# Bombay & Rh Blood Group System

15-11-2009

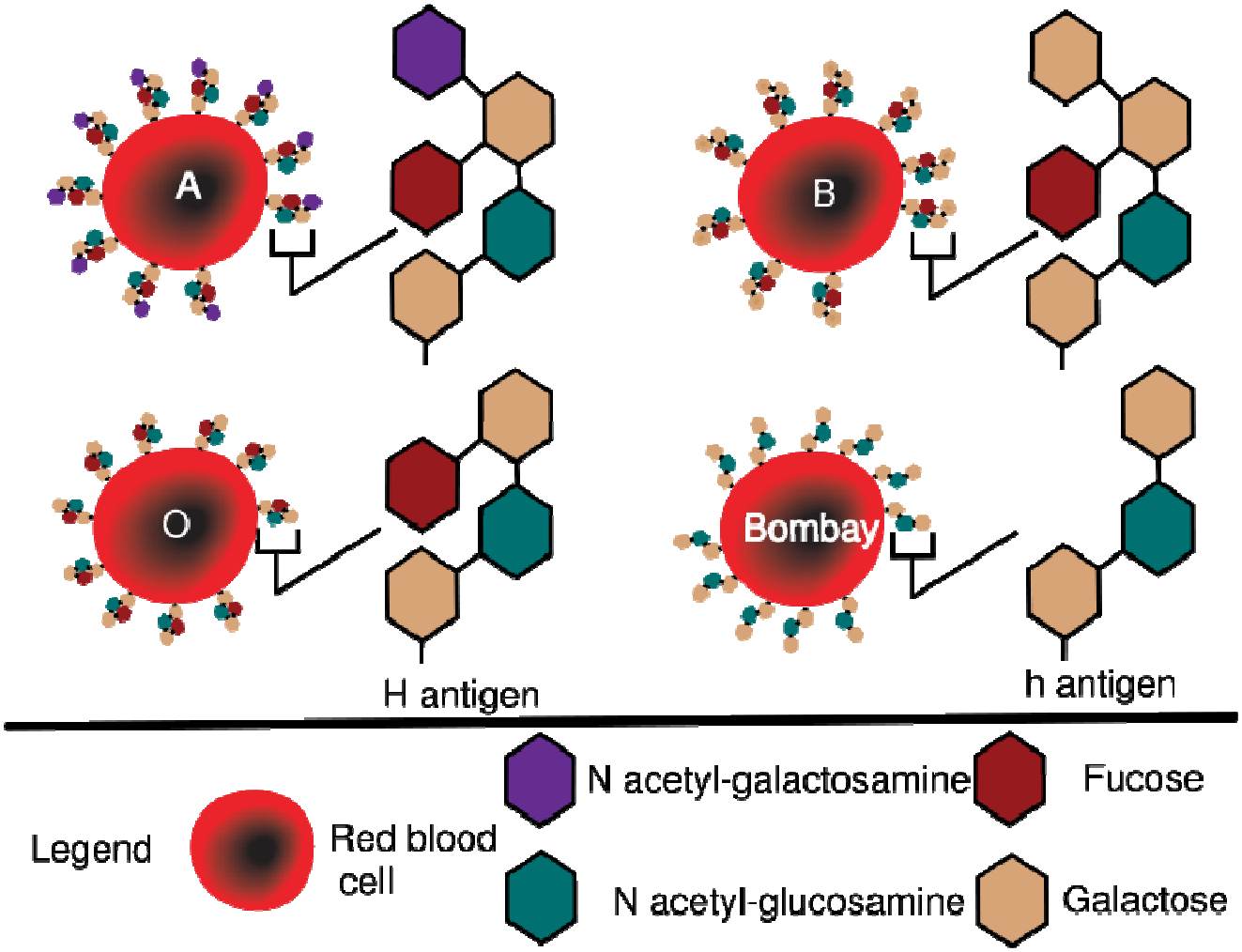
# Bombay blood group

- Individuals with the rare **Bombay phenotype** (*hh*) (also called the **$O_h$** phenotype) do not inherit the very common gene *H and therfore do not* express H antigen.
- As a result, they cannot make A antigen or B antigen on their red blood cells, even if they have the A and or B blood-group genes.
- Those individuals have anti H, anti B, anti A, and anti A,B in the serum.

- people who have Bombay phenotype can donate to any ABO blood group provided that Rh group is compatible.

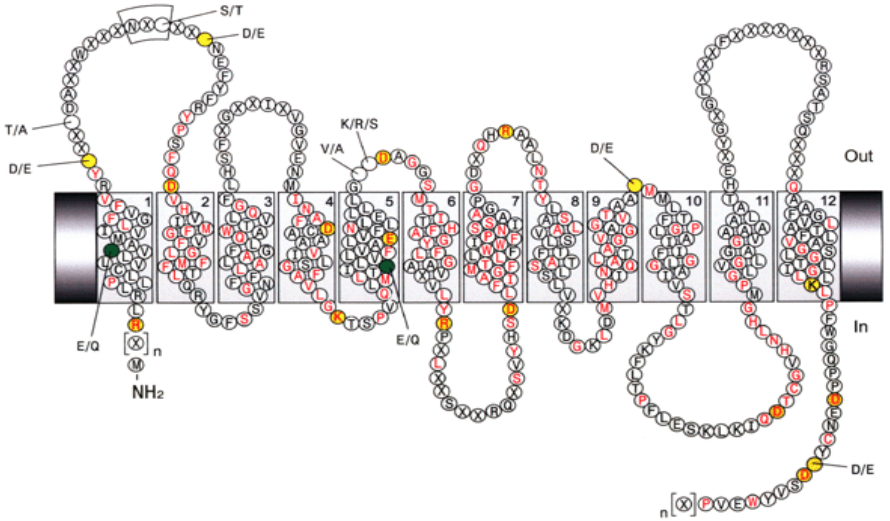
- However, people with Bombay phenotype cannot receive blood from any member of the ABO blood group system (which always contains one or more of A and B and H antigens), but only from people who have Bombay phenotype.

# Bombay blood group




No molecules of L-fucose are present on the precursor substrate in the red cell membrane of Bombay phenotype ➔ so the A and B transferases are inactive and cannot add the sugars required for the A & B antigens.

# Rh Blood Group system



# Introduction

- Rh is one of the most complex blood systems

- The Rh system contain more than 50 antigens. But the most important are D, C, E, c, and e.
- Rh antigens are expressed on polypeptides
- Rh peptides span the red cell membrane exposing six extracellular loops on which the Rh antigens are expressed
- The function of the Rh polypeptides is not fully known, but it seems that it is involved in cation transport across the red cell membrane
- The Rh antigens are developed before birth (they are detectable in 6-week-old foetus)

# Rh antigens

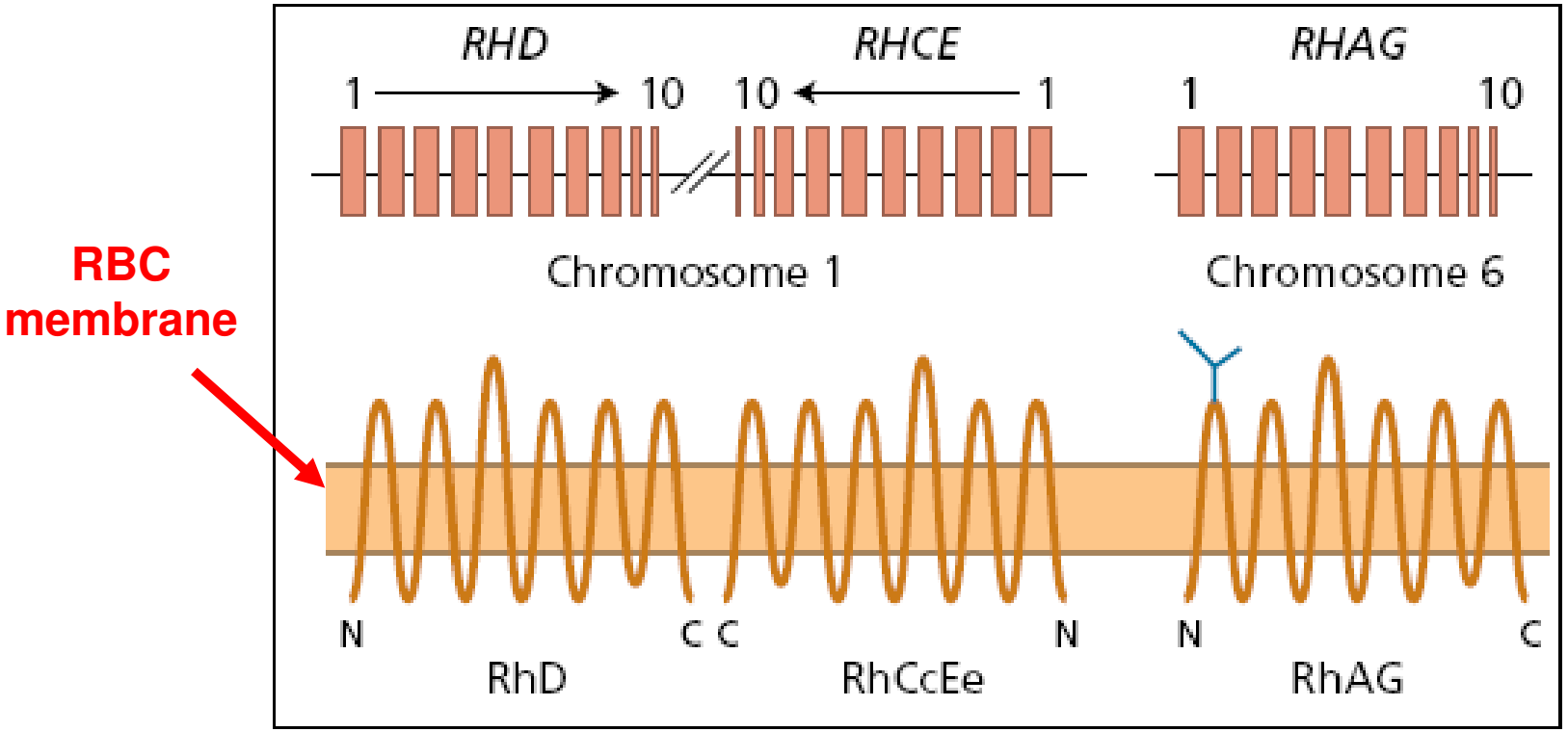
Table 15.11 Antigens of the Rh system.

| *Number* | *Alternative names* | *Frequency** | *Number* | *Alternative names* | *Frequency** |
|---|---|---|---|---|---|
| RH1 | D | Polymorphic | RH31 | $hr^B$ | Polymorphic |
| RH2 | C | Polymorphic | RH32 | $R^N$ | Low |
| RH3 | E | Polymorphic | RH33 | Har | Low |
| RH4 | c | Polymorphic | RH34 | $Hr^B$ | High |
| RH5 | e | Polymorphic | RH35 | $R^N$-like | Low |
| RH6 | ce, f | Polymorphic | RH36 | $Be^a$ | Low |
| RH7 | Ce | Polymorphic | RH37 | Evans | Low |
| RH8 | $C^w$ | Polymorphic | RH39 | C-like | Polymorphic |
| RH9 | $C^x$ | Low | RH40 | Tar | Low |
| RH10 | V | Polymorphic† | RH41 | Ce-like | Polymorphic |
| RH11 | $E^w$ | Low | RH42 | $Cce^s$ | Polymorphic† |
| RH12 | G | Polymorphic | RH43 | Crawford | Low |
| RH17 | $Hr_o$ | High | RH44 | Nou | High |
| RH18 | Hr | High | RH45 | Riv | Low |
| RH19 | $hr^s$ | Polymorphic | RH46 | Sec | High |
| RH20 | VS | Polymorphic† | RH47 | Dav | High |
| RH21 | $C^G$ | Polymorphic | RH48 | JAL | Low |
| RH22 | CE | Low | RH49 | STEM | Low |
| RH23 | $D^w$ | Low | RH50 | FPTT | Low |
| RH26 | c-like | Polymorphic | RH51 | MAR | High |
| RH27 | cE | Polymorphic | RH52 | BARC | Low |
| RH28 | $hr^H$ | Polymorphic† | RH53 | JAHK | Low |
| RH29 | Total Rh | High | RH54 | DAK | Low |
| RH30 | $Go^a$ | Low | RH55 | LOCR | Low |
| | | | RH56 | CENR | Low |

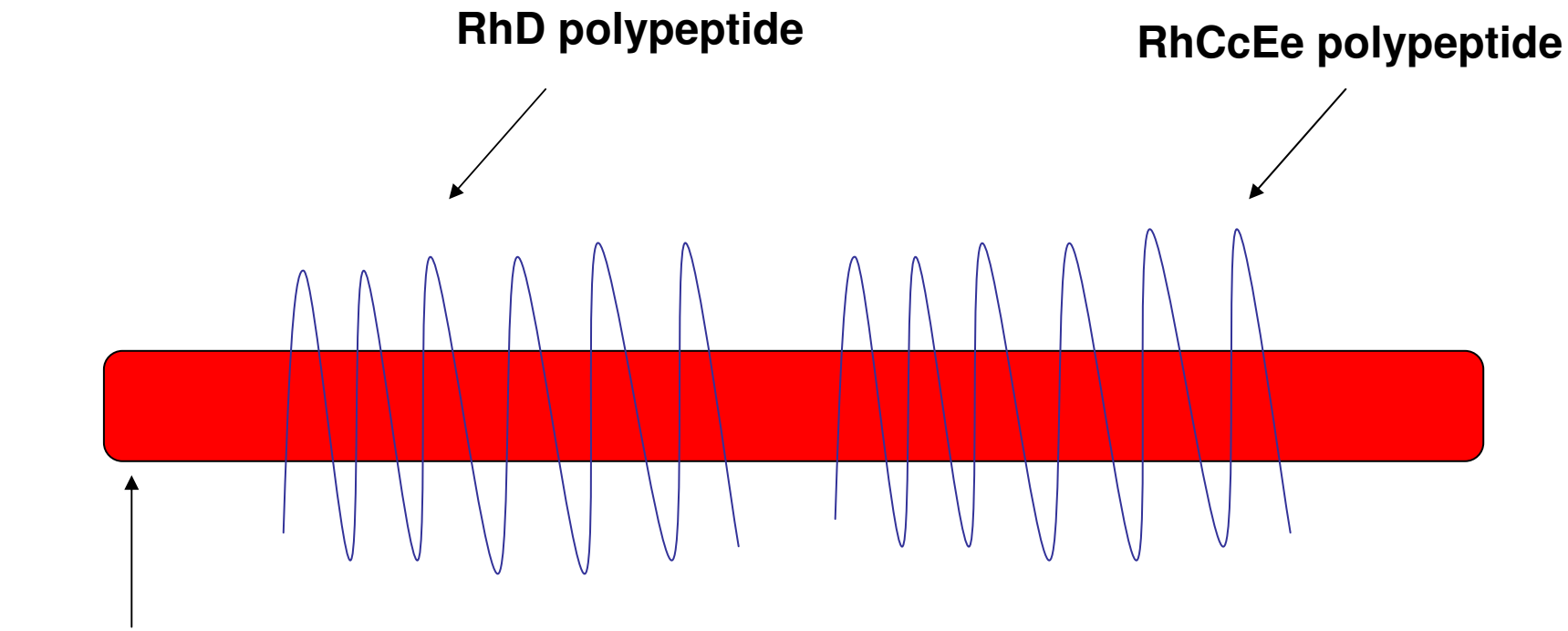
# Rh genes

- The Rh system is controlled by two closely linked genes at the Rh locus on chromosome 1: ***RHD*** and ***RHCE*.**
- The two genes are called Rh gene complex
- One Rh gene complex is inherited from each parent
- Both genes produce two separate proteins (polypeptides) but they are located next to each other on the surface of red cells, forming a complex of antigens
- Each protein comprise around 400 amino acids

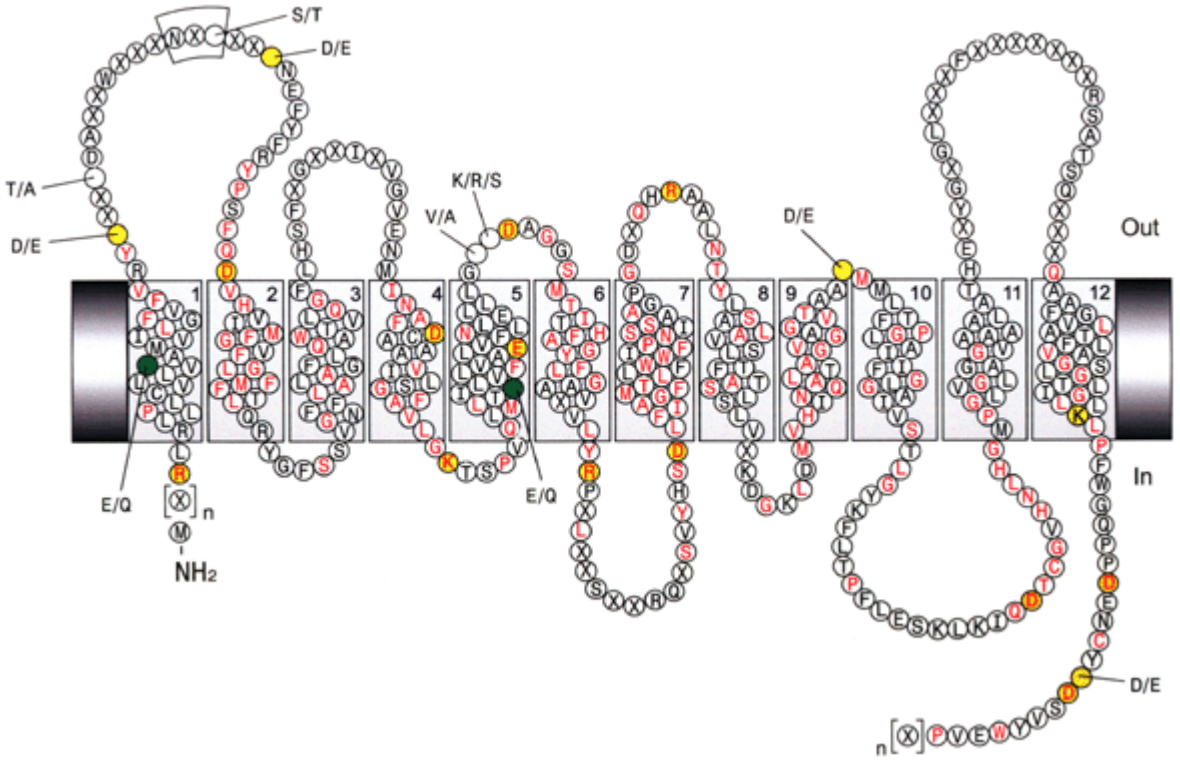
# Rh and related genes and the polypeptides they encode



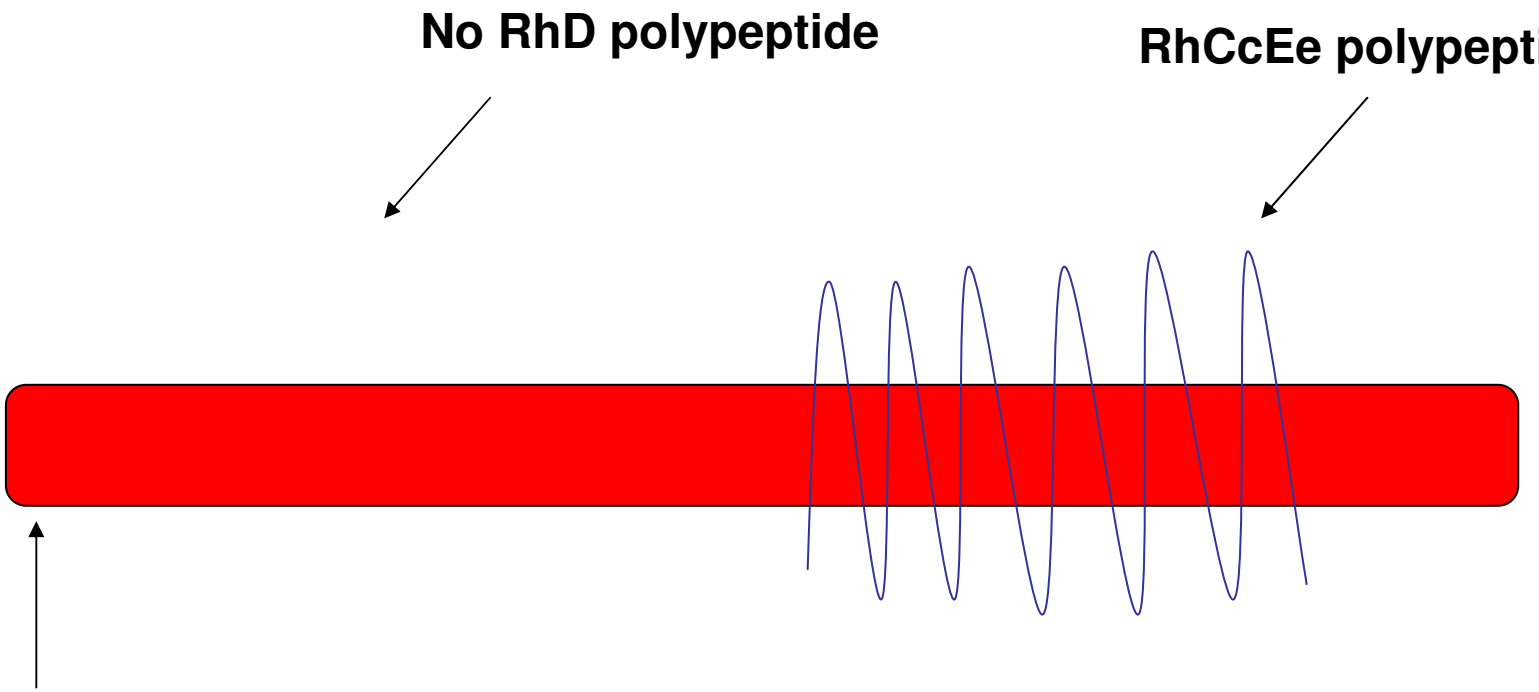
# Rh polypeptides



# RhD



# RhD negative




Individuals who lack the RHD gene will not have the RhD polypeptide. They are typed as D negative

# RHD gene

- Most individuals are either D+ or D-
- A D+ individual may inherit two *RHD* genes from both parents (homozygous) or one gene from either parent (heterozygous)
- The *RHD* gene produces the D antigen.
- D- individual do not have the *RHD* gene, so they do not have the RhD protein on the surface of their red cells.
- The symbol “ d ” is used to denote the absence of the D gene

# RHCE gene

- At the *RHCE* gene locus, depending on the allele present, one of four antigenic combinations are produced:ce, Ce, cE or CE.
- All of these alleles are co-dominant.

- One inherits one allele from each parent. For example if one inherits CE from father and ce from mother, the red cell will express all of the antigens (C, c, E, and e).

- D+ individuals inherit two Rh genes: *RHD* coupled with one of the alleles of *RHCE* from each parent.

- Whereas D- individuals lack the entire RhD polypeptide, the difference between ce and Ce proteins are differences in four amino acids, and ce and cE proteins differ by one amino acid.

# Rh genes

- The presence or absence of the RHD gene and one of the four alleles of the RHCE gene, results in eight possible gene combinations for the Rh blood group system

# Rh genes terminology

| | Rh genes present | | Gene complex/haplotype | Shorthand nomenclature |
|---|---|---|---|---|
| | *RHD gene* | *RHCE gene* | | |
| RhD pos | *D* | *Ce* | *DCe* | $R_1$ |
| | *D* | *cE* | *DcE* | $R_2$ |
| | *D* | *ce* | *Dce* | $R_o$ |
| | *D* | *CE* | *DCE* | $R_z$ |
| RhD neg | *d* | *Ce* | *dCe* | $r^I$ |
| | *d* | *cE* | *dcE* | $r^{II}$ |
| | *d* | *ce* | *dce* | r |
| | *d* | *CE* | *dCE* | $r^y$ |

**The eight possible gene complexes or haplotypes of Rh system**

# Rh gene complex

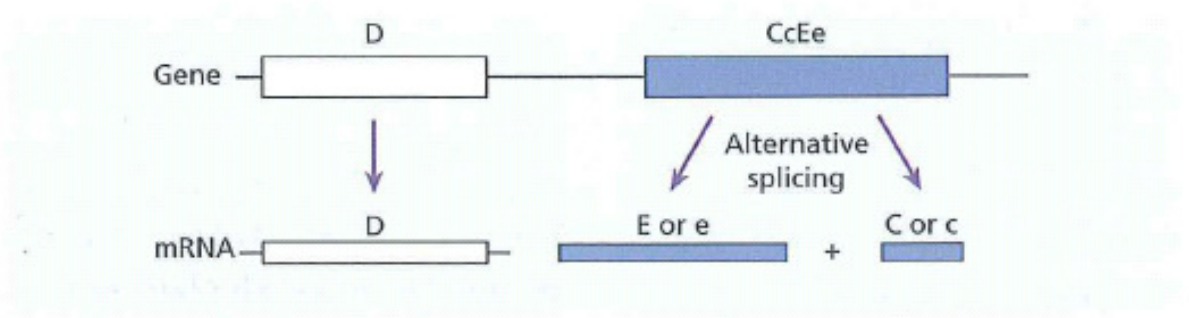



**Fig. 27.4** Molecular genetics of the rhesus blood group. The locus consists of two closely linked genes, *RhD* and *RhCcEe*. The *RhD* gene codes for a single protein which contains the RhD antigen whereas *RhCcEe* mRNA undergoes alternative splicing to three transcripts. One of these encodes the E or e antigen whereas the other two (only one is shown) contain the C or c epitope. A polymorphism at position 226 of the *RhCcEe* gene determines the Ee antigen status whereas the C or c antigens are determined by a four amino acid allelic difference. Some individuals do not have an *RhD* gene and are therefore RhD–.

# Rh genotype

- ***It is not possible to determine the genotype of an individual from the red cell phenotype result !!***

- The Rh haplotypes are named either by the component antigens (e.g., CDe, cde) or by a single shorthand symbol (e.g., R[1] = CDe, r = cde).

- Thus, a person may inherit *CDe* (R[1]) from one parent and *cde* (r) from the other and have the genotype *CDe/cde* (R1r).

# Rh genes complexes

*Remember you inherit one Rh gene complex (haplotype) from each parent. So you will have two of any of the complexes in the table { eg, (DCE/dCe) }.*

| Rh genes present | | Gene | Shorthand |
|---|---|---|---|
| *RHD gene* | *RHCE gene* | complex/haplotype | nomenclature |
| *D* | *Ce* | *DCe* | $R_1$ |
| *D* | *cE* | *DcE* | $R_2$ |
| *D* | *ce* | *Dce* | $R_0$ |
| *D* | *CE* | *DCE* | $R_z$ |
| *d* | *Ce* | *dCe* | $r^I$ |
| *d* | *cE* | *dcE* | $r^{II}$ |
| *d* | *ce* | *dce* | r |
| *d* | *CE* | *dCE* | $r^y$ |

d= no D gene

R= RHD gene

r= no RHD gene

# Rh D antigen frequency

- Similar to ABO gens, the Rh D antigen varies between different populations

| | % pos | % neg |
|---|---|---|
| Europe | 83 | 17 |
| West Africa | 97 | 3 |
| India | 90 | 10 |
| Japan | 99.7 | 0.3 |
| China | 93 | 7 |
| **Saudis** | **92.8** | **7.2** |

# Frequency of other Rh antigens

- Similar to ABO and RhD, the other antigens of the Rh system also varies between populations

| Phenotype | | Ethnicity: percentage frequency | | |
|---|---|---|---|---|
| | | White | Black | Indian |
| DCe/dce | $R_1r$ | 33 | 13 | 30 |
| DCe/DCe | $R_1R_1$ | 18 | < 1 | 48 |
| DcE/dce | $R_2r$ | 13 | 15 | 4 |
| DcE/DcE | $R_2R_2$ | 2 | < 1 | < 1 |
| dce/dce | rr | 14 | 2 | 3 |
| Dce/dce | $R_0r$ | 3 | 66 | 2 |

# RhD typing

- The D antigen is the most clinically significant antigen in the Rh system
- Individuals are divided into D+ or D- depending on the presence or absence of the D antigen on the surface of red cells
- Note: there are various methods to describe the results of D typing, e.g. D+ and D-, or RhD positive and RhD negative..

# Rh phenotyping

- The Rh phenotype is determined by typing the red cells with specific reagents: anti-D, anti-C, anti-c, anti-E, and anti-e.
- Positive and negative test results using the above reagents denote the presence or absence of the Rh antigens and this is known as the "**Rh phenotype**"

# The phenotype of Rh system is usually determined in the lab with anti-D, -C, -c, –E, and -e.

| *Reactions with anti-* | | | | | *Common genotypes* |
|---|---|---|---|---|---|
| *D* | *C* | *c* | *E* | *e* | |
| + | + | + | − | + | *DCe/dce** |
| | | | | | *DCe/Dce* |
| + | + | − | − | + | *DCe/DCe** |
| | | | | | *DCe/dCe* |
| + | − | + | + | + | *DcE/dce** |
| | | | | | *DcE/Dce* |
| + | − | + | + | − | *DcE/DcE** |
| | | | | | *DcE/dcE* |
| + | + | + | + | + | *DCe/DcE** |
| | | | | | *DCE/dce* |
| | | | | | *DcE/dCe* |
| | | | | | *DCe/dcE* |
| | | | | | *DCE/Dce* |
| − | − | + | − | + | *dce/dce* |

*Probable genotype.

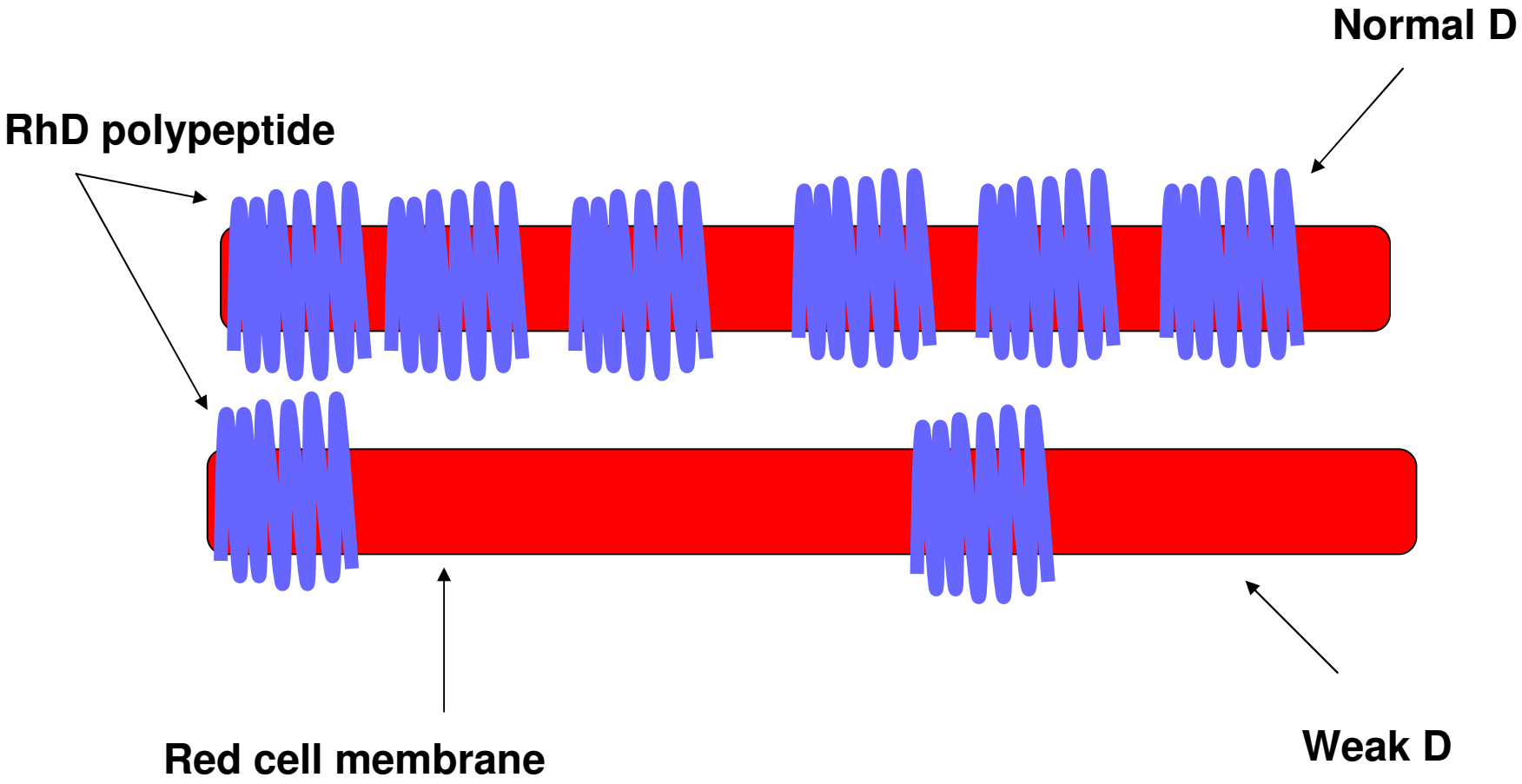
# RhD antigen

- The D antigen is extremely immunogenic (i.e. very likely able to stimulate antibody production in most individuals who are D-)
- Transfusion of RhD positive red cells to an individual who is RhD negative could result in sever haemolytic transfusion reaction, particularly in the second exposure
- RhD antigen is the most clinically significant in the Rh antigens. It is also involved in the haemolytic disease of the foetus and newborn (HDNF)

# Weak D

- Weak D describes a weaker form of D+, where fewer D antigen sites are present on the red cell as compared with a normal D+
- Studies have shown that D+ red cells of the R1r phenotype have about 10 000 antigen sites per cell, whereas R2R2 phenotypes have about 30 000 sites.
- Weak D cells have far less than this number
- Weak D characteristic is usually the result of the inheritance of a genetic variation
- It is important to be able to detect weak D in the laboratory. Donors who have weak D but not detected in the lab, may results in incompatible transfusion if the donor's blood is transfused to a D negative patient

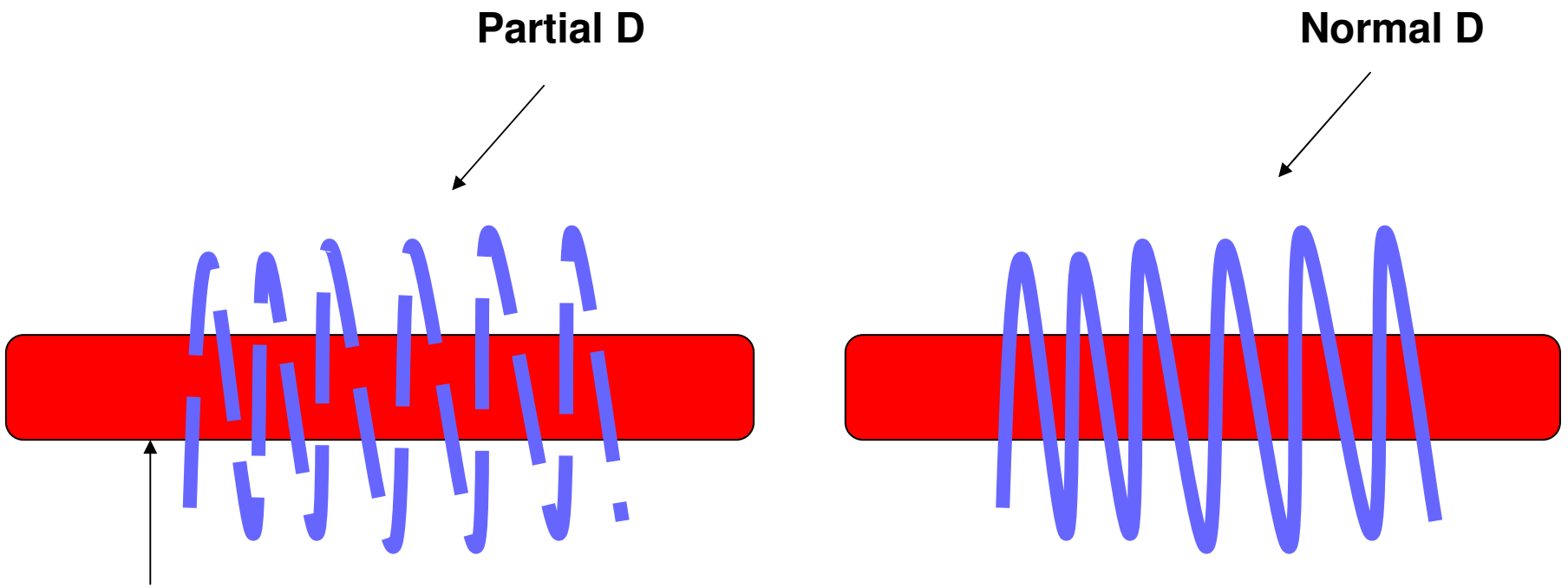
# Weak D



# Partial D

- In 1953 there was a report of a D+ individual who had anti-D in the serum/plasma
- Since then, many examples of D+ with anti-D have been reported, although overall it is a rare occurrence
- The term partial D is used to describe the phenotype of those rare individuals, whose red cells lack one or more of the D epitopes

# Partial D




**Partial D lack many epitopes present in the normal D, therefore, individuals with partial D can produce antibodies to the epitopes they lack and present in the normal D**

# Partial D

- The D antigen is considered to be a mosaic of epitopes. If some D epitopes are missing, then the individual can make an antibody specific for the missing epitope/s if they are exposed to normal D+ cells
- The anti-D produced in this way reacts with all normal D+ cells, which have all the epitopes, but fails to react with their own cells and cells of the same or similar partial D types.
- **Lab. Identification of partial D**:Panels of monoclonal anti-D antibodies are now available to detect partial D types.

# Clinical significance of weak and Partial D

- Weak D individuals do not usually produce anti-D
- In contrast, partial D type individuals may develop clinically significant anti-D if transfused with normal D positive blood.
- Blood donors should be tested for weak D, and their blood transfused into D+ recipients
- Partial D blood donors should be typed as D+

# Clinical significance of the Rh system

- Rh antibodies are nearly always immune type IgG antibodies that have been stimulated by exposure to foreign red blood cells either through pregnancy or transfusion
- Remember: generally, there is no naturally occurring antibodies against Rh antigens, and therefore, pervious exposure to Rh antigens is a prerequisite for the production of antibodies
- The antibodies in the Rh blood group system can cause severe transfusion reactions and are second only to the ABO system in this regard
- The transfusion of D+ blood into D– patients should be avoided, as the D antigen is highly immunogenic and can stimulate antibody production in the recipient
- Group O is considered to be the universal donor. The universal donor should also be D– if the blood is to be transfused into D– patients

# Clinical significance of the Rh system

- The C, c, E, and e antigens are less immunogenic than the D antigen
- If incompatible blood for C, c, E, or e antigens is transfused, the recipient may "occasionally" produce antibodies to the antigen he/she lacks
- In the next transfusion, if the individual is given again incompatible blood he/she may have a haemolytic reaction
- In case of multi-transfused patients or those who require frequent transfusions, Rh compatible blood should be provided. This is to prevent formation of antibodies which may complicate future transfusions.

# Clinical significance of Rh system in haemolytic disease of the newborn (HDN)

- Please refer to chapter 6 (p80)