Genetic Aspects of

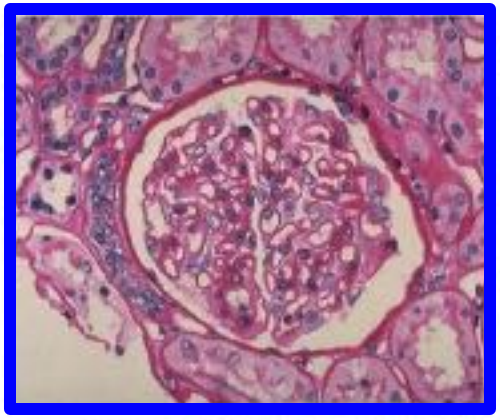
HEMOLYTIC UREMIC SYNDROME

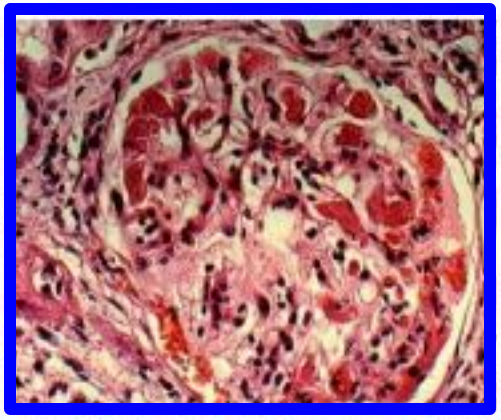
By Ramzi El-Baroudy

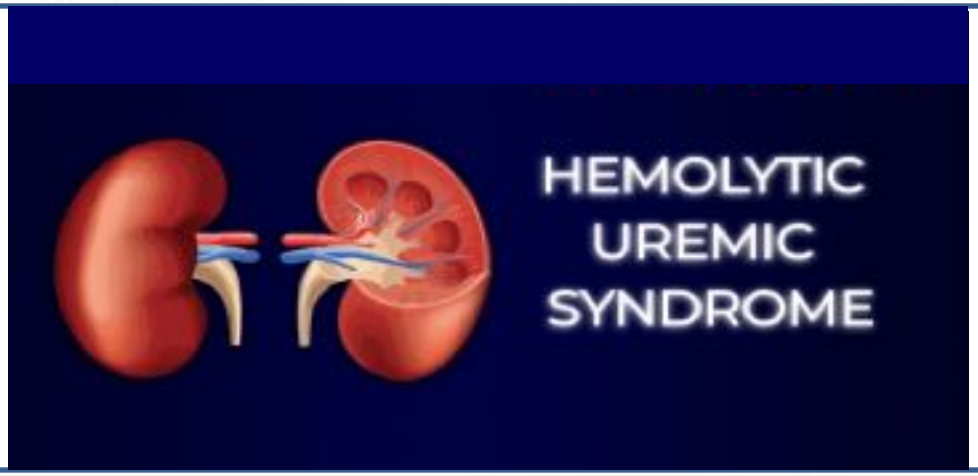
Hemolytic Uremic Syndrome

A thrombotic microangiopathy manifesting with:

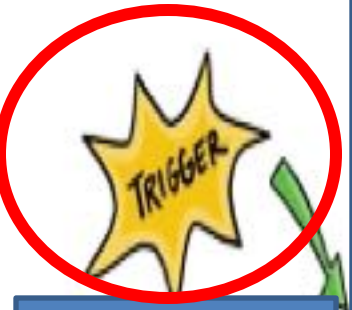
- Micro-angiopathic hemolytic anemia
- Thrombocytopenia
- Acute renal failure



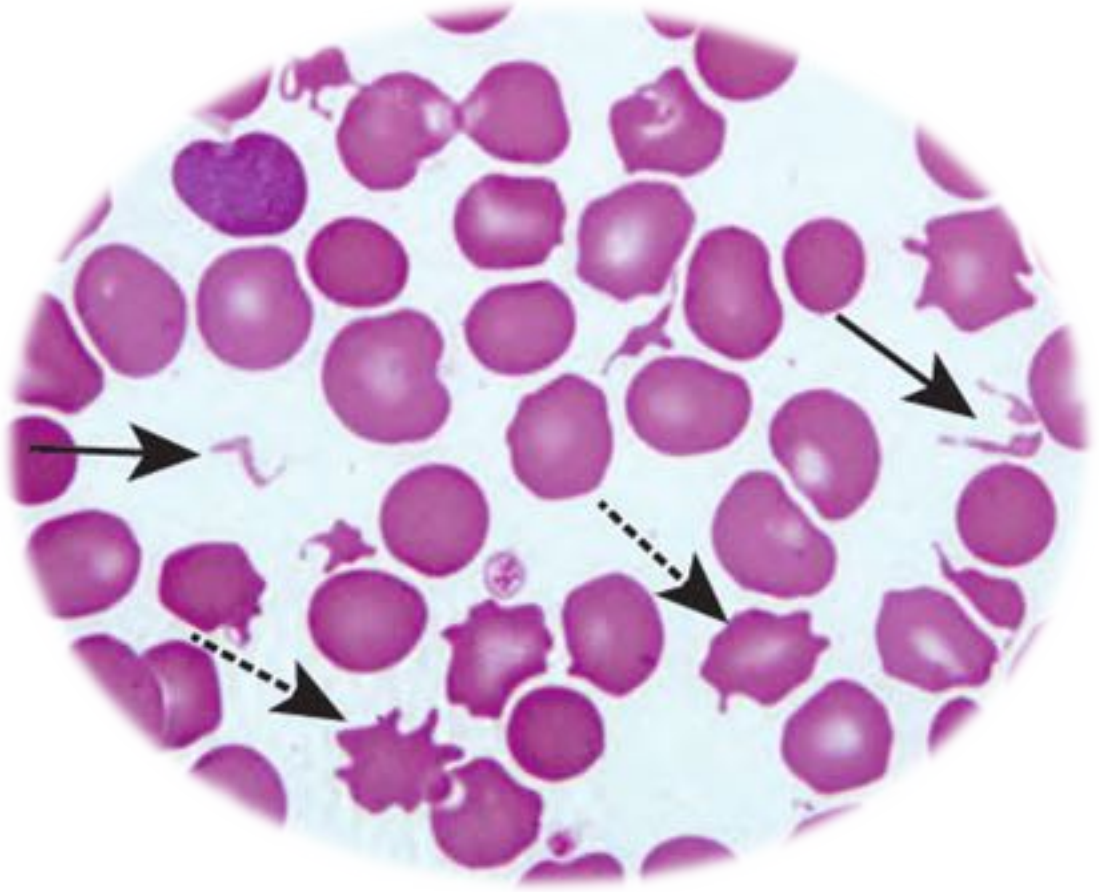




What's meant by Thrombotic MicroAngiopathy (TMA) ?



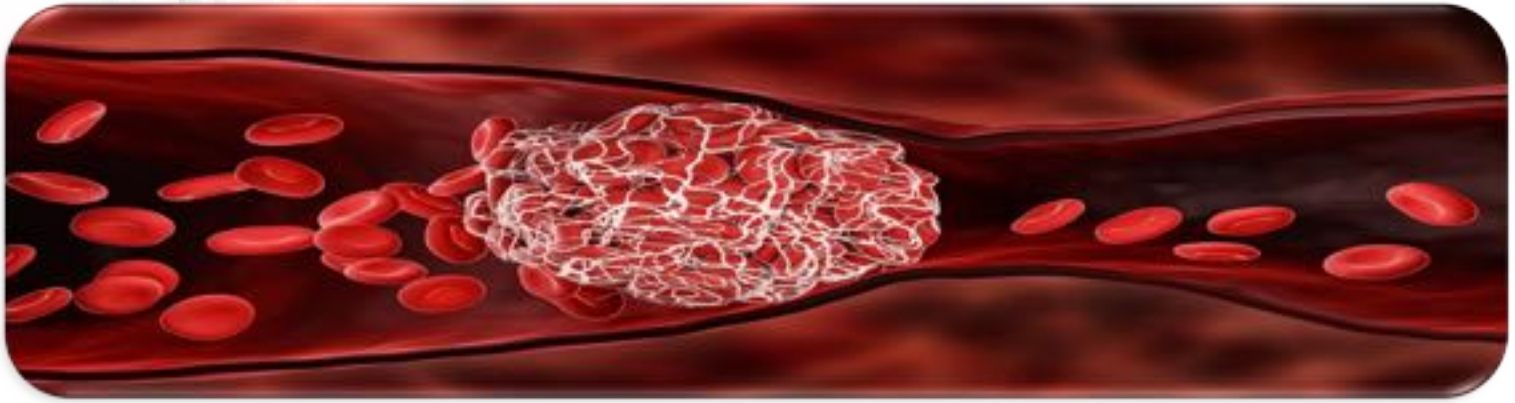
*infection
*Cancer
*Medications
*Pregnancy
*Organ Tx
*Tissue injury

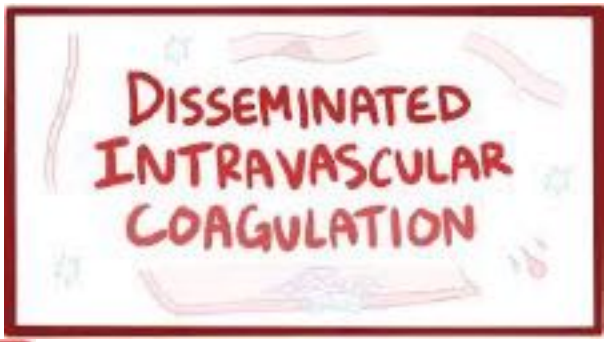


The hallmark of HUS in the peripheral smear is the presence of fragmented, deformed, irregular, or helmet-shaped RBCs (schistocytes).

In addition,

Intraluminal Platelet Thrombosis





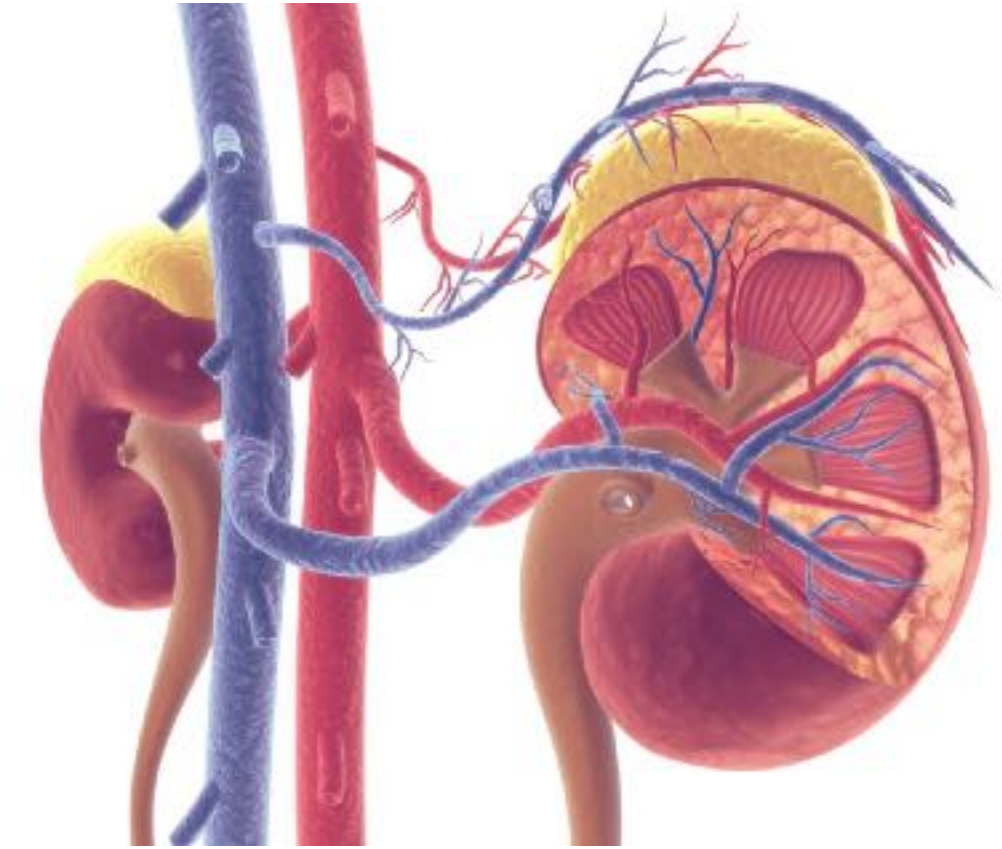
Thrombotic thrombocytopenic purpura (TTP), hemolytic uremic syndrome (HUS), and disseminated intravascular coagulation (DIC) fall under a larger class of pathologies known as thrombotic microangiopathies (TMAs).

TMAs are broadly characterized by microthrombi formation that is secondary to endothelial damage

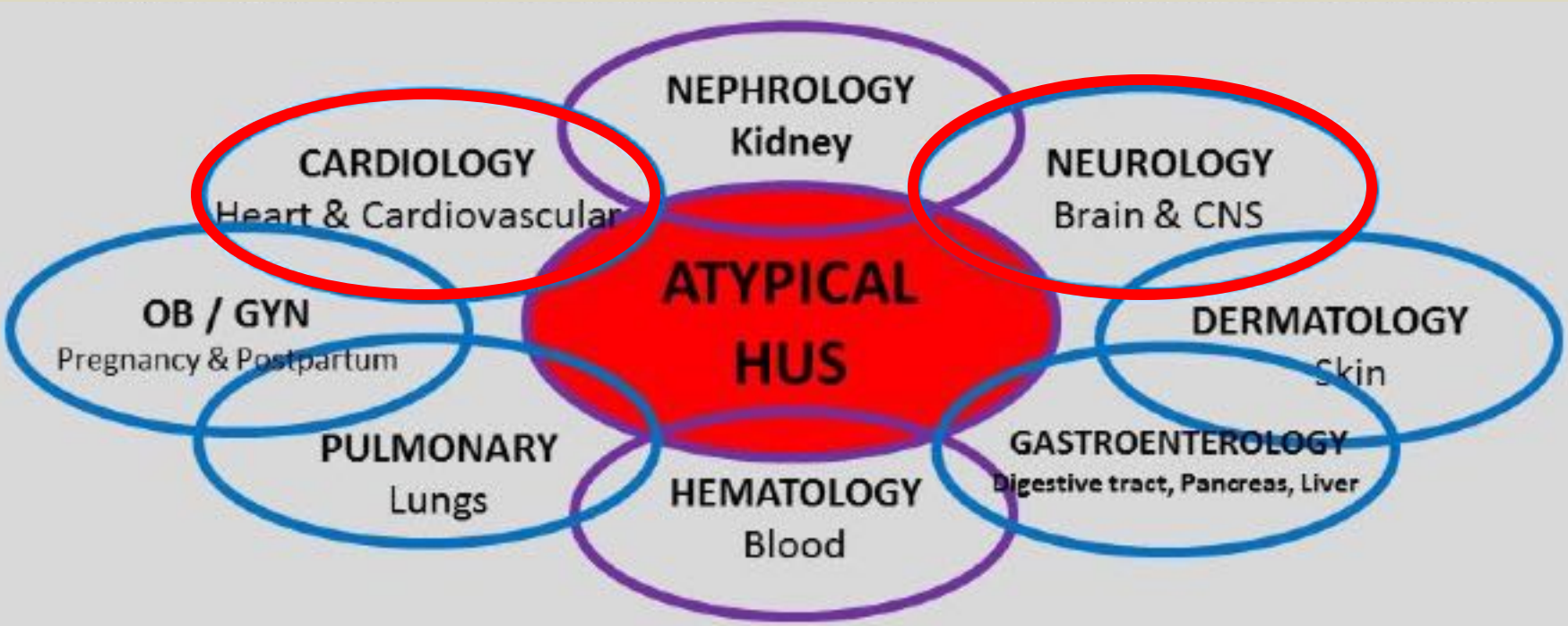
This is pathology, no matter what the trigger is.

If the trigger is complement system overactivation due to a genetic mutation, now, it is referred to as aHUS

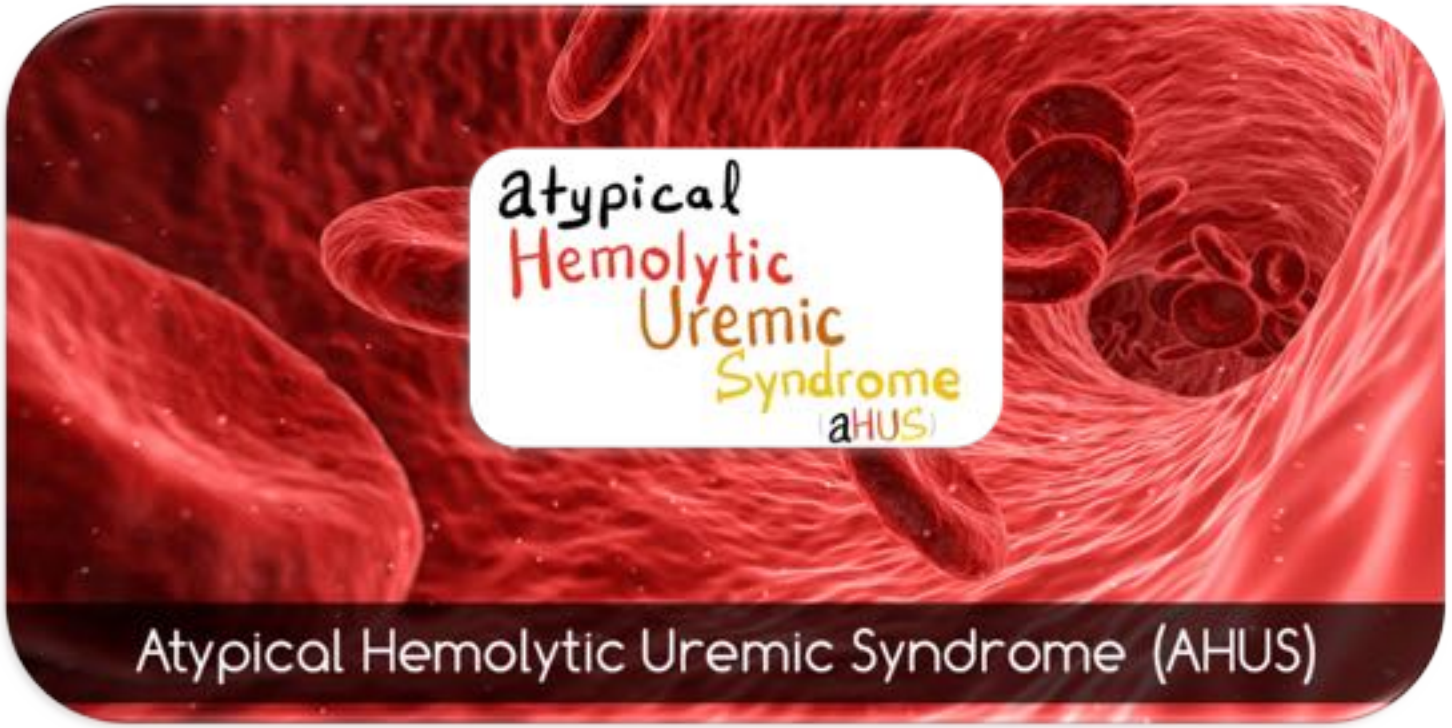
In aHUS, complement starts to attack the body's own cells, especially those that line the blood vessels.
This leads to clots forming within the small vessels.



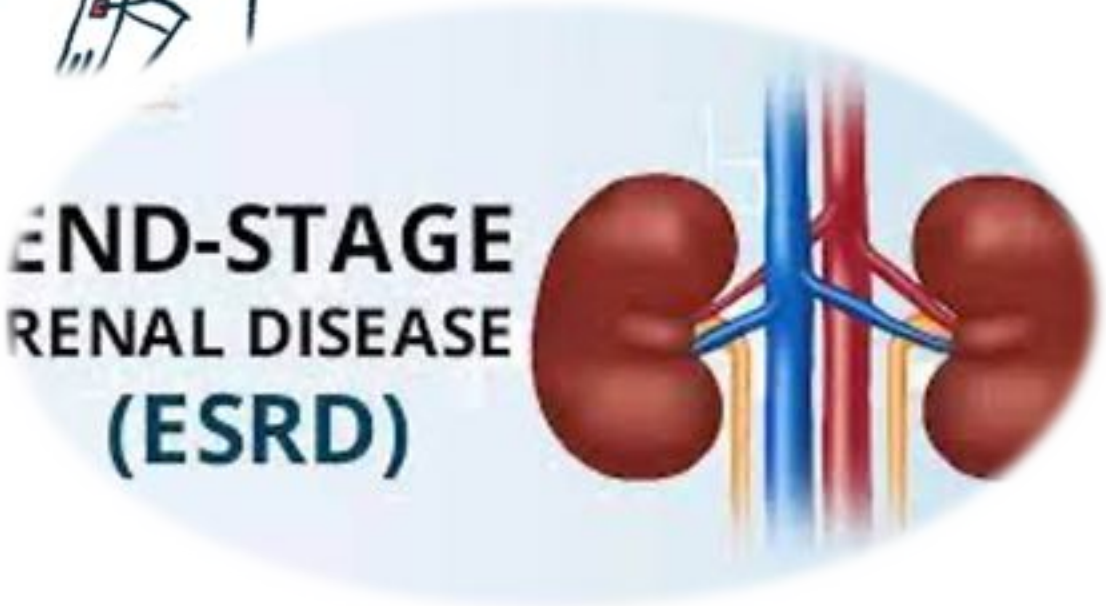
The most commonly affected organ is the kidney but all organs can be affected.



and, one patient in 5 has aHUS affecting organs other than the kidneys;
but most commonly the brain or heart.



aHUS is a **genetic** disease that causes tiny blood clots to form in the blood vessels, blocking blood flow to important organs.



Mortality rates range from 10–15% in the acute phase of the disease.

Within a year of diagnosis, up to 70% of patients progress to ESRD and need dialysis or die.

This occurs due to mutations in the genes encoding the complement regulators, particularly, factors H and I.

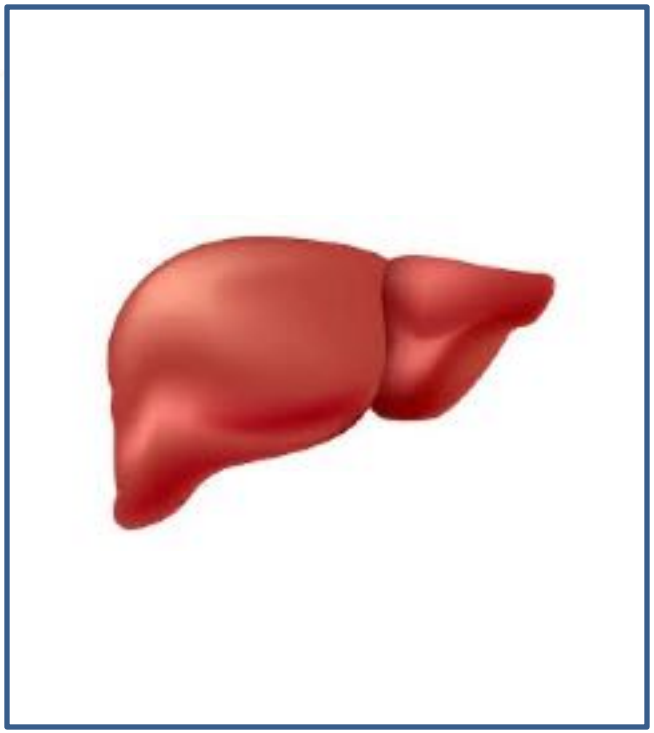
A short stop here,

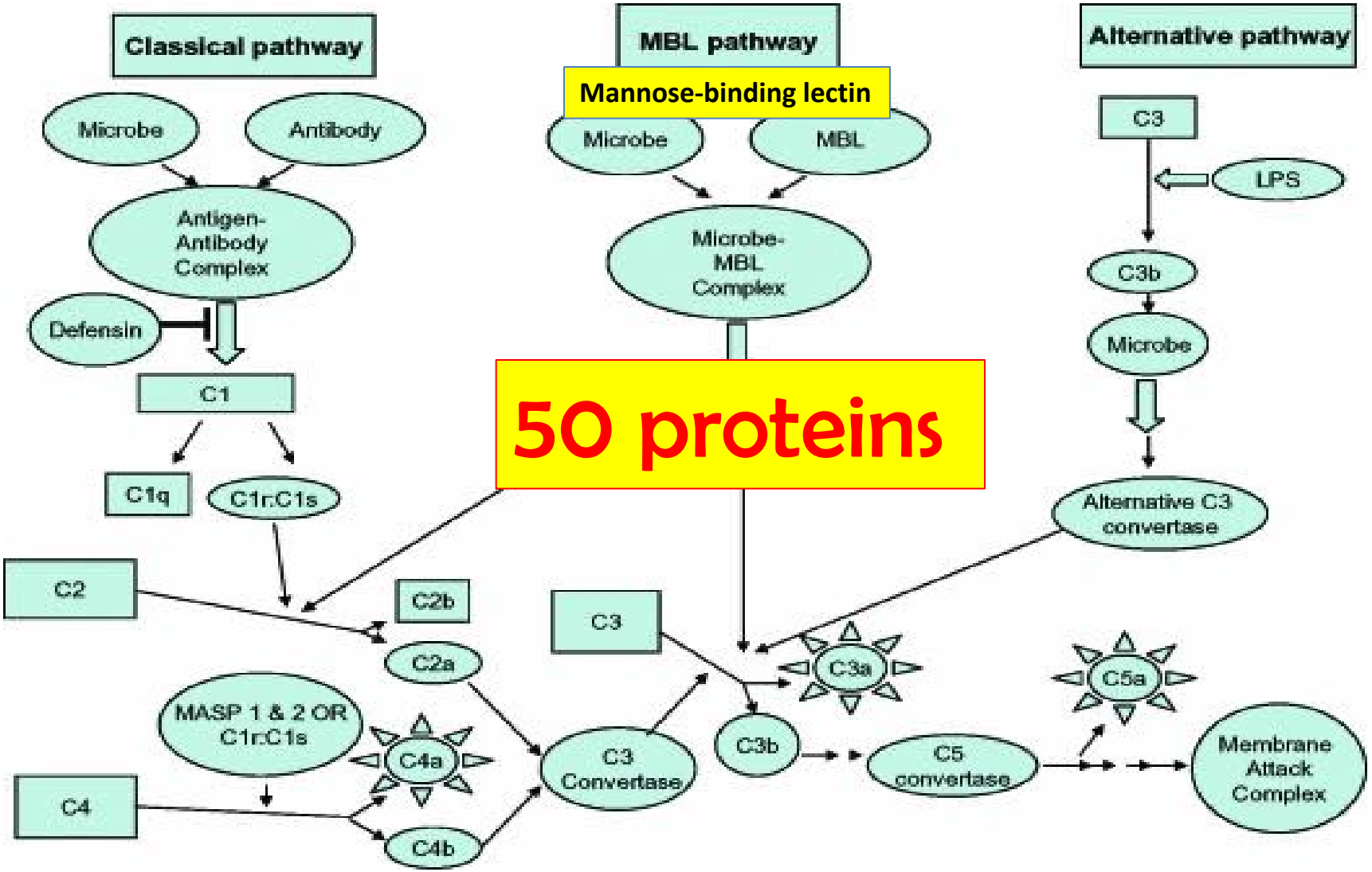
What is the complement system ?

THE COMPLEMENT SYSTEM

* GROUP OF PLASMA PROTEINS

* PRODUCED IN THE LIVER

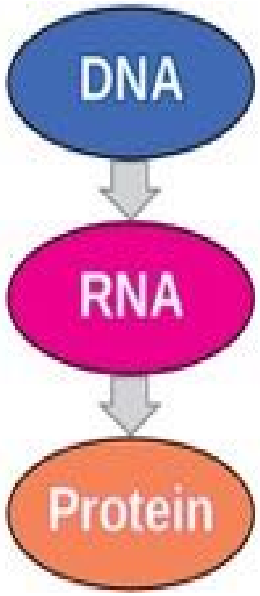




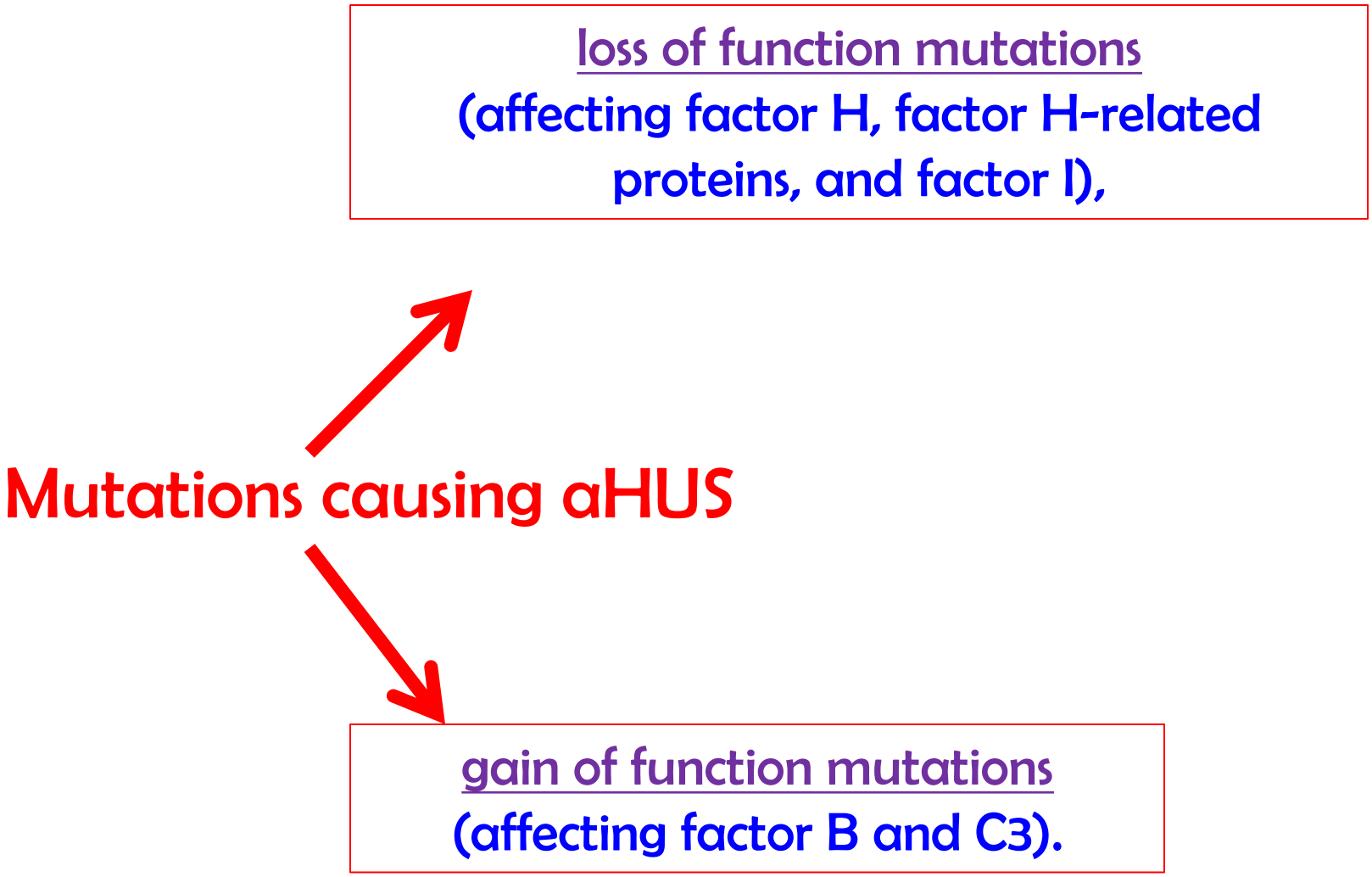
About 50 proteins make up the body's complement system.

These proteins circulate throughout blood and tissues.

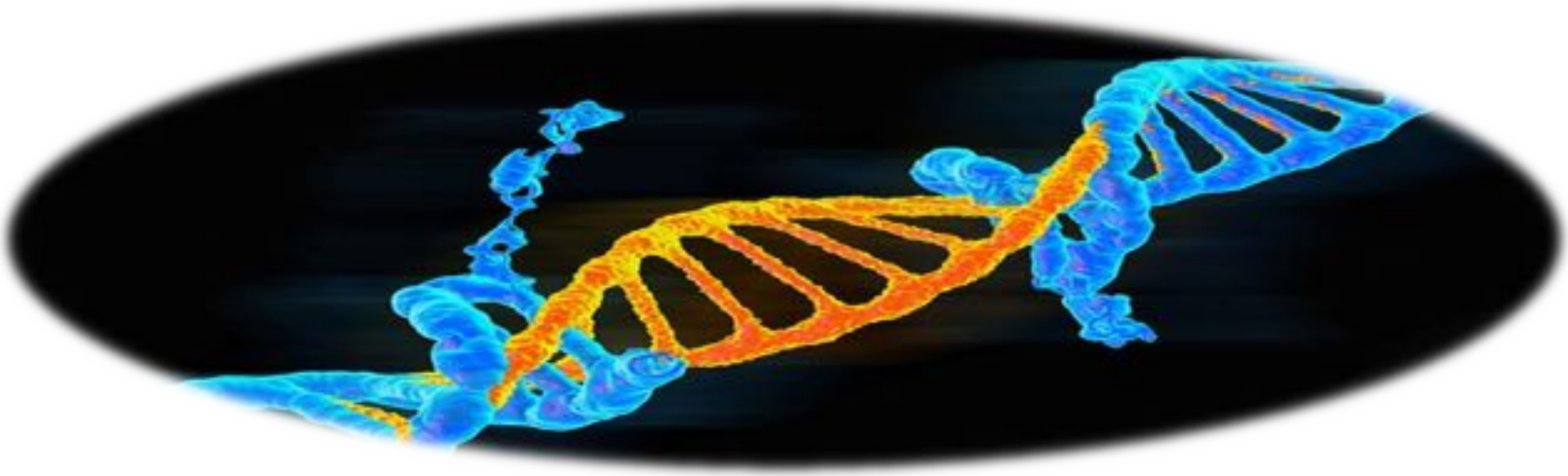
And as long as the complement members are proteins,
They are under the direct control of the protein building units i.e. genes



And with this huge number of proteins, you can imagine the genetic influence in this area.


loss of function mutations
(affecting factor H, factor H-related proteins, and factor I),
Mutations causing aHUS
gain of function mutations
(affecting factor B and C3).

loss-of-function mutation (LOM)
results in an inactive or less active product,
and are generally recessive.



Gain-of-function Mutation (GOM)
results in a more active product, or a product with
a different function,
and are almost always Dominant .

In particular,

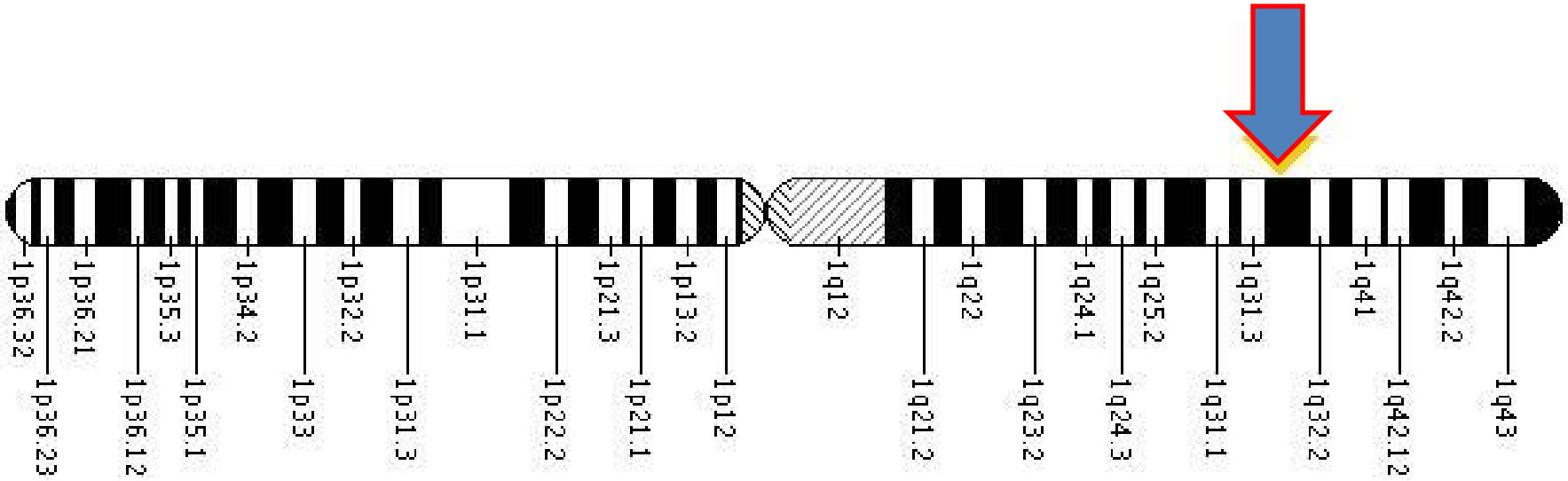
the pathogenesis of aHUS is commonly related
to a rare heterozygous
loss-of-function (LOF) mutation
in the gene for complement factor H (CFH),
complement factor I (CFI), or
membrane cofactor protein (MCP)
or a gain-of-function (GOF) mutation
secondary to a variant in factor B (CFB) or C3.

With corruption of the whole system...

and

uncontrolled

complement activation in the alternative pathway (AP).

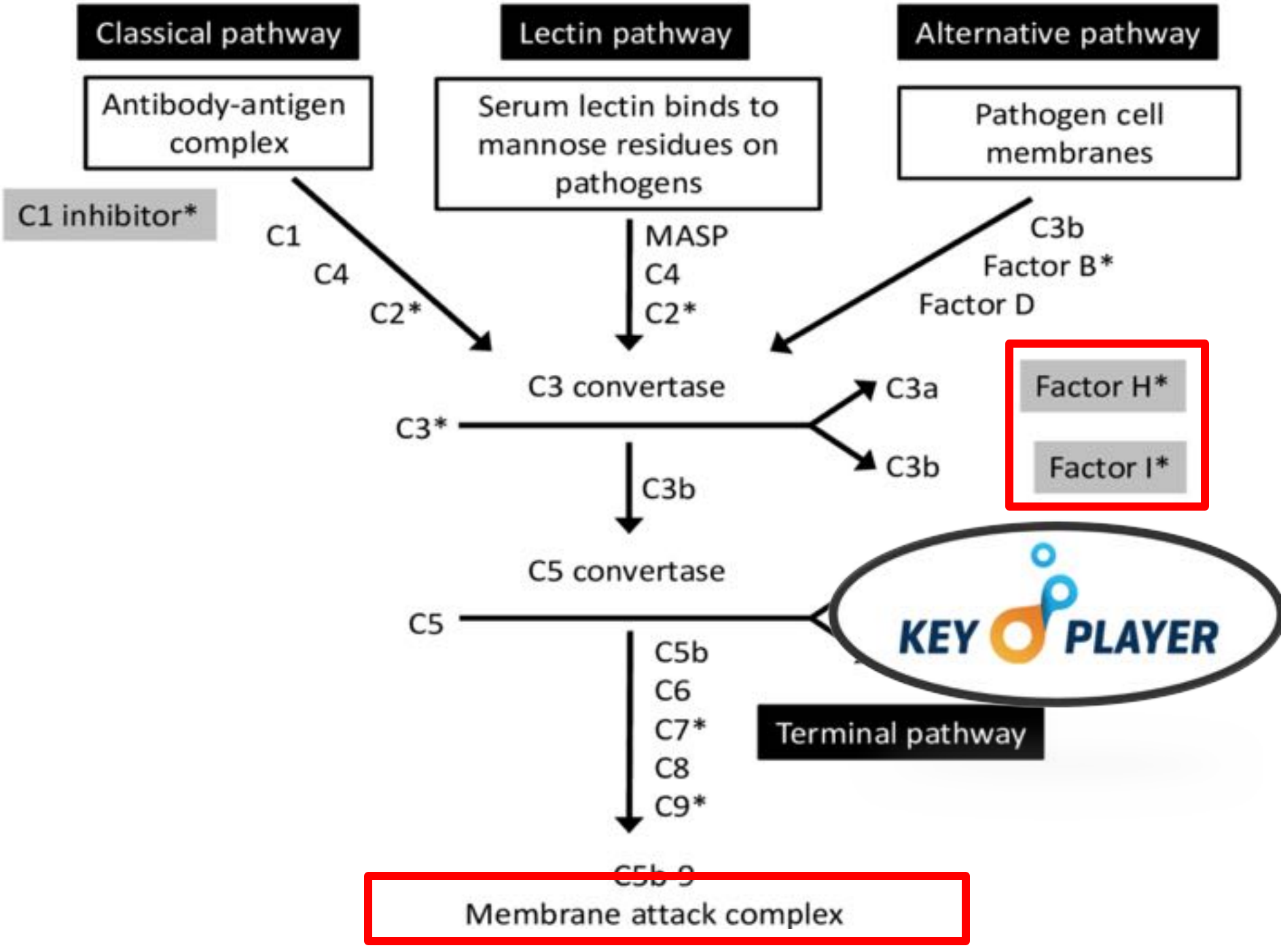


About 30% of aHUS is associated with

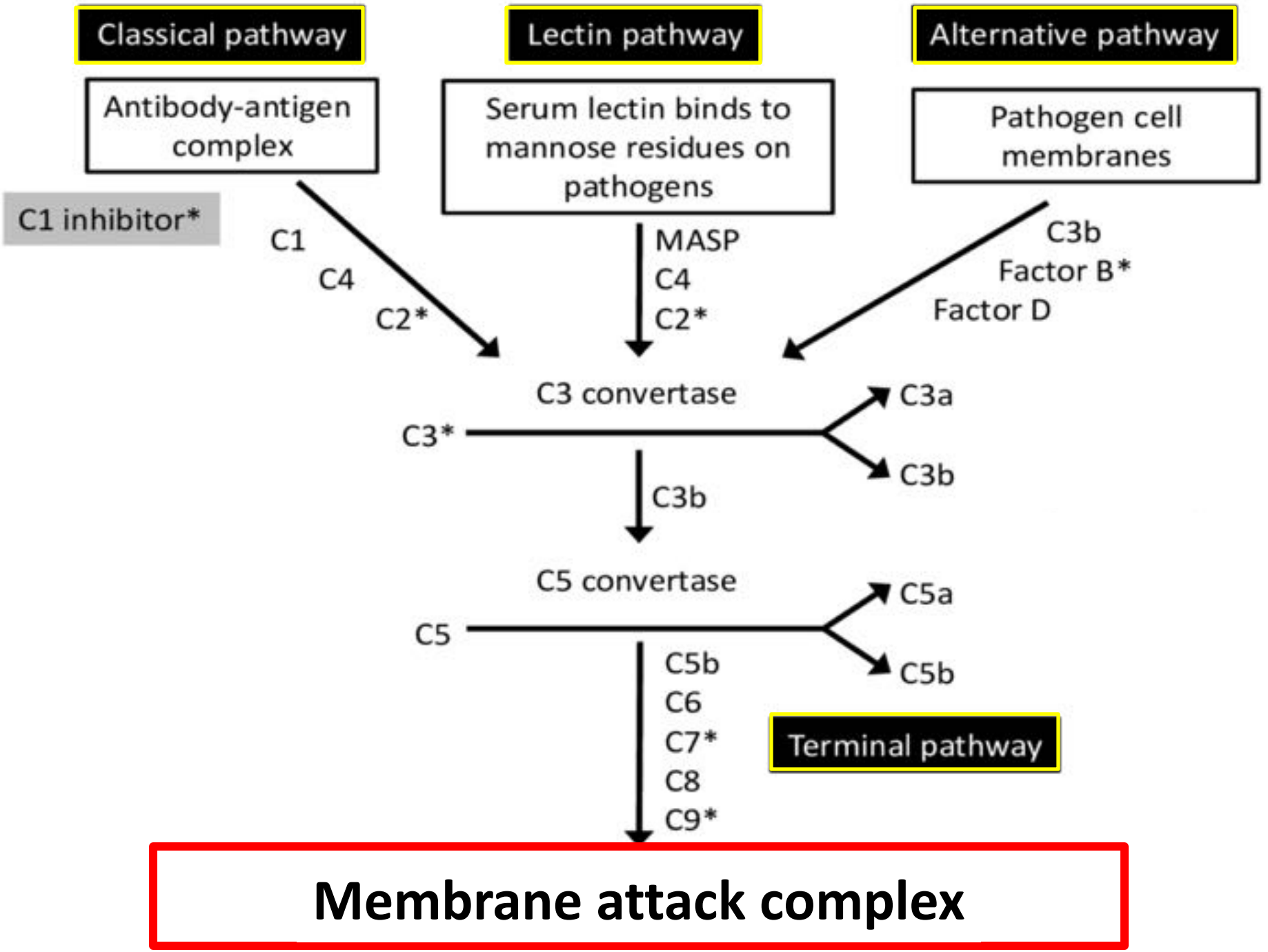
a loss of function mutation

in the gene (CFH), located on chromosome 1,
and responsible for the production of
a blood protein known as factor H that
protects blood vessels from injury.

This is the most common gene mutation associated with aHUS.


Classical pathway
Lectin pathway
Alternative pathway
Antibody-antigen complex
Serum lectin binds to mannose residues on pathogens
Pathogen cell membranes
C1 inhibitor*
C1
C4
C2*
MASP
C4
C2*
C3b
Factor B*
Factor D
C3 convertase
C3*
C3a
C3b
Factor H*
Factor I*
C3b
C5 convertase
C5
KEY PLAYER
C5b
C6
C7*
C8
C9*
Terminal pathway
C5b-9
Membrane attack complex

as we all know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C2*
C3b
Factor B*
Factor D
C3 convertase
C3*
C3a
C3b
C3b
C5 convertase
C5
C5a
C5b
C5b
C6
C7*
C8
C9*
Terminal pathway
Membrane attack complex

What's the idea behind this

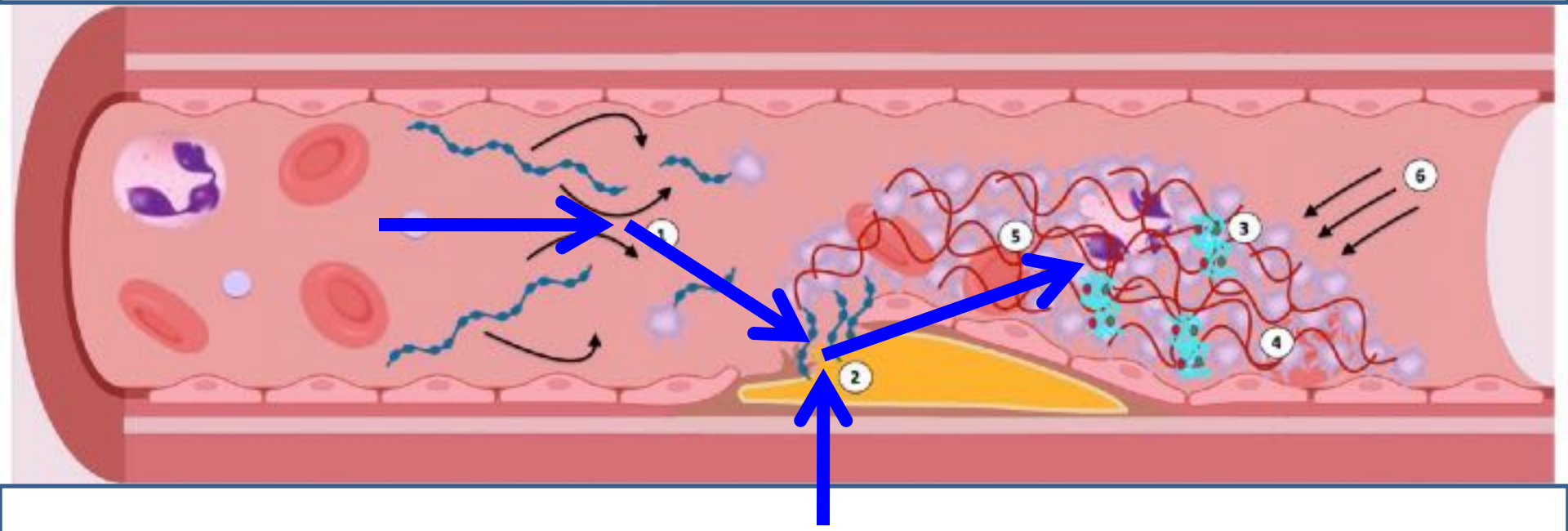
Membrane Attack Complex (MAC)

Microbial cell membrane

مش خلايا الجسم
الطبيعية أبدا

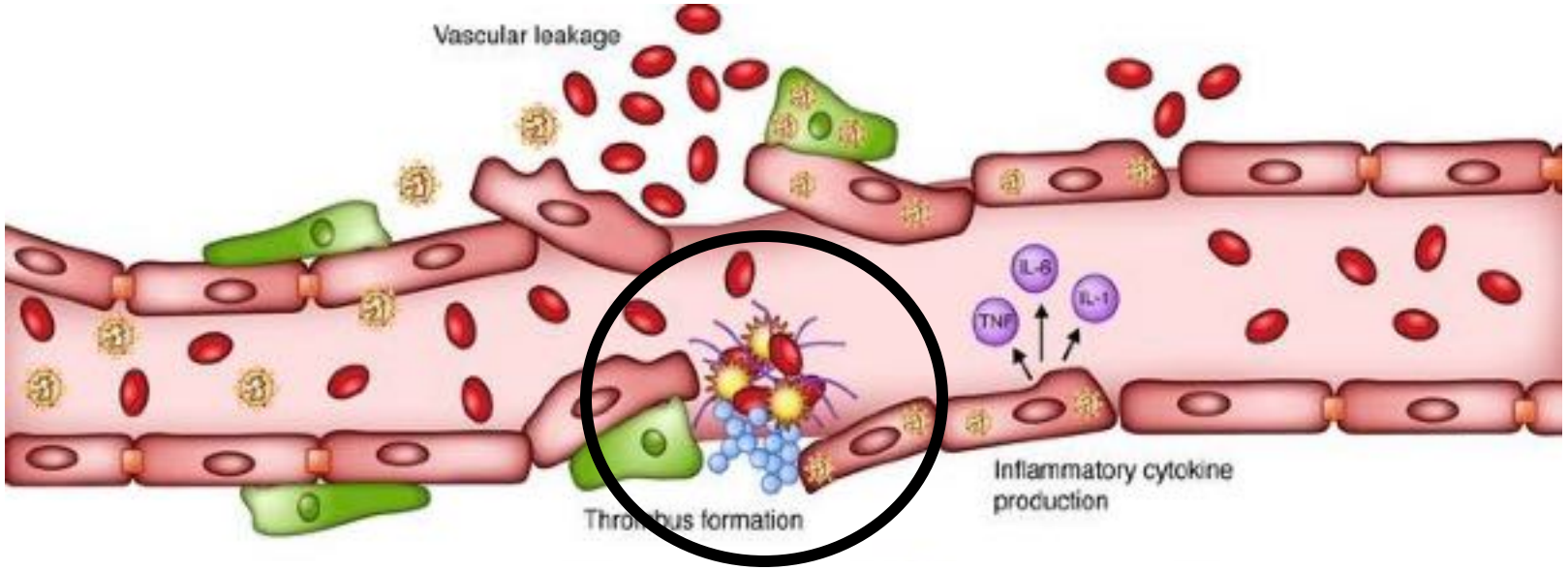

BUT

In aHUS,



dysfunction in the complement cascade with uncontrolled complement activation in the alternative pathway (AP) leads to complement deposition on endothelial cells, endothelial swelling and detachment, and thrombus formation.

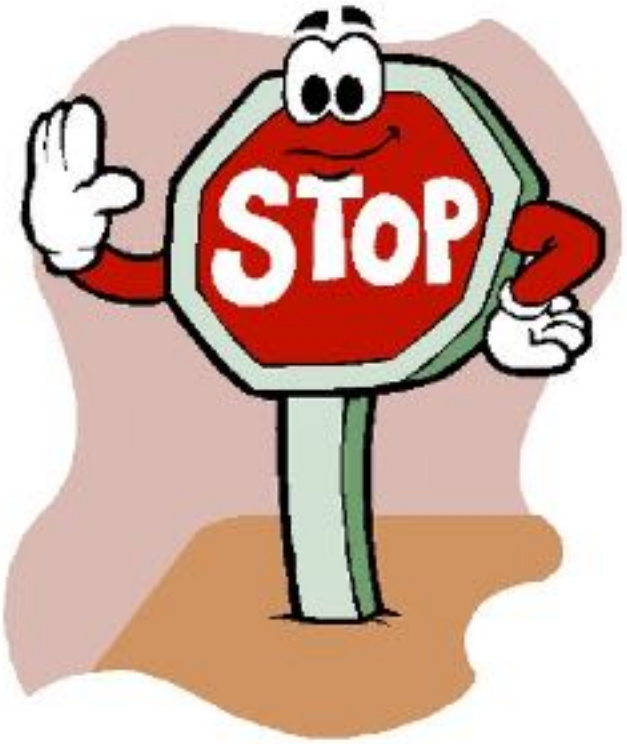

نقول كمان !!



The overactive complement system attacks cells that line blood vessels in the kidneys and many other organs, causing inflammation, endothelial damage, and the formation of abnormal clots.

What is the most common mutation in complement regulatory proteins leading to aHUS?

Mutations of CFH are the most frequent genetic abnormality in aHUS, accounting for 20–30% of aHUS



Complement factor H (CFH), together with several related proteins, protects healthy cells by

preventing

the complement system from being activated when it is

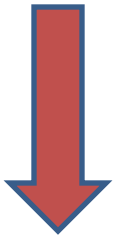
not

needed.

CFH gene provides instructions for making this protein.

Besides CFH, many other **gene mutations** are associated with **genetic** aHUS, and include:
C3, Membrane cofactor protein (MCP; CD46), CFB, CFH (R1, R3, R4, R5), CFI, THBD (thrombomodulin), VTN (Vitronectin), ADAMTS13 (a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13)—also known as von Willebrand factor-cleaving protease (VWFCP) (responsible too, for TTP and p-aHUS), CD59, MMACHC (Methylmalonic aciduria and homocystinuria type C protein) and PLG (Plasminogen).

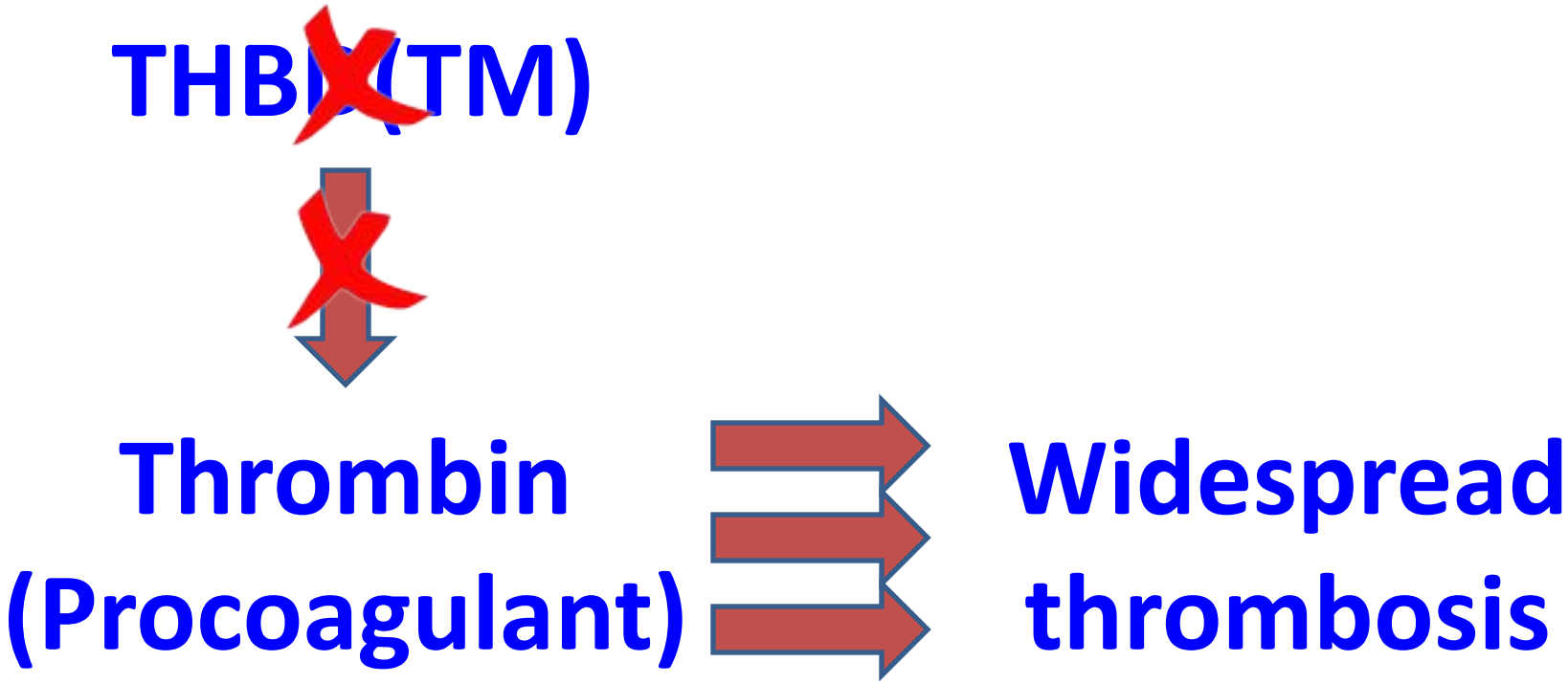
THBD(TM)



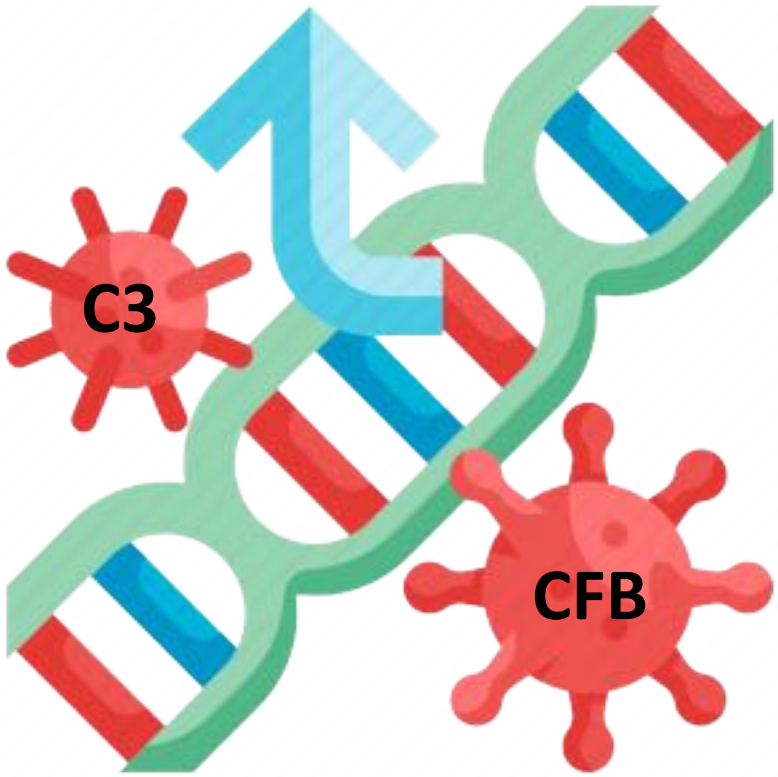
Thrombin (Procoagulant)

Anticoagulant

THBD has a high affinity of binding to thrombin and converts thrombin from a procoagulant to an anticoagulant.



Mutations of THBD will set free thrombin procoagulant activity un-hindered and widespread thrombosis will occur.



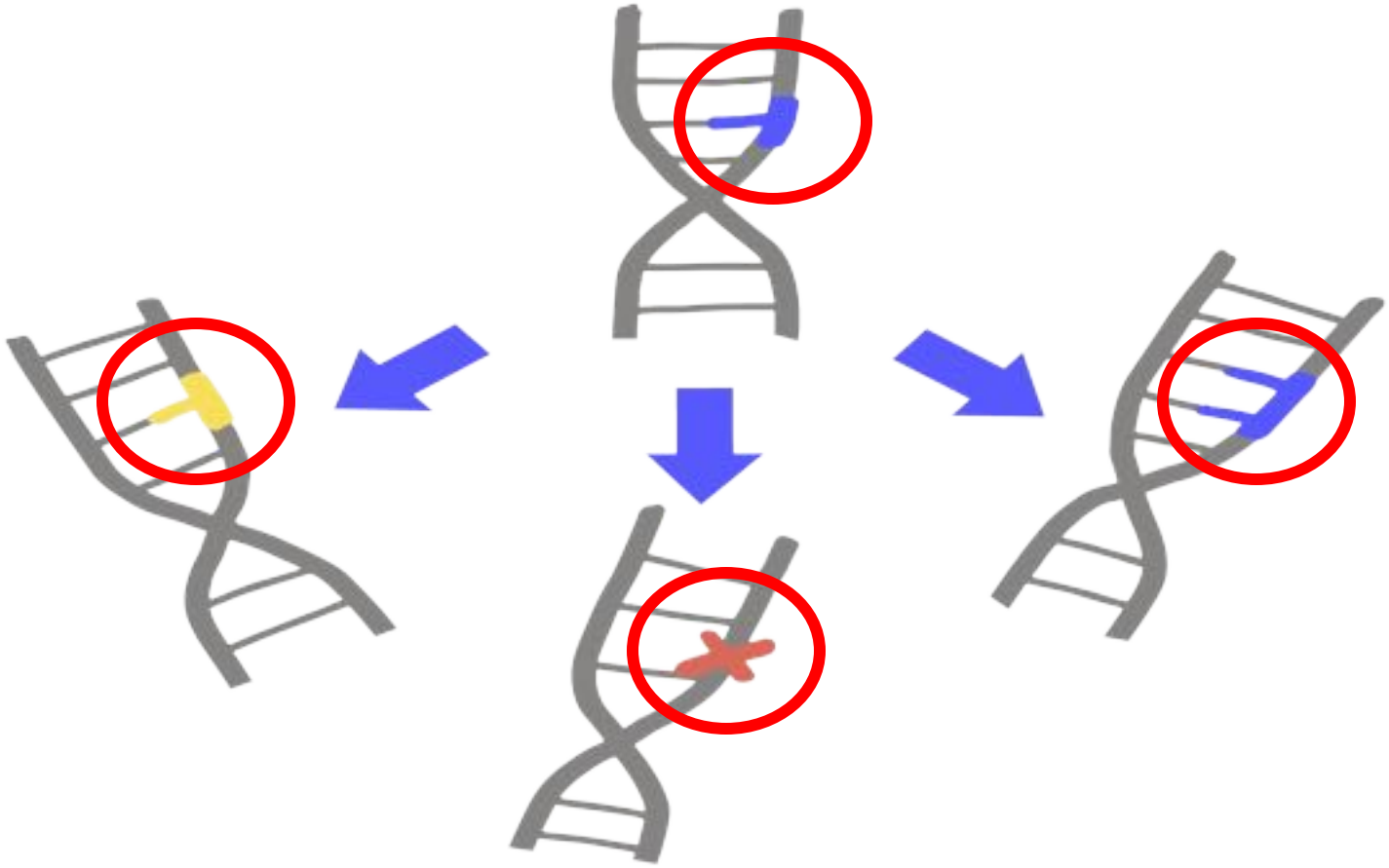
Complement factor B (CFB) mutations and C3 mutations
result in increased activity for C3 convertase
due to a
(Gain-of-function mutation)

These patients have a continuously activated alternative pathway.

This cluster of genes are all related to the complement system

Does this mean that any disorder overshooting the alternative pathway of the complement system can result in aHUS ?

The complement proteins are clearly involved in all types of TMA: HUS, aHUS and TTP. Abnormalities in complement genes are definitely part of the play.



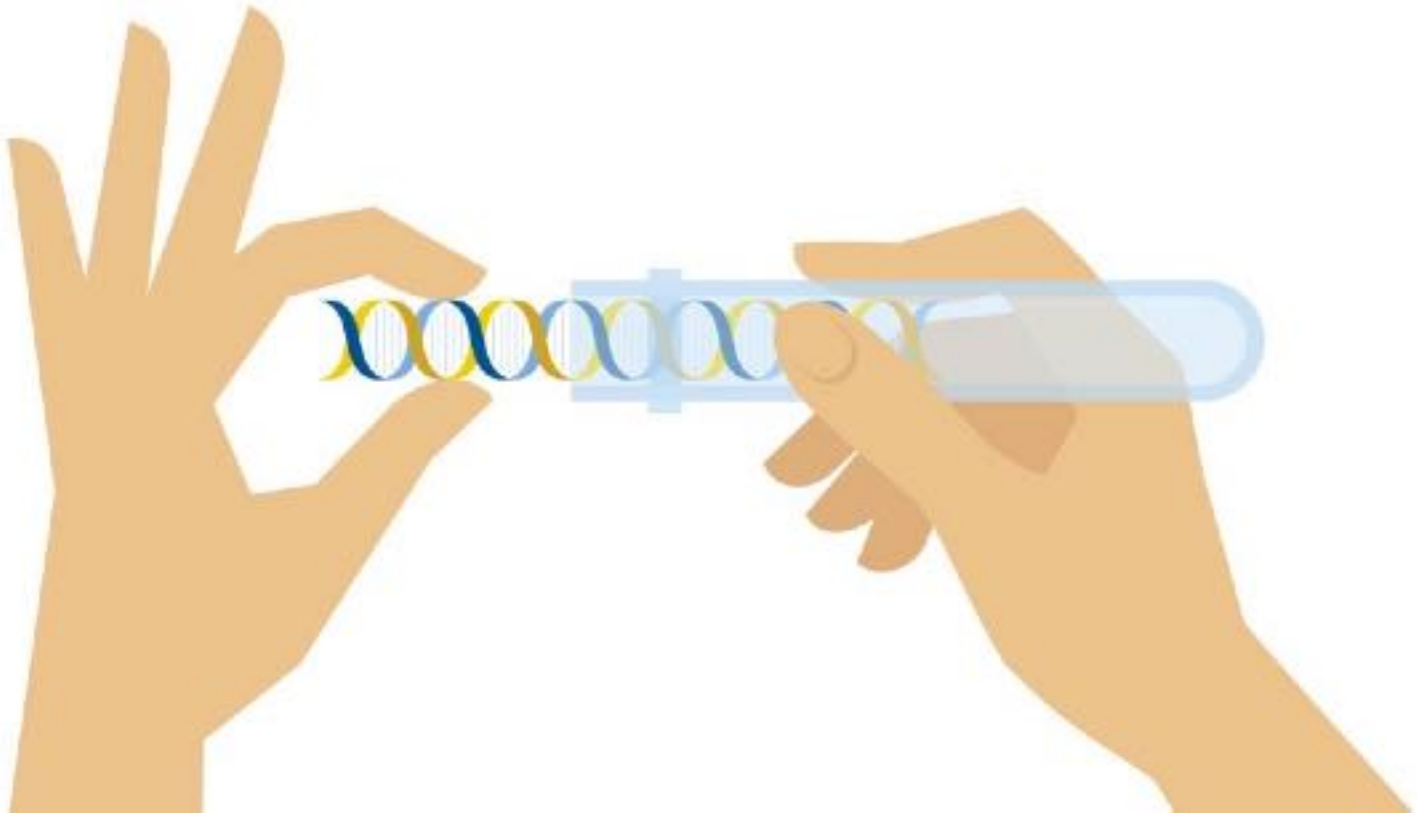
Up to 12% of patients with aHUS have

Combined

mutations with two or more mutations in

CFH, CFI, MCP, THBD, CFB and *C3*.

Death rates among aHUS patients are as high as 25%.

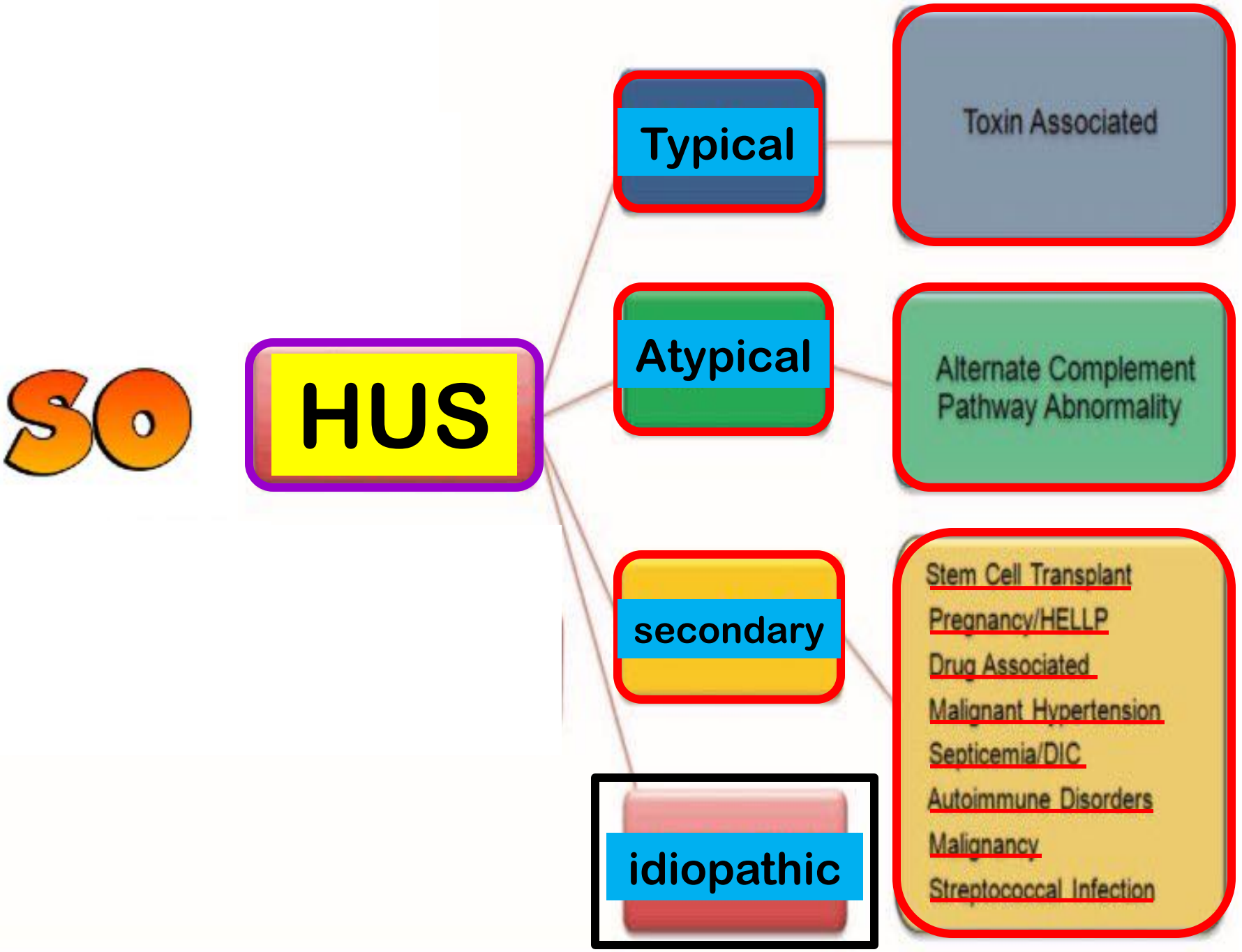


genetic analysis in the form of a
multi-gene panel test
is essential for all patients suspected to have aHUS,
along with anti-CFH autoantibody test,
particularly in pediatric patients.

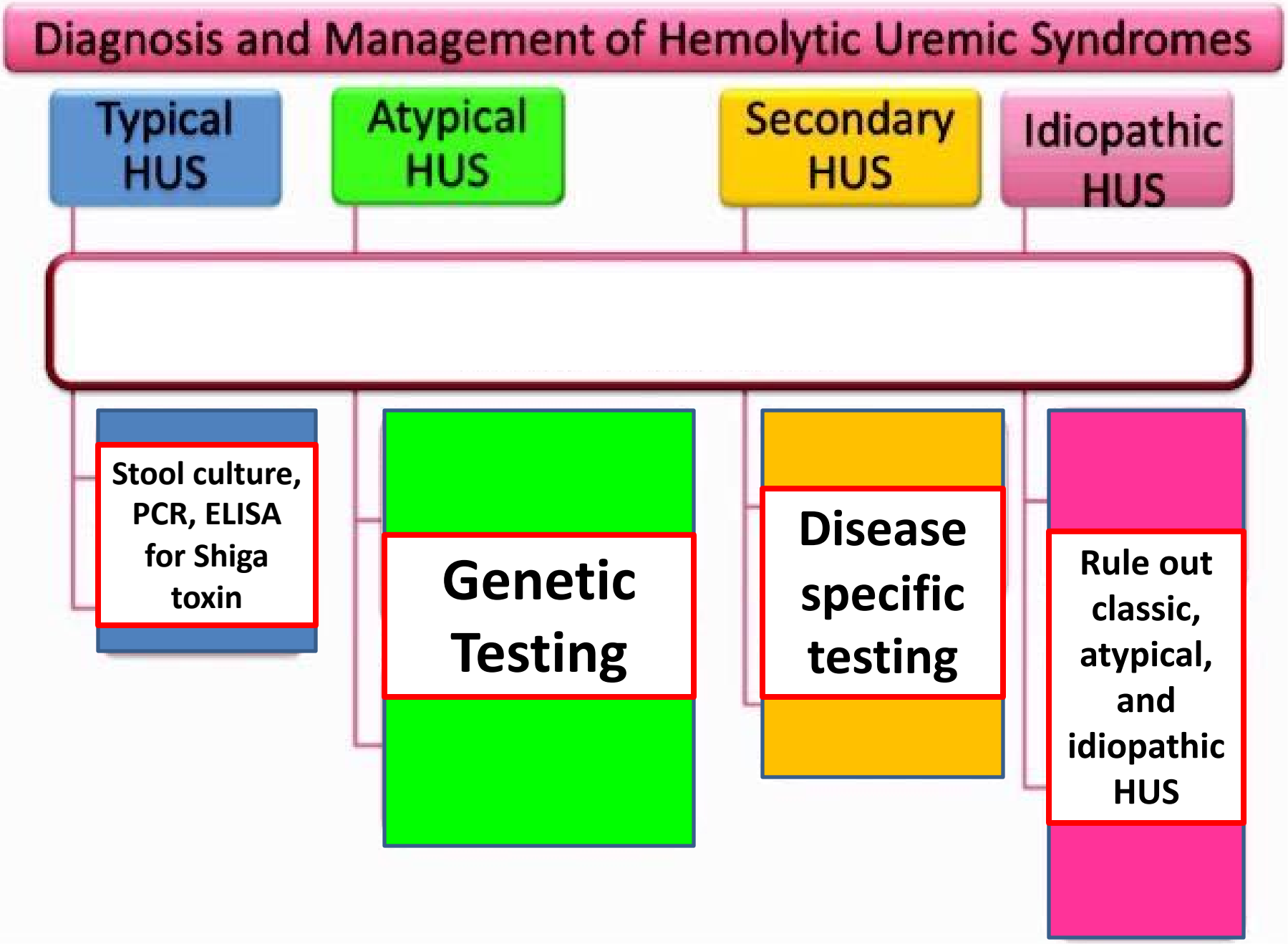
In conclusion, one or more abnormalities in the regulatory complement system have been documented in 70% of aHUS.

sporadic

In contrast, in 30% of aHUS no abnormality has been found.


SO
HUS
Typical
Toxin Associated
Atypical
Alternate Complement Pathway Abnormality
secondary
Stem Cell Transplant
Pregnancy/HELLP
Drug Associated
Malignant Hypertension
Septicemia/DIC
Autoimmune Disorders
Malignancy
Streptococcal Infection
idiopathic

Diagnostic recommendations


Diagnosis and Management of Hemolytic Uremic Syndromes
Typical HUS
Atypical HUS
Secondary HUS
Idiopathic HUS
Stool culture, PCR, ELISA for Shiga toxin
Genetic Testing
Disease specific testing
Rule out classic, atypical, and idiopathic HUS


HOPE


TAKE
HOME

Will they ever make or add a test to the routine newborn screening to determine if a baby has a predisposition to aHus, therefore allowing them to receive treatment before an episode, thus preventing misdiagnosis, kidney failure, even death?

Ramzi El-Baroudy