The Lewis System

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Objectives

- Discuss the genetic interactions of *Le* genes with *ABH* and *Se* genes.
- Describe the formation and secretion of Lewis antigens and their adsorption onto the red cell membrane.
- Describe the clinical significance of anti-Le^a and anti-Le^b

Objectives

- Describe in detail the phenotypes capable of forming Anti-Le^a and Anti-Le^b.
- Define the term *transitional phenotype* as it relates to the age of the patient.
- Describe the changes in Lewis phenotypes and presence of Lewis antibodies during pregnancy and clinical significance.
- Given results of a secretor inhibition study, correctly interpret whether substances are present or not present. Based on these results, apply your knowledge of gene interaction to identify the likely *Le*, *Se*, and *ABH* genes present.

The Lewis system is unique.

Lewis system—the liquid antigen system

1. *Lea* and *Leb* are NOT alleles of a blood group system.
2. Genes *Le* and *le* (amorph)
3. The *Le* gene must be present for a precursor substance to be converted to Le^a.
4. But, the *Se* gene must be present for conversion to Le^b.

The most important items

	Gene	Locus
ABO	*ABO*	9q

	Gene	Locus
ABO	*ABO*	9q
H	*FUT1*	19q

	Gene	Locus
ABO	*ABO*	9q
H	*FUT1*	19q
Se	*FUT2*	19q

99.99% inherit *H (FUT1)* gene
~80% inherit *Se (FUT2)* gene

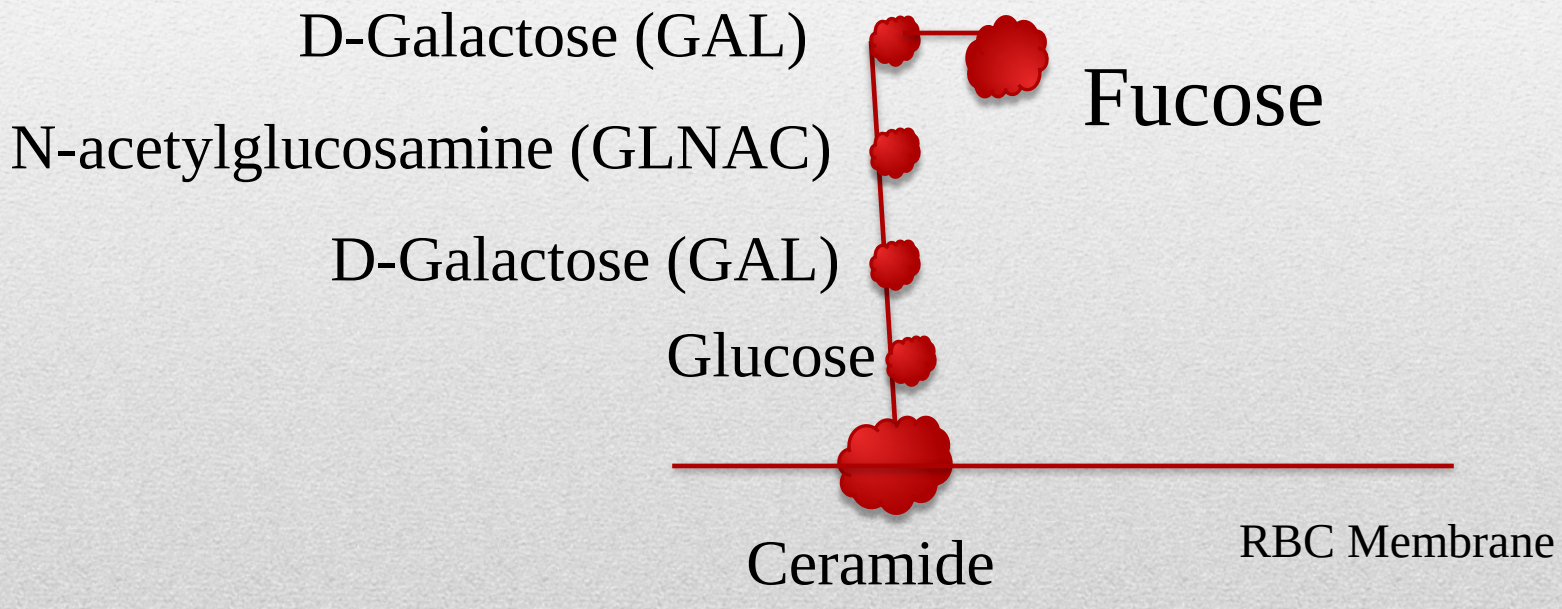
Secretors in U.S. populations

	Gene	Locus
ABO	*ABO*	9q
H	*FUT1*	19q
Se	*FUT2*	19q
Le	*FUT3*	19p

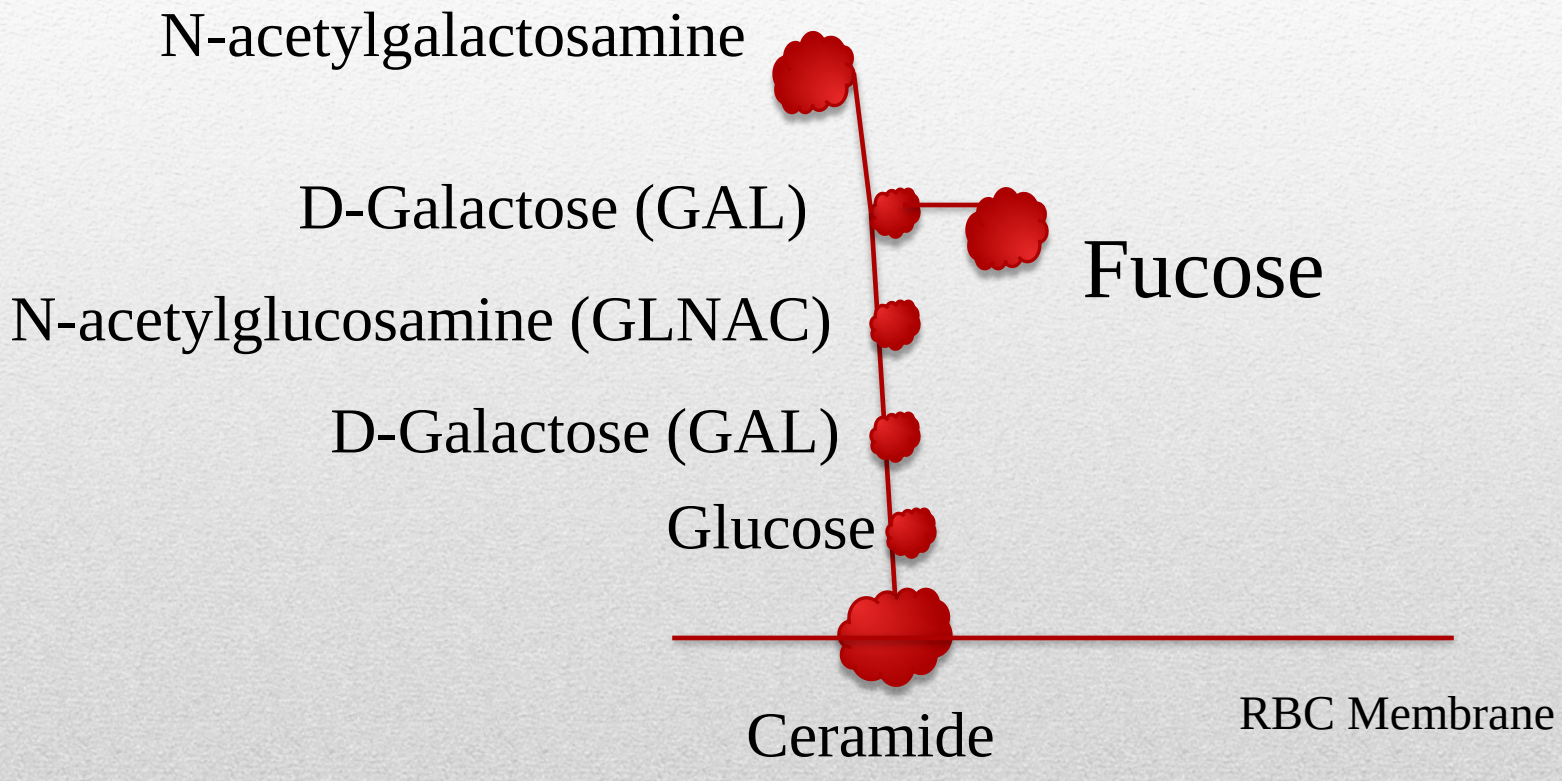
~90% inherit *Le (FUT3)* gene*

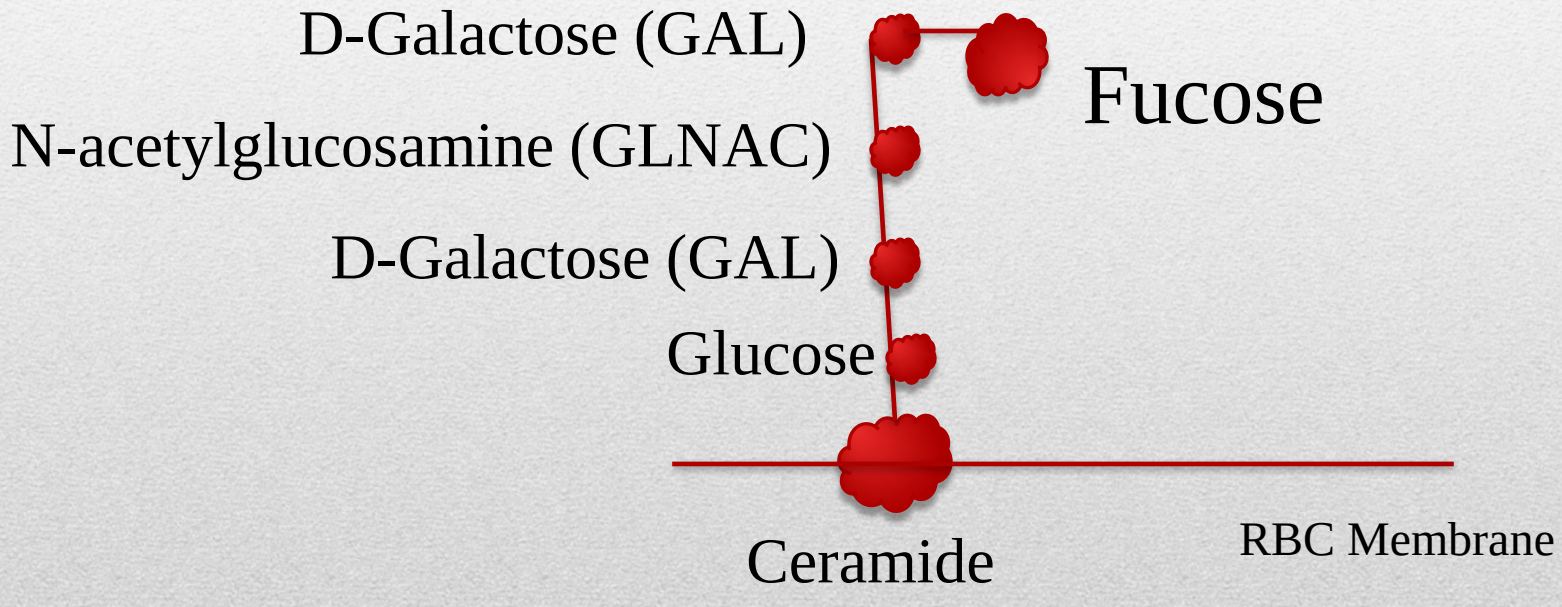
*Lewis gene in U.S. Caucasians

H antigen on RBC

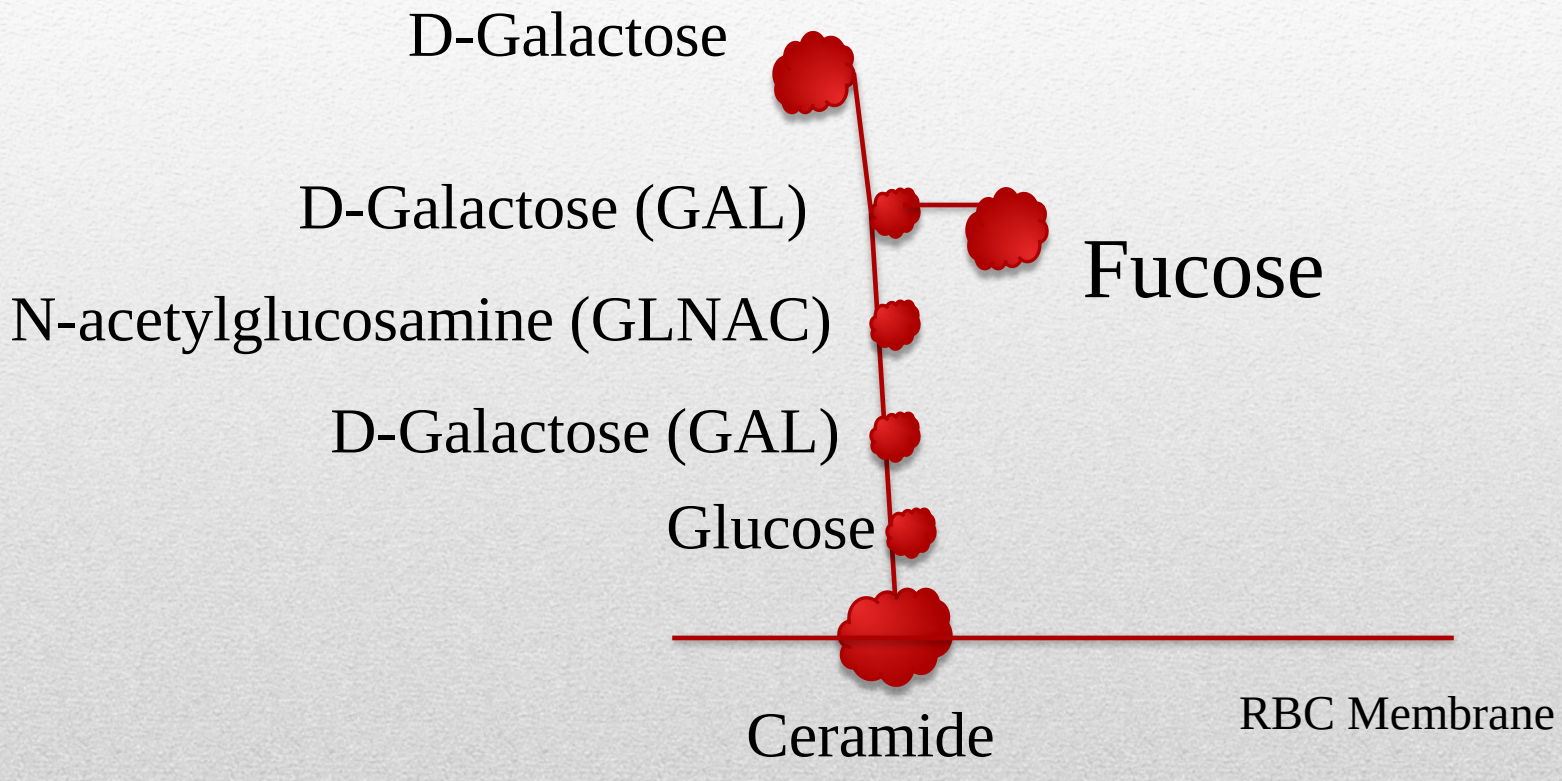


A antigen on RBC



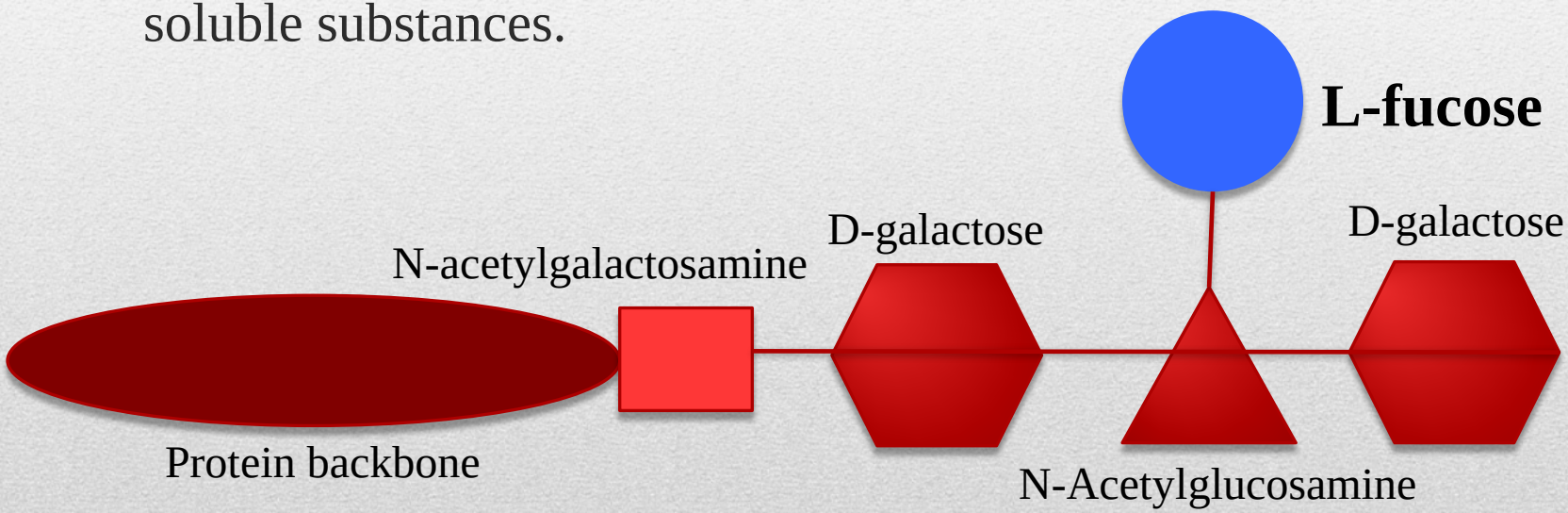

D-Galactose (GAL)
N-acetylglucosamine (GLNAC)
D-Galactose (GAL)
Glucose
Fucose
Ceramide
RBC Membrane

B antigen on RBC



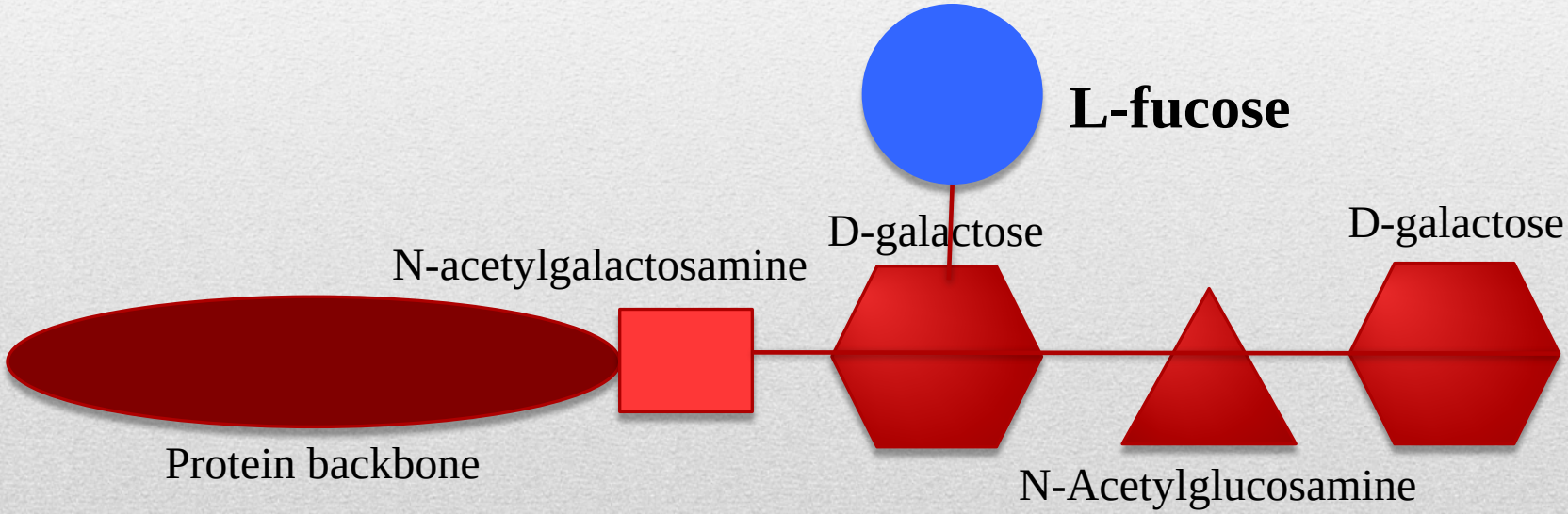
Formation of Le^a

- Formation of Lewis and ABO antigens is similar:
  - The *Le* gene produces L-fucosyltransferase to add **L-fucose** to the basic precursor substance.
  - This acts in competition with ABO, as L-fucose is added to soluble substances.



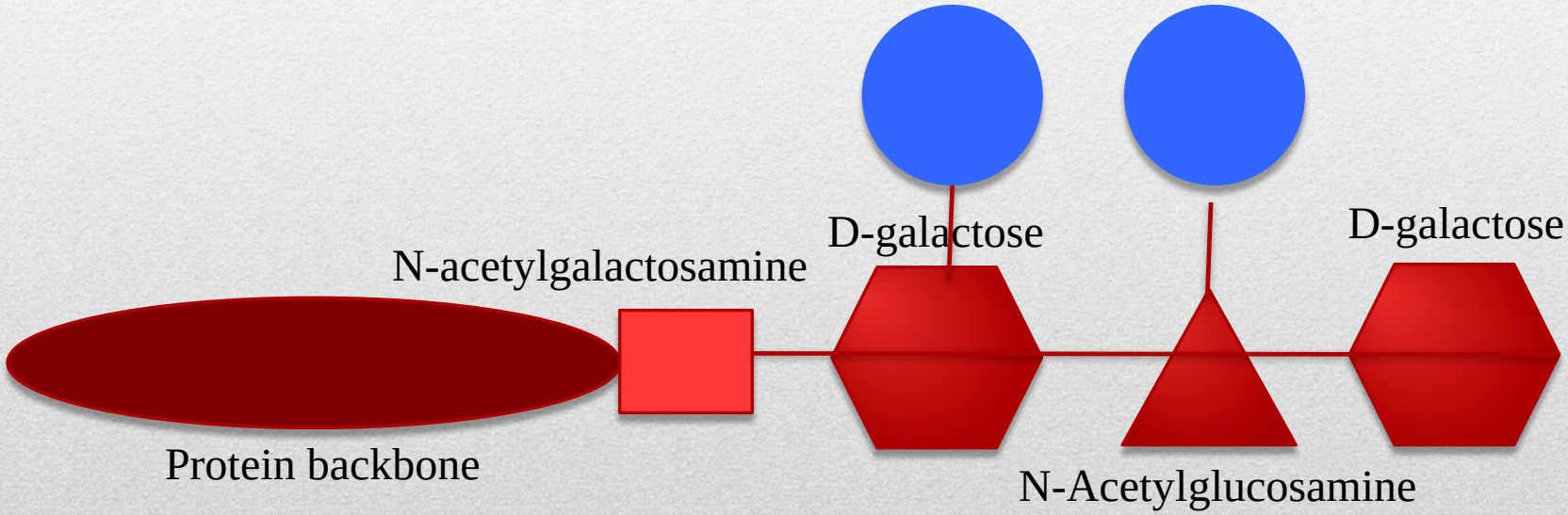
Soluble H substance

- A person who has inherited the *H* gene and the *Se* gene will have the following in secretions (soluble H):



Formation of Le^b

- When both *Le* and *Se* genes are inherited, the structure is further modified, producing Le^b antigen:



- *Adult* with RBC phenotype: Le(a-b-)
  - Lack *Le* gene.
  - *le/le*
  - ***Either*** secretors (*Se*) or non secretors (*se/se*).
- 6% Caucasians, 22% African Americans
- Can form antibodies to Le^a and/or Le^b without RBC stimulus.
  - *What do we call this type of antibody?*

le/le

Non-RBC Immune

Le and *se/se*

- *Le* gene present, non-secretor (*se/se*):
  - Le^a antigen produced, present in secretions
  - Le^a antigen adsorbs onto RBC membrane
  - *Adult* RBC phenotype:
    - Le(a+b-)

Le and *Se/se*

- *Le* gene present, secretor (*Se/se*):
  - Le^a antigen produced, present in secretions
  - Le^a antigen further modified by secretor gene to also produce Le^b antigen (in higher concentrations)
  - RBC membrane absorption: Le^b antigen competes with Le^a and WINS!!!
  - *Adult* RBC phenotype:
    - Le(a-b+)

- The formation of Le^b substances is **only possible with the inheritance and genetic interaction of both *Le and Se* genes.**
- **Both** Le^a and Le^b substances occur in secretions
- **Only** Le^b substance is absorbed onto the RBC membrane, **Le(a-b+)**

Remember!

And now a quiz!

Question 1

- *Lele*, *Sese*, *A/B/H* genes results in what in secretions, and what on the RBCs?

  Secretions: Le^a, Le^b, A, B, and H

  RBC antigens: A, B, H, Le(a-b+)

Question 2

- *Lele*, *sese*, *O/O/H* genes results in what in secretions, and what on the RBCs?

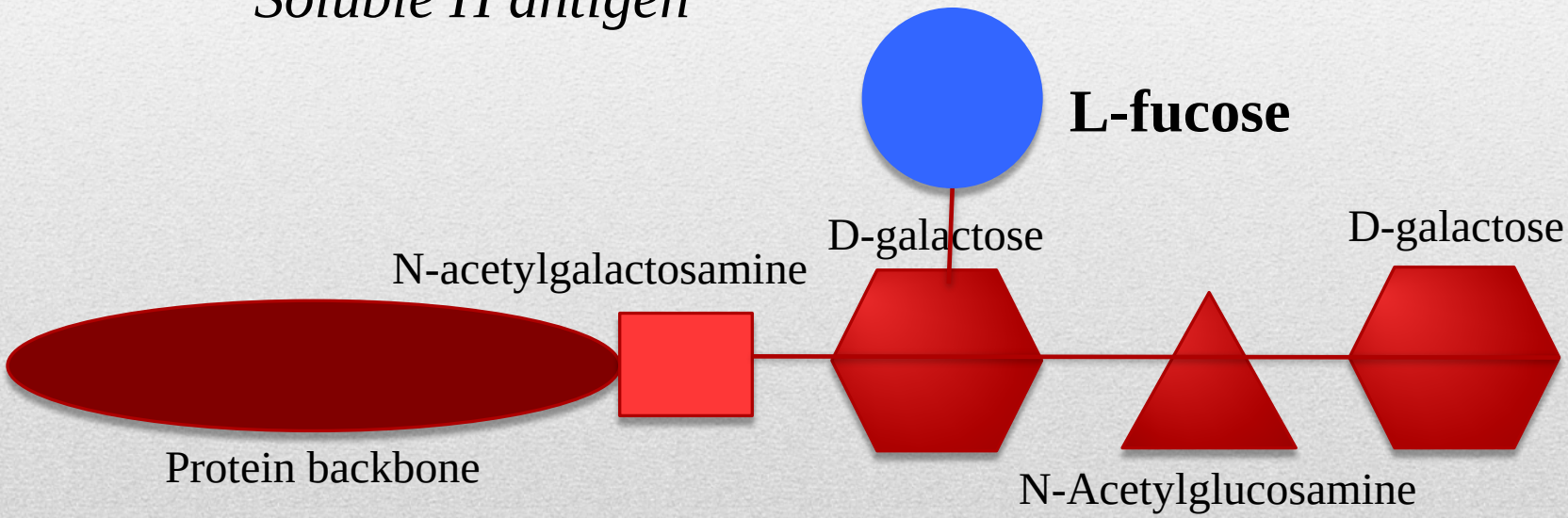
Secretions: Le^a

RBC antigens: H, Le(a+b-)

Question 3

- What is the following structure?

Soluble H antigen



Question 4

- Can a person with the RBC phenotype Le(a-b+) make anti-Le^a?
- No. Le(a-b+) is the result of Le^a substance being further modified to Le^b by the action of the *Se* gene. Both Le^a and Le^b antigens are present in secretions. Therefore, the individual does not *normally* form anti-Le^a.

Phenotype development

- Regardless of inheritance, “all” neonates type as Le(a-b-)
- If a person has inherited *Le* and *Se*, they will eventually end up typing as Le(a-b+).
- But, this is a process:
  - Neonate begins as Le(a-b-)
  - RBCs can then transform to Le(a+b-) after 10 days
  - Le(a+b+) ***transitional*** phenotype.
  - Finally, Le(a-b+) phenotype is expressed as the true phenotype after 6-7 years.

Le(a-b-)

Neonate

Le(a+b-)

After 10 days

Le(a+b+)

“Transitional phenotype”

Le(a-b+)

After 6-7 years

- The Lewis system is ***not*** implicated in hemolytic disease of the fetus and newborn (HDFN) ***Why***?
  - Regardless of inheritance, fetal blood is Le(a-b-)

More strange stuff about the Lewis system…

Changes in Lewis phenotype

- *Phenotype can change.*
- Lewis antigens can disappear during pregnancy:
  - Le(a-b-) phenotype during gestation.
  - Anti-Le^a and/or anti-Le^b present in serum.
- Lack of Lewis antigen expression on RBCs can also occur in patients with:
  - cancer
  - alcoholic cirrhosis
  - viral and parasitic infections

Le(a+b+)

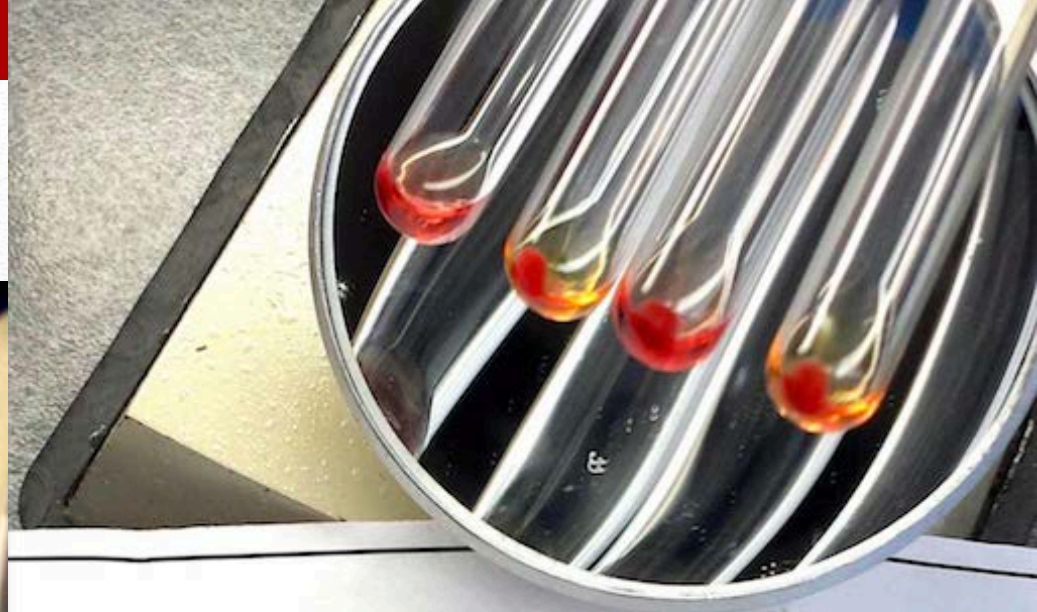
- The Le(a+b+) phenotype in adults is rare in Caucasians and African Americans
- Asians: 10-40%
  - Weaker *Se* gene, more common in Asia, produces a fucosyltransferase that competes less effectively with the *Le* fucosyltransferase.
  - Both Le^a and Le^b are adsorbed onto the RBC membrane.

Lewis Antibodies

anti-Le^a

- Non-RBC Immune (naturally occurring)
  - Produced without exposure to foreign RBCs
  - Generally IgM, cold reactive
  - *Generally* produced by patients with Le(a-b-) phenotype.
  - Anti-Le^a can be stronger than anti-Le^b
    - Can cause in vitro/ in vivo hemolysis (rare)

Hemolysis observed



ell			Duffy		Kidd		Lewis		P	MN				Luth-eran		X_g		
Kp^b	Js^{a*}	Js^b	Fy^a	Fy^b	Jk^a	Jk^b	Le^a	Le^b	P_1	M	N	S	s	Lu^a	Lu^b	Xg^{a}		
+	0	+	+	+	+	0	+	0	W	0	+	+	0	0	+	0		
+	0	+	+	0	+	+	0	+	0	+	0	0	+	0	+	0		
+	0	+	0	+	0	+	+	0	+	+	0	+	0	0	+	+		

Ficin (fig)
Papain (papaya)
Trypsin (pig stomach)
Bromelin (pineapple)

Enhanced!

Effect of enzyme treatment?

anti-Le^a

- Anti-Le^a is more commonly encountered than anti-Le^b.
- It is produced in approximately 20% of individuals of the Le(a-b-) phenotype.
- Primarily of IgM class, but some may have IgG components or be entirely IgG.
- Anti-Le^a is frequently detected with saline suspended red cells at room temperature. However, it sometimes reacts at 37°C and AHG and is capable of causing hemolytic transfusion reactions.

anti-Le^b

- Anti-Le^b is not as common, and generally does not act as strongly as anti-Le^a.
- Like anti-Le^a, it is produced by individuals with Le(a-b-) phenotype.
- However, it can be produced by Le(a+b-) individuals. (Remember *Le*, *sese* inheritors have no Le^b present in secretions, only Le^a substance.)

Clinical significance of Lewis antibodies

- Anti-Le^a is capable of causing HTR (rare).
- If detected at 37°C or AHG phase, it is considered to be ***clinically significant***
  - Only crossmatch compatible blood should be transfused.

Clinical significance of Lewis antibodies

- Lewis antibodies are ***generally*** considered **insignificant** in blood transfusion practices because:

1. Neutralized by soluble Lewis Ag in secretions
2. Ag positive donor cells can become Ag negative in recipient
3. IgM= do not cross placenta, also Ag not formed on fetal cells (no HDFN)

Additional Antibodies

- Anti-Le^{ab} reacts with:
  - Le(a+b-)
  - Le(a-b+)
  - ~90% of cord blood cells, serologically Le(a-b-)

- Anti-Le^{bH} reacts with:
  - Group O Le(b+)
  - Group A_2 Le(b+)

Additional Antibodies

Additional Antibodies

- Anti-ALe^{b} reacts with:
  - Group A_1 Le(b+)
  - Group A_1B Le(b+)
- Anti-BLe^{b} reacts with:
  - Group B Le(b+)
  - Group A_1B Le(b+)

Problem Solving:
Secretor Inhibition Studies

Secretor Inhibition

- We can use the Secretor Inhibition Test to determine if Lewis, H, and ABO soluble antigens are present in saliva.
- How the test works:
  - Antibody of a known specificity is added to the person's prepared saliva specimen.
  - If soluble antigen is present in the saliva, it will neutralize the antibody.

- Red blood cells with the corresponding antigen are then added to the test.
  - If “+” reaction, the antibody was NOT neutralized (soluble antigen NOT present in saliva).
  - If “0” reaction, the antibody WAS neutralized (soluble antigen IS present in saliva).

Secretor Inhibition

	A_1 Cells	B Cells	O Cells Le(a+)	O Cells Le(a-) (Control)
Saliva + Anti-A				
Saliva+ Anti-B				
Saliva + Anti-Lea				
Saliva + Anti-H				

For this test, assume NO individuals are O_h Bombay phenotype *h/h*

	A_1 Cells	B Cells	O Cells Le(a+)	O Cells Le(a-) (Control)
Saliva + Anti-A				
Saliva+ Anti-B				
Saliva + Anti-Lea				
Saliva + Anti-H				

	A_1 Cells	B Cells	O Cells Le(a+)	O Cells Le(a-) (Control)
Saliva + Anti-A	+			
Saliva+ Anti-B				
Saliva + Anti-Lea				
Saliva + Anti-H				

Saliva + Anti-A + A1 Cells = Positive Reaction
This means the Anti-A in the tube was NOT neutralized
Therefore, the saliva does NOT have A substance

	A_1 Cells	B Cells	O Cells Le(a+)	O Cells Le(a-) (Control)
Saliva + Anti-A	+			
Saliva+ Anti-B		+		
Saliva + Anti-Lea			+	0
Saliva + Anti-H			0	0

B Substance NOT present
Lea Substance NOT present
H substance is present
Remember, O cells are RICH in H antigen

	A_1 Cells	B Cells	O Cells Le(a+)	O Cells Le(a-) (Control)
Saliva + Anti-A	+			
Saliva+ Anti-B		+		
Saliva + Anti-Lea			+	0
Saliva + Anti-H			0	0

No A, B, or Lea, in saliva, but the person secretes H substance. Which genes are present?

H gene, *Se* gene, *le/le*

And, we know the person is *O/O*

If they are secreting H substance, but no A or B, they must be type O

	A_1 Cells	B Cells	O Cells Le(a+)	O Cells Le(a-) (Control)
Saliva + Anti-A	+			
Saliva+ Anti-B		0		
Saliva + Anti-Lea			0	0
Saliva + Anti-H			0	0

No A substance in saliva

Have B substance, Lea substance, and H substance in Saliva

Genes present?

H, *B*, *Le*, and *Se*

	A_1 Cells	B Cells	O Cells Le(a+)	O Cells Le(a-) (Control)
Saliva + Anti-A	+			
Saliva+ Anti-B		+		
Saliva + Anti-Lea			+	0
Saliva + Anti-H			+	+

No A, B, Lea, or H in saliva

Negative Control Anti-Lea with Le(a-) cells produced no reaction

Genes present?

No *Le*, No *Se*. Because this person is a non-Secretor, can't make assumptions about ABO

	A_1 Cells	B Cells	O Cells Le(a+)	O Cells Le(a-) (Control)
Saliva + Anti-A	0			
Saliva+ Anti-B		0		
Saliva + Anti-Lea			0	0
Saliva + Anti-H			0	0

Practice Problem: What substances are present in saliva? Based on this information, what gene(s) might be present?

- Substances present: A, B, Le^a, and H
- Genes present: *Se*, *Le*, *H*, *A/B*

Answer

Follow-up Question

- Based upon this information, can you make assumptions about what antigen(s) is/are present on the person's RBCs?
- *H*, and *A/B* genes: Person's RBC type is AB
- *Le* and *Se* genes: Person's RBC type is likely Le(a-b+)

Thank you!

References

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