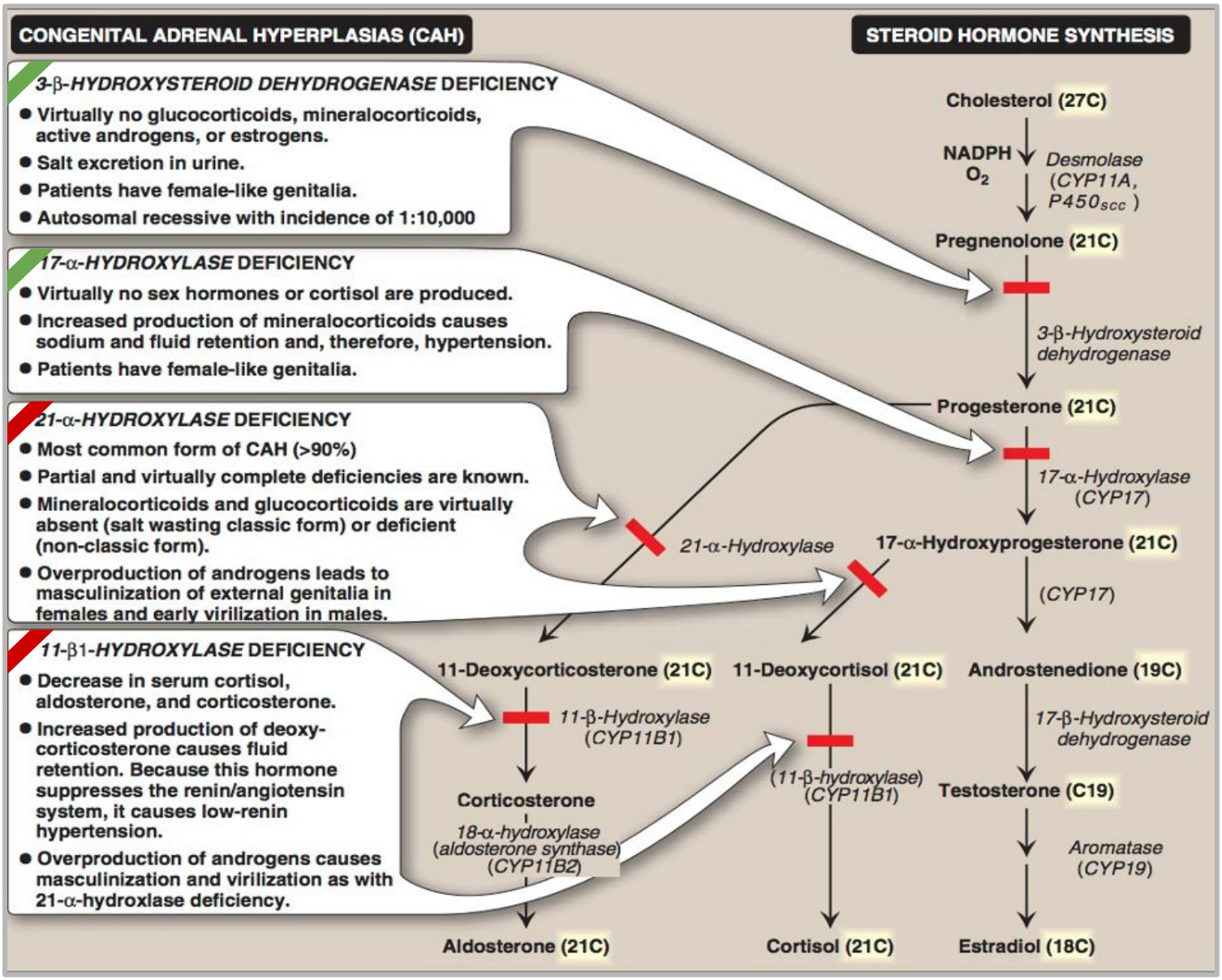


- Accumulation vs deficient Enzymes above^
- It is the most common among other enzymes deficiencies
1) Mutation of the active site of the enzyme .
2) Mutation of any part of the enzyme other than the active site.

21 a-Hydroxylase Deficiency Cont.

MCQ

All Types / Syndromes are required (This Figure is VERY Important)



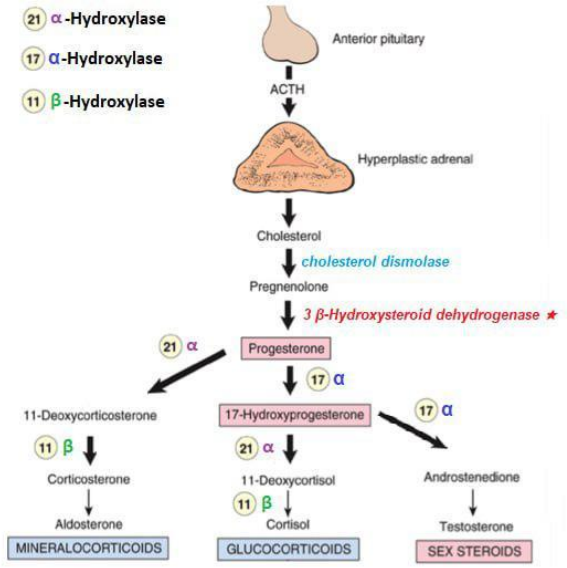
Read IMPORTANT

Dr. Notes:

1) 90% of the cases are due to 21 a-Hydroxylase deficiency
2) Autosomal recessive condition.
3) Cortisol & Aldosteron are absent or very low
4) High level of sex hormones
5) Increase virilization of female "masculinization"
6) Early puberty on male

Very Very IMPORTANT to differentiate between

- 21 a-Hydroxylase deficiency = Hypotension due to **low** levels of **Aldosterone**.
- 11 B-Hydroxylase deficiency = Hypertension due to **high** levels of **11-deoxycorticosterone with mineralocorticoid effect (salt and water retention).**



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21 a-Hydroxylase Deficiency cont..

Genetics

Mutations in the CYP21 gene:
- Deletions, Nonsense, Missense.

DNA testing of CYP21:
- **For prenatal diagnosis** and confirmation of diagnosis.

Diagnosis

- Serum sample taken **at least 2 days after birth** (earlier samples may contain maternally derived **17-α-hydroxyprogesterone**):
  - ↑ plasma [17-α hydroxyprogesterone] as early as 4 days after birth but not before 2 days. Measure the precursor not the enzyme itself.

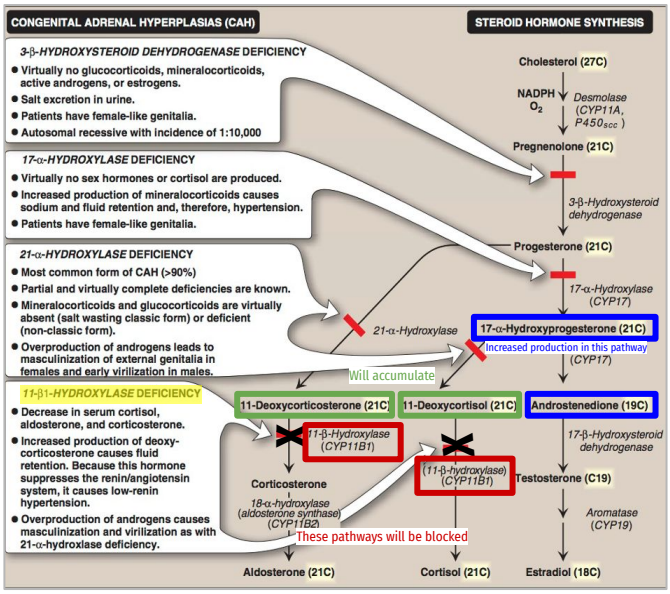
1. **Classic (complete) deficiency:** is characterized by markedly elevated serum levels of 17-α-hydroxyprogesterone.
2. **Late-onset (partial) deficiency:** may require corticotropin (ACTH) stimulation test:
   - Measure baseline and stimulated levels of 17-α-hydroxyprogesterone. Because it's the most common
   - High level of 17-α-hydroxyprogesterone after stimulation is diagnostic.

When we give ACTH to:

- Normal baby → high cortisol level
- Baby with deficient enzyme → high 17-α-hydroxyprogesterone
- For newborn CAH diagnosis: When we start early measuring, it can be like we are detecting the 17-α-hydroxyprogesterone of the mother, so we wait for 24-36 hrs then we take the sample to make sure that elevation of the enzyme is from baby not from maternal blood

11B-Hydroxylase Deficiency

- Leads to high concentrations of 11-deoxycortisol.
- Leads to **high** levels of 11-deoxycorticosterone with **mineralocorticoid effect (salt and water retention).**
- Suppresses renin/angiotensin system → low renin hypertension.
- Masculinization in females (FPH) and early virilization in males.

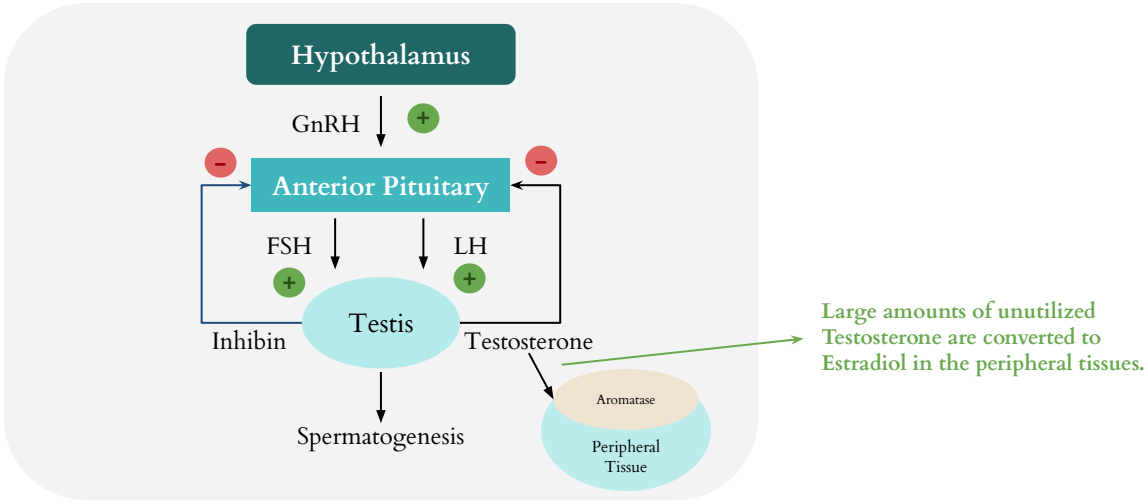


Disorders of Male Sexual Differentiation

They are rare group of disorders.

The defect may be in:
Androgen receptors (inactive androgen receptors → target tissues cannot respond to stimulation by circulating testosterone **e.g. Testicular feminization syndrome)**

Control of Testicular Function by The Gonadotropins:



Testicular Feminization Syndrome (TFS)

1. 46, XY karyotype (Normal Male).

2. **X-linked recessive disorder.**

Androgen receptor resistance. (can't bind to receptor) → High testosterone blood level. → In peripheral tissue, testosterone will be converted by aromatase into estradiol. → Feminization

3. Patients have normal testes & produce normal amounts of **müllerian-inhibiting tissue factor (MIF)1**, therefore, affected individuals **do not have** fallopian tubes, a uterus, or a proximal (upper) vagina .

Med438 : Sertoli cells secrete Müllerian inhibitory factor (MIF also known as, anti mullerian hormone) that suppresses Estradiol development of paramesonephric ducts.

4. The problem is not the production of testosterone, But how to utilise the testosterone in the blood and how to uptake it by the cell is the problem = **(Receptor Mutation)**

MCQ

Clinical picture

Complete androgen insensitivity syndrome (CAIS)	Partial androgen insensitivity syndrome (PAIS)
- Female external genitalia with normal labia. - Clitoris. - Vaginal introitus (**MPH**: male pseudohermaphrodite)	- **Mildly virilized female external genitalia** female external genitalia (clitorimegaly without other external anomalies) to **mildly undervirilized male external genitalia** (hypospadias and/or diminished penile size).

Laboratory Diagnosis

Karyotype: differentiate an under-masculinized male from a masculinized female. Result : 46, XY

Increased (or normal) testosterone and dihydrotestosterone blood levels.

Fluorescent in situ hybridization (FISH): Presence of a "Y" chromosome can be confirmed by probes for the **SRY** region of the Y chromosome.
These offer a much quicker turnaround time than conventional karyotypes.

DNA tests and mutation analysis for androgen receptor gene: Complete or partial gene deletions, point mutations, or small insertions deletions

Further Investigations

Imaging studies "Pelvic Ultrasound " Absence of fallopian tubes and uterus

Lecture Summary

Zona glomerulosa	Aldosterone	Zona fasciculata	Cortisol	Zona reticularis	Androgens

Hermaphroditism

True hermaphrodite	Female Pseudohermaphrodite (FPH)	Male Pseudohermaphrodite (MPH)
Ovary + Testis	Only ovary	Only testis

Congenital Adrenal Hyperplasia (CAH)

Deficiency	Glucocorticoid	Mineralocorticosteroids	Androgens	Features	Accumulated Hormones	Notes
21-α-Hydroxylase	↓	↓ "Hypovolemia and shock"	↑	Rapid growth ♀: -Masculinization - Virilization - FPH - Male-like genitalia ♂: - Early virilization - Precocious puberty	2 days after birth ↑ plasma 17-α-hydroxyprogesterone	- Most common CAH - CYP21 gene mutation - Autosomal recessive
11-β-Hydroxylase	↓	↓	↑	♀: -Masculinization - FPH ♂: - Early virilization	- ↑ 11-deoxycortisol - ↑ 11-deoxycorticosterone → ↓ RAS → low-renin HTN.	-
17-α-Hydroxylase	No	↑ "HTN"	No	Female-like genitalia	-	-
3-β-Hydroxysteroid dehydrogenase	No	No "Salt excretion in urine"	No	Female-like genitalia	-	Autosomal recessive

Testicular Feminization Syndrome (TFS) | Androgen Insensitivity Syndrome

Genetics	X-linked recessive disorder 46, XY karyotype	**Diagnosis**	**Blood:** ↑ testosterone **Peripheral:** testosterone → estradiol (feminization)
Pathology	Androgen receptor resistance	**Clinical Picture**	Normal testes & MIF No fallopian tube, uterus, proximal/upper vagina

1. Complete androgen insensitivity syndrome (CAIS)	2. Partial androgen insensitivity syndrome (PAIS)
Female external genitalia Normal labia, clitoris, and vaginal introitus (MPH)	Mildly virilized female external genitalia to mildly undervirilized male external genitalia - Clitorimegaly without other external anomalies - Hypospadias and/or diminished penile size

Laboratory Diagnosis	**Karyotype:** differentiate an under masculinized male from a masculinized female.	FISH: SRY region of Y chromosome	Blood: ↑/N testosterone & dihydrotestosterone	**DNA tests + mutation analysis for androgen receptor gene**	**Pelvic US:** No fallopian tubes and uterus.

MCQs

Q1. Which one of the following is the most common enzyme deficiency in case of congenital adrenal hyperplasia?			
A. 17-α-Hydroxylase	B. 21-α-Hydroxylase	C. 11-β-Hydroxylase	D. 3-β-Hydroxysteroid dehydrogenase
Q2. 21-α-Hydroxylase enzyme deficiency leads to an increase in which one of the following circulating hormones?			
A. Aldosterone	B. Cortisol	C. 11-Deoxycorticosterone	D. 17-α-Hydroxyprogesterone
Q3. Which of the following represent Congenital adrenal hyperplasia?			
A. True Hermaphrodite	B. Male Pseudohermaphrodite	C. Female Pseudohermaphrodite	D. 46 XX
Q4. Which of the following is related to Testicular feminization syndrome?			
A. SRY region analysis by FISH	B. Autosomal Recessive	C. 46.XX karyotype	D. Female Pseudohermaphrodite
Q5. Which one of the following is a finding in a patient with Testicular feminization syndrome?			
A. True Hermaphrodite	B. Increased Mullerian inhibiting hormone	C. Inactive androgen receptors	D. Female Pseudohermaphrodite
Q6. Deficiency of 3-β-Hydroxysteroid dehydrogenase will have Which one of the following features?			
A. Male like Genitalia	B. Female like Genitalia	C. Both Female & Male Genitalia	D. Low Renin Hypertension

A1. B A2. D A3. C A4. A A5. C A6. B

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Special Thanks to Aleen Alkulyah for the Wonderful Design!

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