

Rhesus-D positief of Rhesus-D negatief?

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Disclosure belangen spreker bijeenkomst Onderwijsbijeenkomst Kennisplatform Transfusiegeneskunde ZO

Naam: Ron Straat

Geen (potentiële) belangenverstrengeling

Voor bijeenkomst mogelijk relevante relaties¹

n.v.t.

- **Sponsoring of onderzoeksgeld²**
- **Honorarium of andere (financiële) vergoeding³**
- **Aandeelhouder⁴**
- **Andere relatie, namelijk ...⁵**

n.v.t.

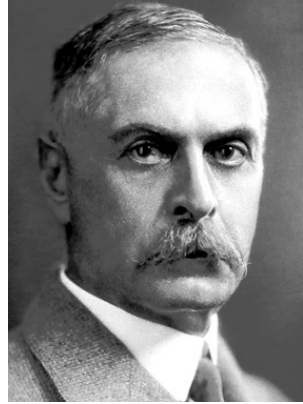
n.v.t.

n.v.t.

n.v.t.

Het Rhesus systeem

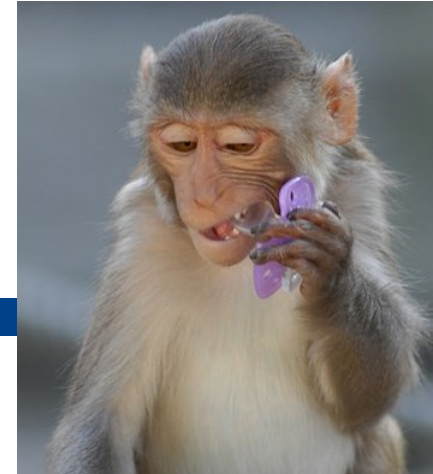
- In 1940 door Landsteiner en Wiener ontdekt.
- Geen natuurlijk voorkomende antistoffen.
- Tot nu toe >50 Rhesus antigenen ontdekt:
hoogfrequent, laagfrequent en polymorf.
- In de bloedtransfusie praktijk het belangrijkste systeem na het ABO-bloedgroepensysteem.
- Rhesus-D is belangrijkste antigeen.



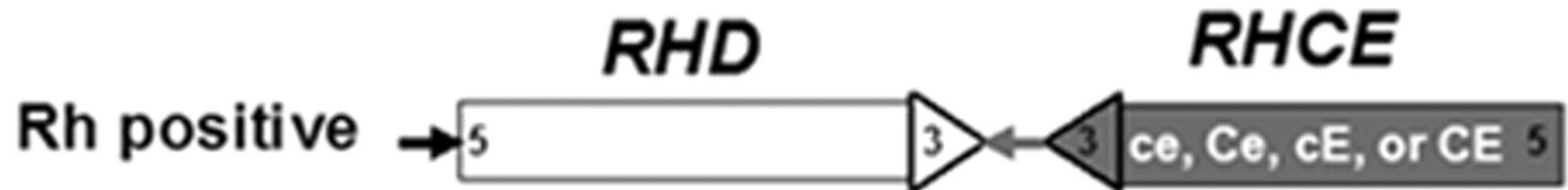
Karl Landsteiner,
(14-6-1868 / 26-6-1943)



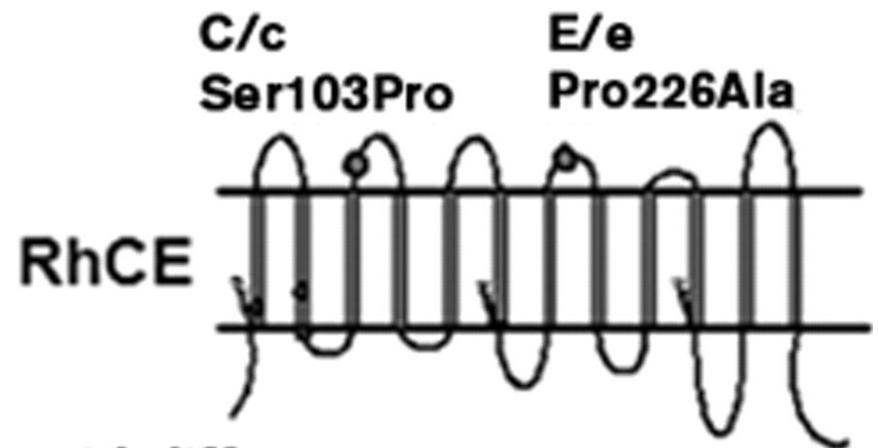
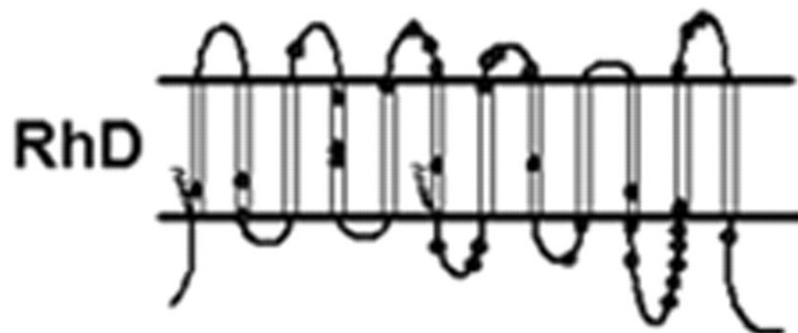
Alexander Solomon Wiener
(March 16-3-1907 / 6-11-1976)



RH LOCUS

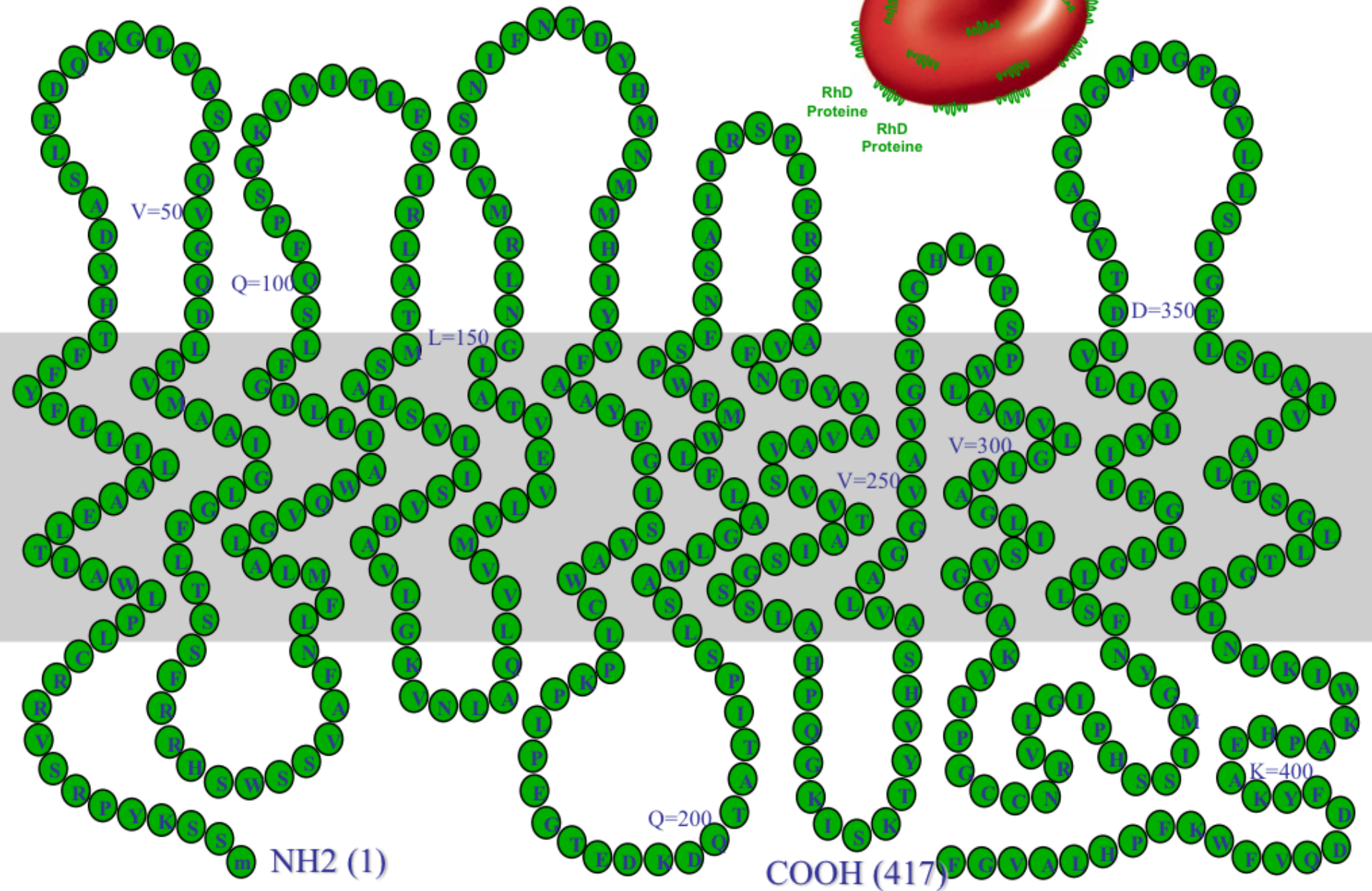


Rh proteins



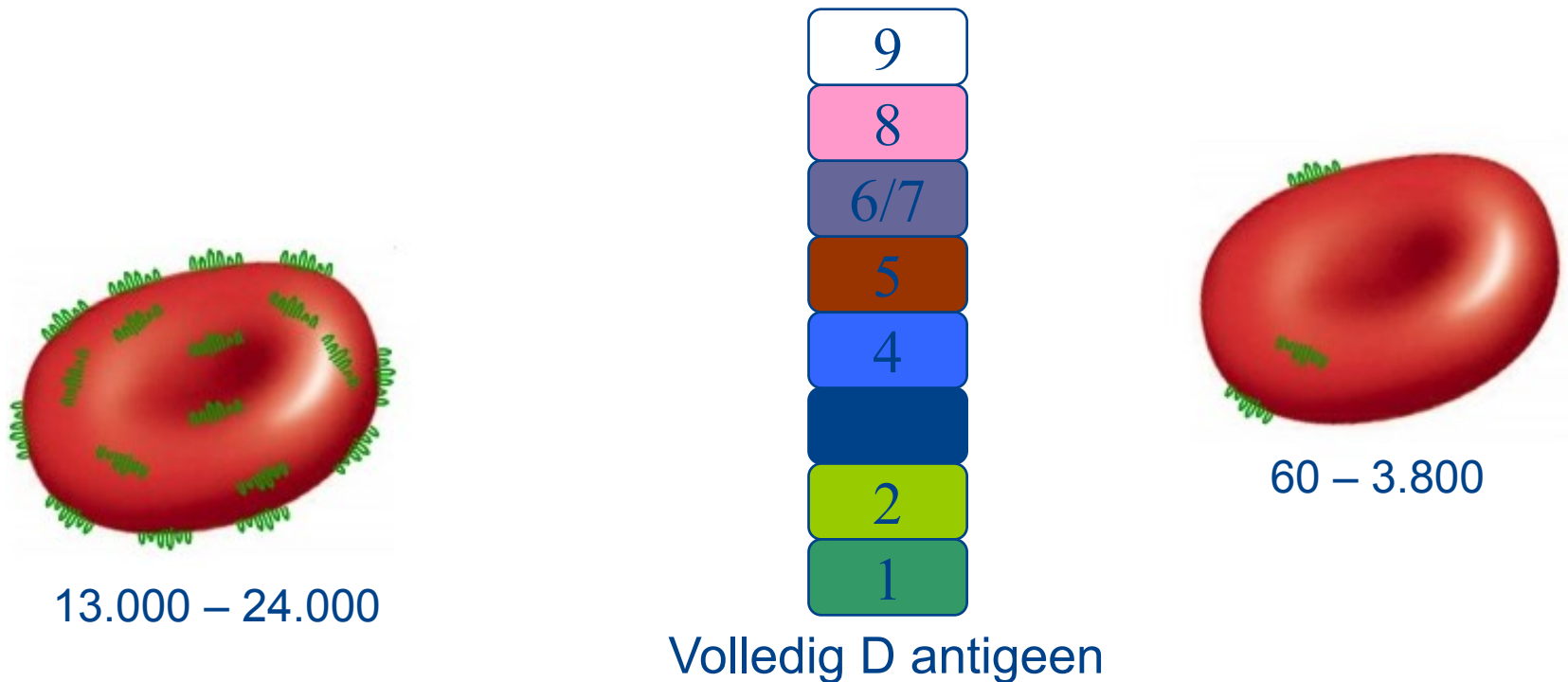
32-35 amino acid differences

RhD protein membrane topology



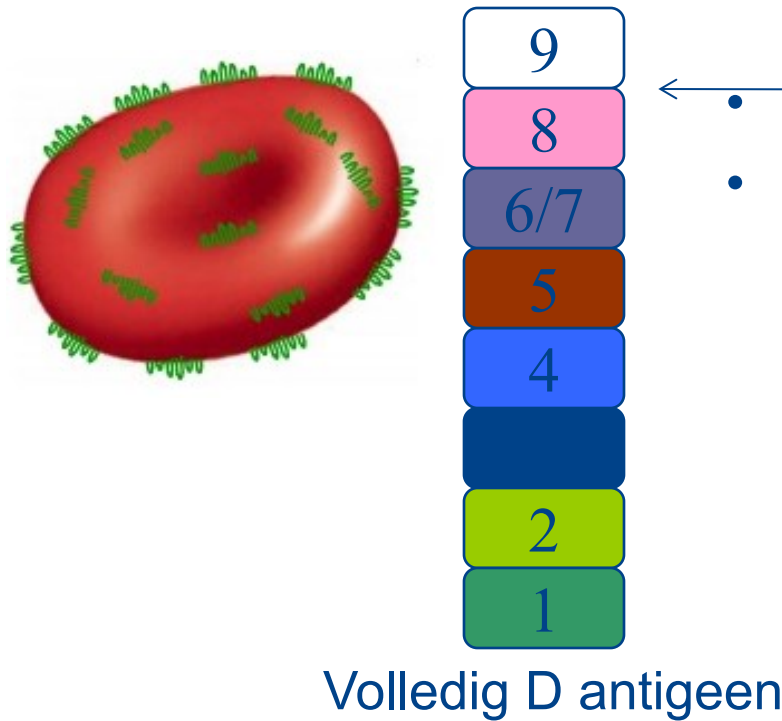
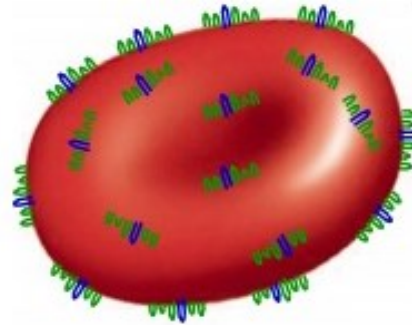
Kwantitatieve variatie

- Mensen met een zwak D-antigeen hebben minder antigenen op het celmembraan dan mensen met een normaal D-antigeen.
- Zwakke D-antigenen brengen alle epitopen tot expressie



Kwalitatieve variatie

Epitooop verlies.



9 epitopen
epitooopverlies = variant



As. Vorming o.a.

- D-V^a
- D-VI.
- D-VII

Bepaling van de bloedgroep

Controle: negatief

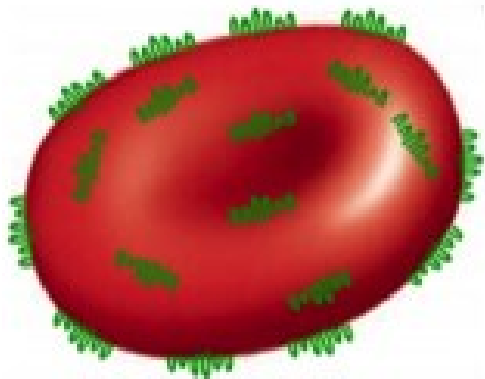
ABO bloedgroep:

- Voorkant: 3+, 4+ of negatief
- Achterkant: positief of negatief.

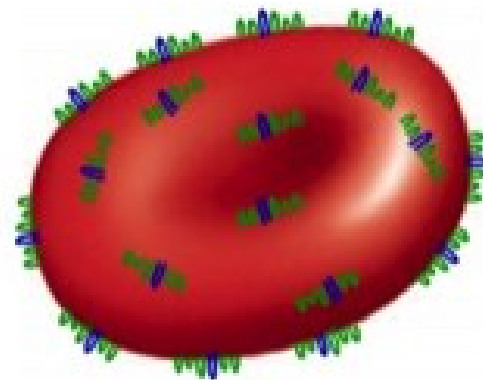
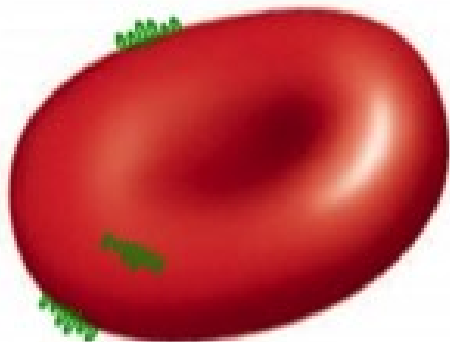
Altijd 2 positieve en 2 negatieve reacties

Rhesus D: 3+, 4+ of negatief

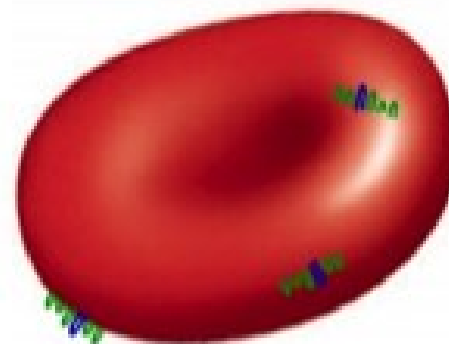




Positief



Variant



Negatief



Dhr. Z
13 jaar

Op 15-5-2017 opgenomen op VEB2

Anti-D VI-
50092.0604/18.02/548774
Comment:



Current Results

1	2	3	4	5	6	4	5	6
Anti-A	Anti-B	Anti-D VI-	Ctl	A1	B	I	II	III
++++	-	-*	-	-	+++	-	-	-

Bloodgroup A-B-D(VI-)-ctl Rev. A1-B / Anti-D VI-
Sample: 158133907
Machine result: ++
Result reading:
time: 15/05/2017 18:08
User: IH-1000 0401057
First reading:
time: 16/05/2017 14:32
User: diamed
Last changed:
time: 16/05/2017 14:32
User: diamed
Current value: -
Verification:
time: 16/05/2017 14:32
User: diamed

Result:
A Rh D negative A

ABO:

Phenotype: DAT:

Rhesus-D: Auto ctrl.:

Kell:

Antibodies / other antigens:

Details ...

Accept all

Kaartje:

DVI+ 2+

DVI- 2+

Bloedgroep in buisjes

Anti-D monoclonaal: 2+

Controle monoclonaal: neg.

The R₀^{Har} Rh:33 phenotype results from substitution of exon 5 of the *RHCE* gene by the corresponding exon of the *RHD* gene

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Received 20 July 1995; accepted for publication 2 November 1995

Summary. The highly polymorphic Rh (Rhesus) system is encoded by two homologous genes, one encoding the D polypeptide and the other the CcEe polypeptides. Partial D

transcripts, a new Rh transcript, *RHc(D)(e)*, was identified in three unrelated individuals expressing R₀^{Har} Rh:33. The *RHc(D)(e)* transcript showed the same sequence as the *RHce*

Rh33 ANTIGEN**Terminology**

ISBT symbol (number)
Other names
History

RH33 (004.033)
Har, R₀^{Har}, D^{Har}
Reported in 1971 and given the next Rh number. Although the complex expressing Rh33 was first detected on RBCs from a German donor, the complex was named R₀^{Har} after the name of an English donor with an informative family

Occurrence

Less than 0.01%. Rh33 may be more common in people of German ancestry.

Expression

Cord RBCs
Altered

Presumed expressed
R₁^{Lisa}¹

Molecular basis associated with Rh33 antigen

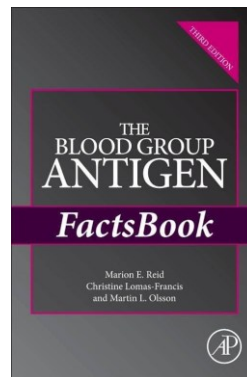
In the partial D phenotype R₀^{Har}, Rh33 is associated with an *RH(ce-D-ce)* gene in which exon 5 of *RHce* is replaced by exon 5 of *RHD*². The *RHCeVA* allele, a hybrid *RH(Ce-D-Ce)* gene with exon 5 originating from *RHD* encodes Rh33 and weak C and e antigens. *RHCeVA* may be the allele encoding R₁^{Lisa}³. See system pages.

Effect of enzymes/chemicals on Rh33 antigen on intact RBCs

Ficin/papain	Resistant (↑↑)
Trypsin	Presumed resistant
α-Chymotrypsin	Presumed resistant
Pronase	Presumed resistant
Sialidase	Presumed resistant
DTT 200 mM	Presumed resistant
Acid	Presumed resistant

In vitro characteristics of alloanti-Rh33

Immunoglobulin class	IgM
Optimal technique	RT; enzymes
Complement binding	No



<0,01%
Exon 5 vervangen

Partieel D

Normaal c antigeen
Zwak e- en f-antigeen
Geen C-, E- en G-antigeen

Clinical significance of alloanti-Rh33

No data are available.

Comments

Rh33 is encoded by an unusual Rh complex R₀^{Har}. This complex also encodes a partial D antigen, normal c (RH4), weak c (RH5), weak f (RH6) and weak Hr₀ (RH17) antigens; it does not encode C (RH2), E (RH3), G (RH12), hr^S (RH19) or Hr (RH18) antigens.

Rh33 is also expressed by the rare complexes D^{Iva}(C), R₀^{JOH} and R₁^{Lisa}. All Rh33+ RBCs also express the low incidence antigen FPTT (RH50).

Anti-Rh33 is a rare specificity. Two examples were in serum also containing anti-D.

References

- ¹ Moores, P. et al. (1991) Transfusion 31, 759–761.
- ² Beckers, E.A.M. et al. (1996) Br. J. Haematol. 92, 751–757.
- ³ Noizat-Pirenne, F. et al. (2002) Transfusion 42, 627–633.

RH:33, R0^{HAR} of DHAR

DHAR betreft een complete deletie van Rhesus D gen.

Maar in het *RHCE* gen is exon 5 vervangen door exon 5 van het Rhesus D gen waardoor enkele epitopen van D nog tot expressie komen.

Deze kunnen een zwakke tot normale reactie geven met monoclonale anti-D sera.

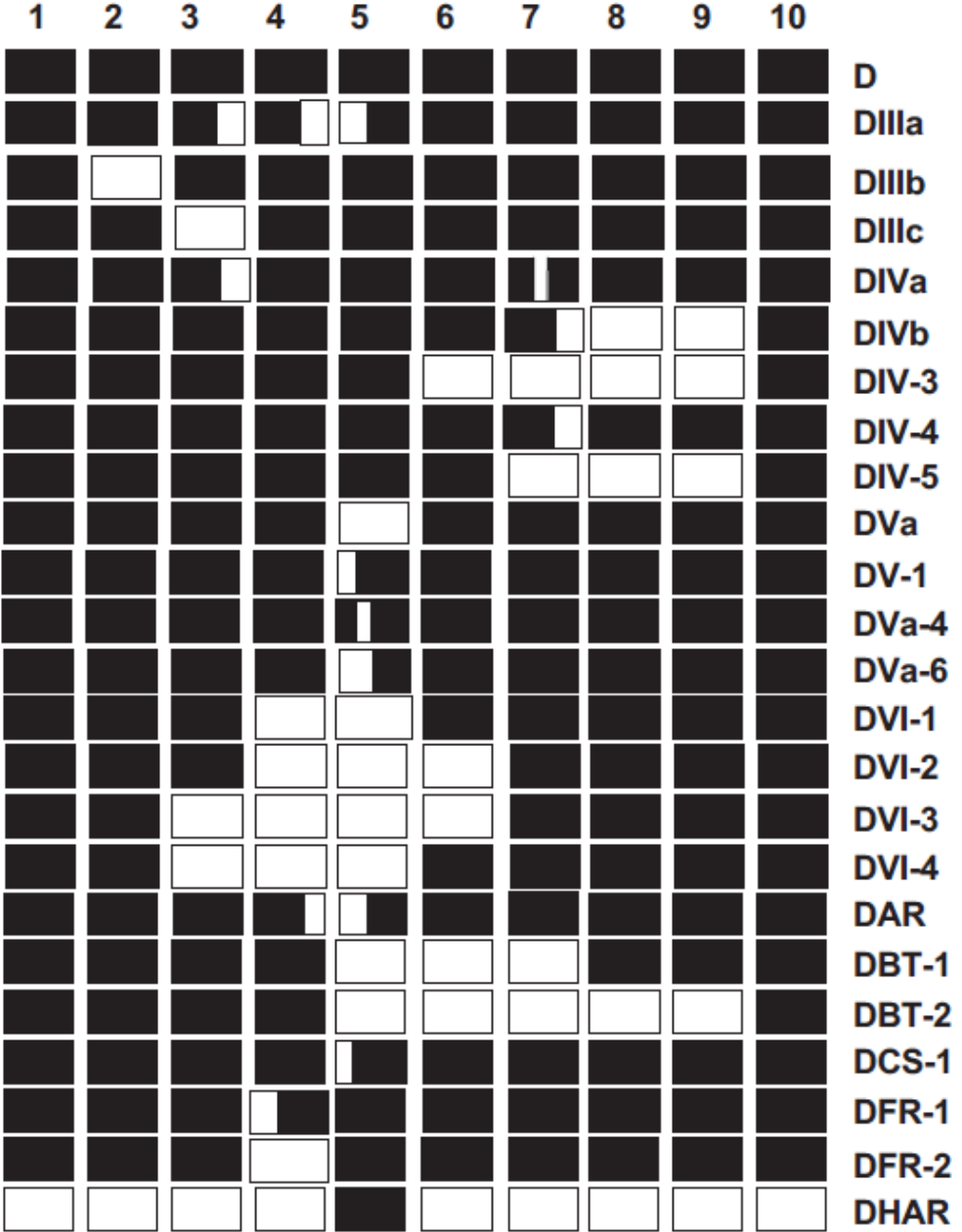


Fig. 2. *RHD* exons (black boxes) and *RHCE* exons (white boxes) of hybrid genes in some D variants.

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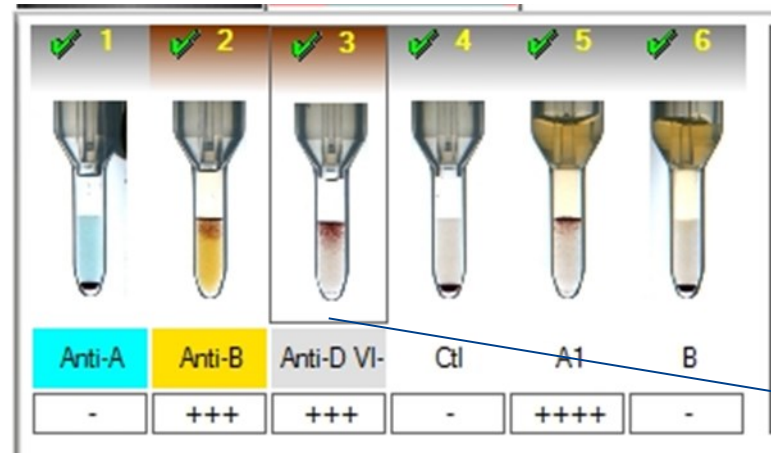
Casus 2

Dhr. S
69 jaar

Op 1-6-2017 opgenomen op VEA5

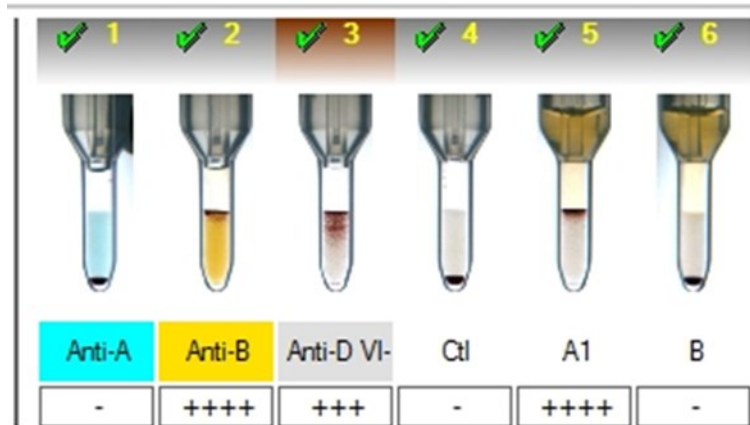
BRI 1-6-2017

B positief
Screening negatief



BRI 12-6-2017

B positief
Screening negatief



Zondag 25-6-17 Transfusie 2 EC

B positief

Screening negatief



Niet laten zien bij intake.....



Zondag 25-6-17 Transfusie 2 EC

Hoe nu verder?



Morgen zoeken we het wel verder uit. Nu kunnen we gewoon B Rhesus D-negatieve producten uitgeven. Opmerking in LABOSYS dat patiënt voorlopig Rh-D negatieve producten krijgt.



Sample: 258014907
Bloodgroup: A-B-D Confirmation for patients (...)

Test time:
25/06/2017 11:57

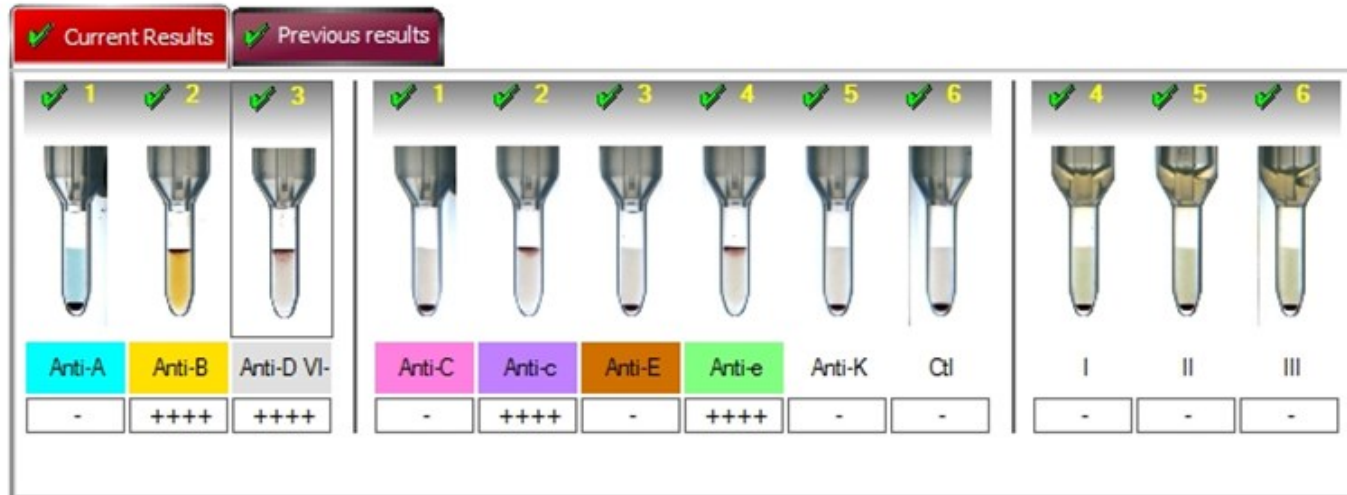
Tested by:
Verified by:

automatically accepted

Anti-D VI-

50053.0503/18.01/322371

Comment:



Bloedgroep B positief, Rh-Fenotype ccDee, IRA negatief.

Bloedgroep in buisjes

Anti-D monoclonaal: 3+

Controle monoclonaal: negatief

Anti-D Enhanced: 2+

Enhanced controle: negatief



Onderzoek erythrocyten ABO
bloedgroep : B
rhesus (D) antigeen : D variant

.....variant RHD allel zwak D type 4. Dit betreft een zeldzaam voorkomende variatie van het RhD eiwit en het is niet bekend of deze patient alloantistoffen anti-RhD zal vormen.

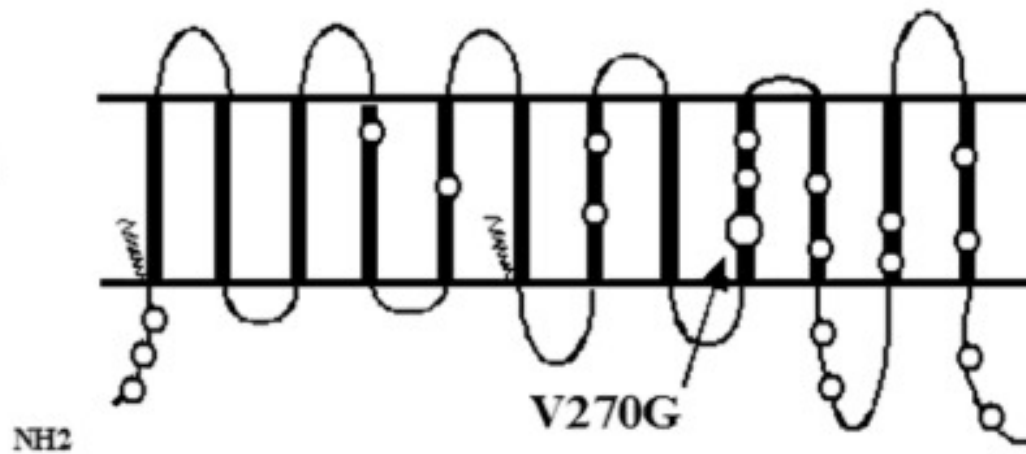
Conclusie:

Er is sprake van een RhD variant.

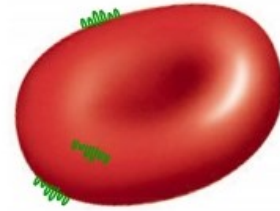
Mensen met een RhD variant dienen als bloedontvanger RhD negatief en als donor RhD positief beschouwd te worden.

A

**Weak
D**



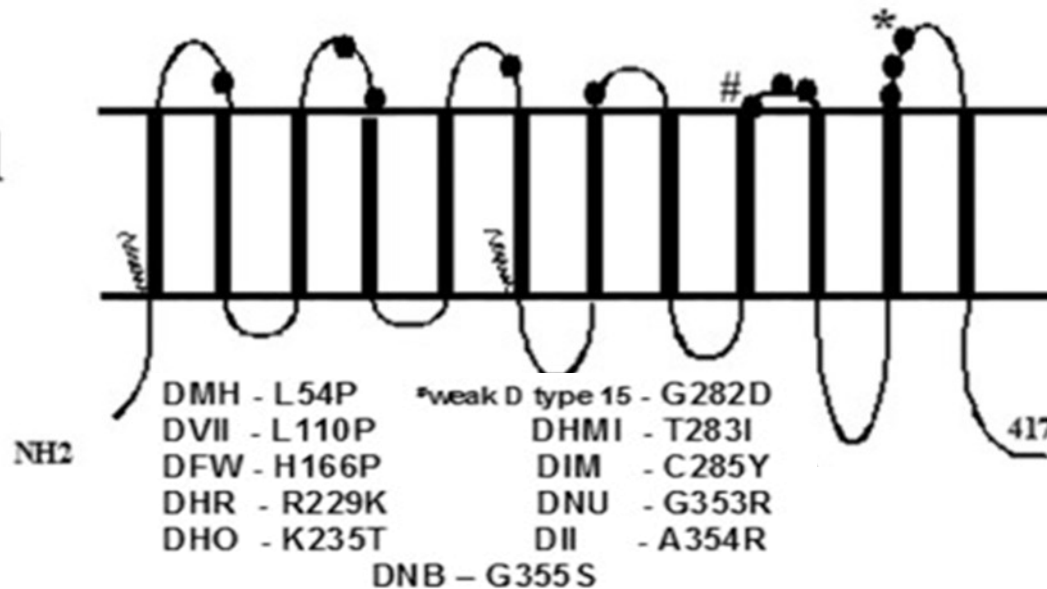
Volledig D antigeen



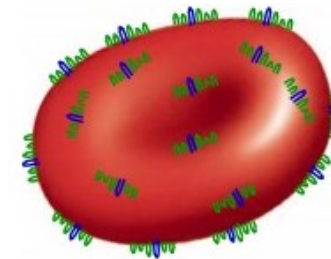
variant RHD allel zwak D type 4

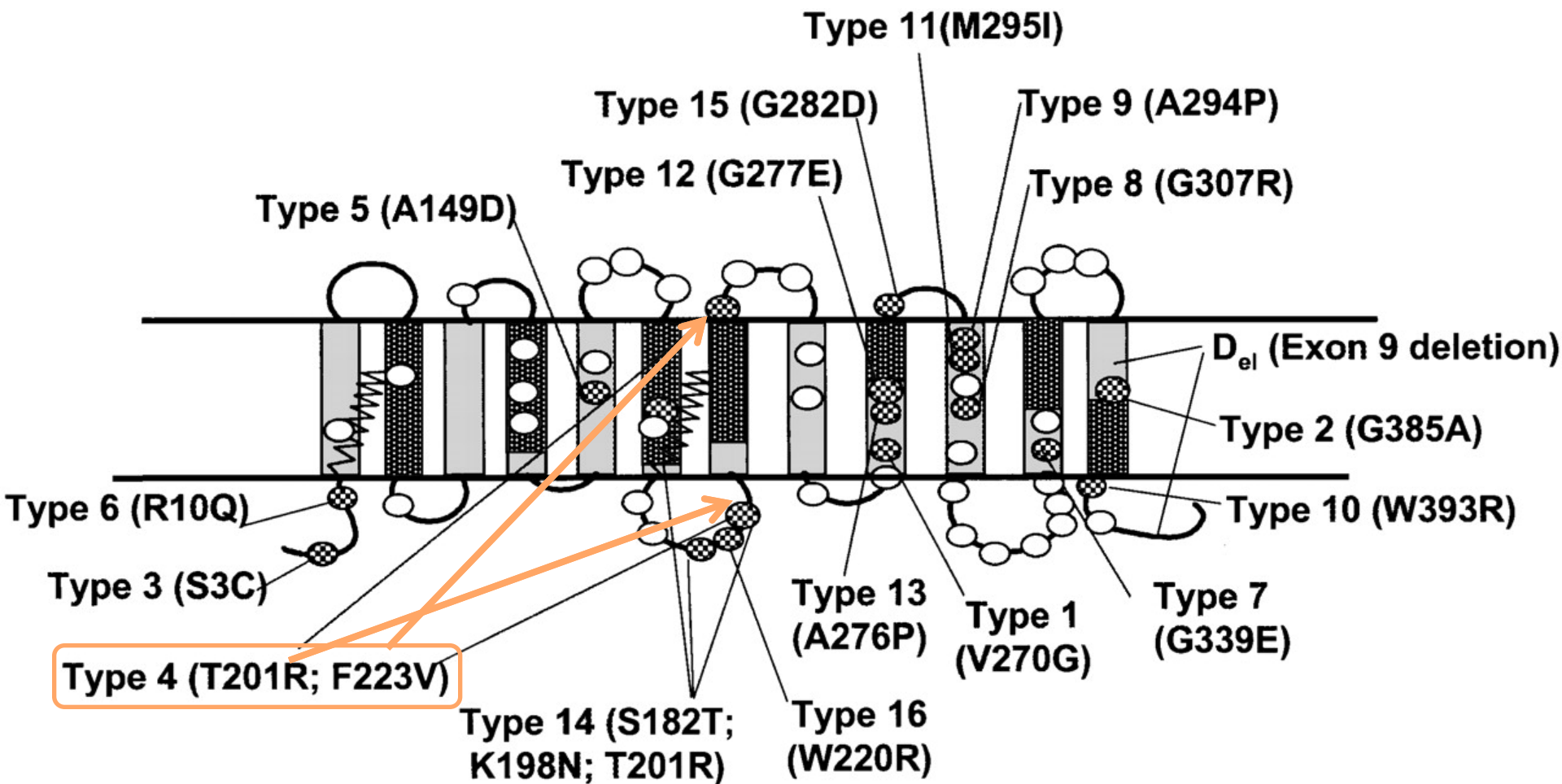
B

**Partial
D**



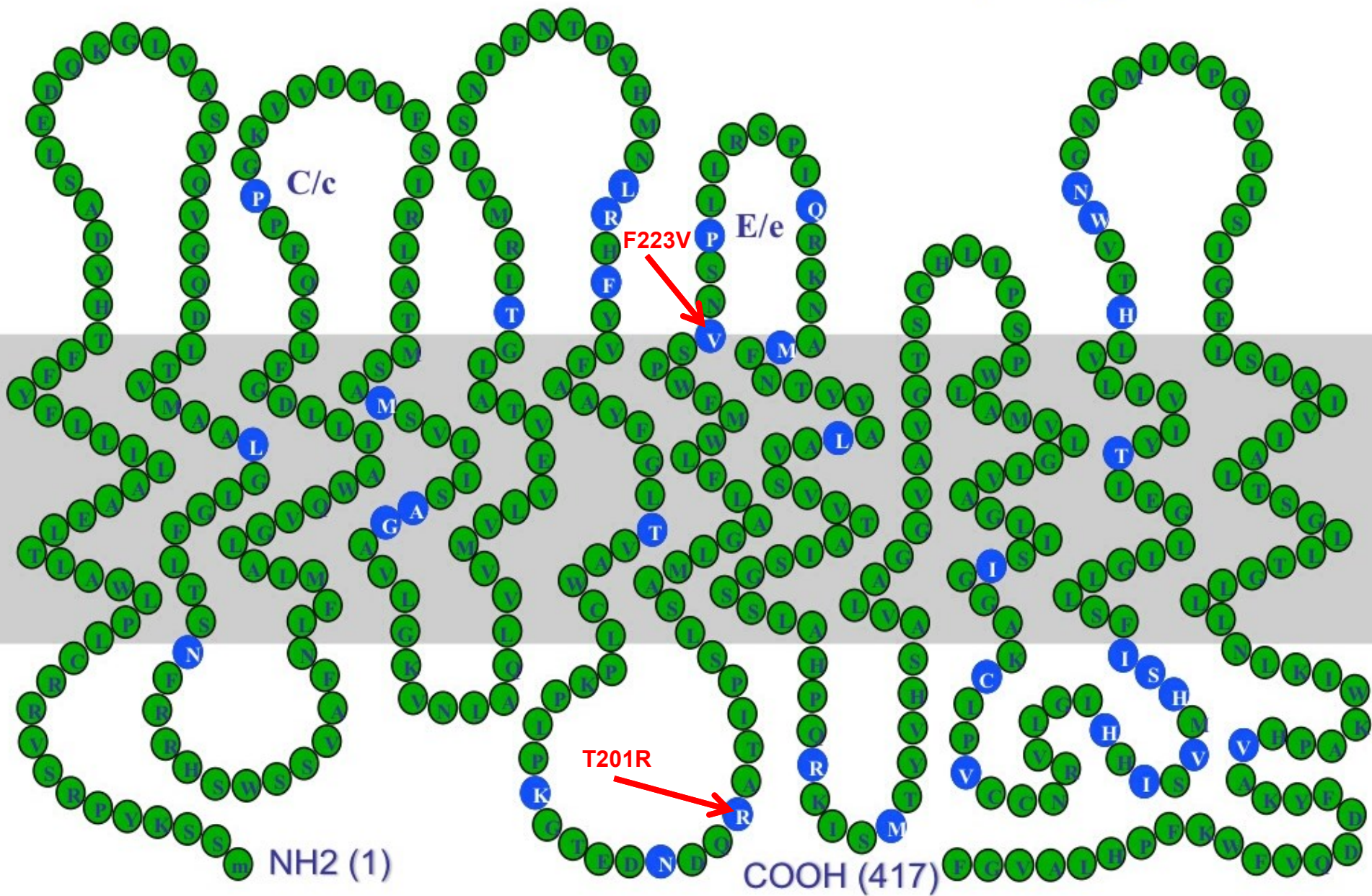
D VI variant





variant RHD allele zwak D type 4

RHD/Ce Protein Membrane Topology



Designation	ISBT name	Cluster	Haplotype	Mechanism	Alterations	First mention	Definitive publication
weak D type 4.0	RHD*09.03.01 RHD*DAR3	weak D type 4 cluster	cDe	Multiple missense mutations	602C>G (T201R) 667T>G (F223V) 819G>A	1999	1999
weak D type 4.0.1	RHD*09.03 RHD*DAR3	weak D type 4 cluster	cDe	Multiple missense mutations	602C>G (T201R) 667T>G (F223V)		
weak D type 4.1	RHD*09.04 RHD*DAR4	weak D type 4 cluster	cDe	Multiple missense mutations	48G>C (W16C) 602C>G (T201R) 667T>G (F223V) 819G>A	2000	2000
weak D type 4.2.1 (DAR1.1)	RHD*09.01.01 RHD*DAR1.01 RHD*weak 4.2	weak D type 4 cluster	cDe	Multiple missense mutations	1025T>C (I342T) 602C>G (T201R) 667T>G (F223V) 957 G>A	2000	2000
weak D type 4.2.2 (DAR1.2)	RHD*09.01.02	weak D type 4 cluster	cDe	Multiple missense mutations	1025T>C (I342T) 602C>G (T201R) 667T>G (F223V) 744C>T 957 G>A	2000	2000
weak D type 4.2.3 (DAR1.3)	RHD*09.01.03 RHD*DAR1.03	weak D type 4 cluster	cDe	Multiple missense mutations	1025T>C (I342T) 602C>G (T201R) 667T>G (F223V) 744C>T	2008	
weak D type 4.3	RHD*09. 05 RHD*weak 4.3	weak D type 4 cluster	cDe	Multiple missense mutations	602C>G (T201R) 667T>G (F223V) 819G>A 872C>G (P291R)	2004	
weak D type 4.4		weak D type 4 cluster	not reported	Multiple missense mutations	594A>T (K198N) 602C>G (T201R) 667T>G (F223V) 819G>A	2016	
weak D type 4.5		weak D type 4 cluster	not reported	Multiple missense mutations	1063G>A (G355S) 602C>G (T201R) 667T>G (F223V) 819G>A	2016	

Some Weak D Types

- Type 1
 - Type 2
 - Type 3
 - Type 4.0
- 
- Account for 90% of Weak D;
Do not produce Anti-D
- Type 4.2
 - Type 5
 - Type 11
 - Type 15
 - Type 19
 - Type 20
- 
- Known to form Anti-D
when exposed to D+
RBCs

Weak D Phenotypes

- **Weak D phenotypes given numbers**
 - Weak D type 1, type 2, type 3.....up to 76 with some sub-types (4.1, 4.2 etc)
- **Weak D classification is tricky**
 - Can be reagent and method dependent
 - Sample can be 2+ in tube at IS, stronger in gel and negative in solid phase
 - Very 'fluid' statistics for prevalence of weak D based on serology
- **Weak D types usually cannot be distinguished serologically; requires DNA analysis**

UK Blood Service Policy

Patients

- Identified weak D types 1,2 and 3 treat as D+
- Weak D type 4 onwards treat as D-
- Partial D treat as D-

Rhesus-D interpretatie

4+

3+

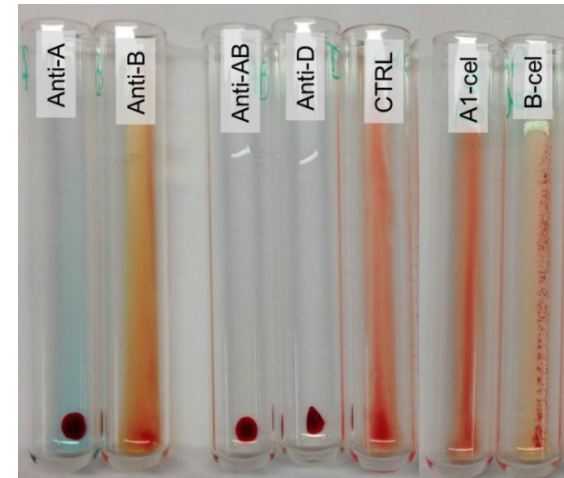


2+

1+

(+)

Rhesus-D ?



negatief



Rhesus-D positief of Rhesus-D negatief?





Bedankt voor uw aandacht