Altered red blood cell e antigen expression in variant RHCE*ce alleles. Is it worth doing a molecular analysis?

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Objectives

- Understand the basics of RHCE gene and RhCE proteins.
- Understand how a variant RHCE*ce allele can have altered expression of e antigen.
- Understand the importance of differentiating between an auto anti-e (RH5) versus an allo anti-e (RH5) due to partial e expression.
- Understand the importance of molecular analysis in proper identification of clinically significant antibody.

Case Study

22 year old female presented to the ER due to sickle cell crisis.

Chief complaint

- Pain located in her arms and legs, more severe in wrists with associated chills and intermittent dizziness.

Patient history

- Sickle cell anemia, asthma, and migraines.
- Patient has no primary or hematologist

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Additional History

Transfusion/Pregnancy:

- No record of transfusion or pregnancy at the current hospital.
- 11/3/2017- transfused 1 unit of pRBC at a different facility
  - Febrile transfusion reaction after first unit on 11/3/2017
- 11/5/2017- transfused 1 unit of pRBC (same hospital- previous)

Medications:

- Aleve to manage pain
  - 0.9% NaCl infusion
  - Oxycodone and acetaminophen
  - Ondansetron
  - Morphine
  - Ketorolac
  - Folic acid

Labs: CBC

Component	Latest Ref Rng & Units	1/18/2018	1/17/2018	1/16/2018	1/15/2018
WBC	4.4 - 10.7 x10E9/L	**14.7 (H)**	**14.7 (H)**	**18.9 (H)**	**19.5 (H)**
RBC	3.80 - 5.20 x10E12/L	**2.49 (L)**	**1.96 (L)**	**2.14 (L)**	**2.04 (L)**
Hemoglobin	12.0 - 15.6 gm/dL	**8.5 (L)**	**6.6 (L)**	**7.1 (L)**	**6.9 (L)**
Hematocrit	35.9 - 45.5 %	**24.3 (L)**	**19.4 (LL)**	**20.6 (L)**	**19.0 (LL)**
MCV	80.7 - 98.3 fl	97.6	**99.0 (H)**	96.3	93.1
MCH	26.7 - 34.0 pg	**34.1 (H)**	**33.7**	33.2	33.8
MCHC	30.8 - 35.9 gm/dL	35.0	**34.0**	34.5	**36.3 (H)**
PLATELET	153 - 416 x10E9/L	**518 (H)**	**405**	**495 (H)**	409
RDW-CV	12.1 - 14.9 %	**21.8 (H)**	**21.7 (H)**	**20.7 (H)**	**19.6 (H)**
MPV	9.4 - 12.9 fl	10.4	**10.6**	10.4	10.1
Neutro	44.0 - 73.0 %	55.8		54.2	67.9
Lymph	20.0 - 43.0 %	28.0		32.6	**18.4 (L)**
Monocyte %	5.0 - 13.0 %	12.4		10.7	11.9
Eos	0.0 - 6.0 %	2.0		0.6	0.2
Baso	0.0 - 2.0 %	0.7		0.5	0.3
Immature Gran	0 - 1 %	**1.1 (H)**		**1.4 (H)**	**1.3 (H)**
Neutro Abs	2.01 - 7.14 x10E9/L	**8.20 (H)**		**10.20 (H)**	**13.23 (H)**
Lymph Abs	1.07 - 3.94 x10E9/L	**4.12 (H)**		**6.15 (H)**	3.58
Mono Abs	0.26 - 1.07 x10E9/L	**1.82 (H)**		**2.02 (H)**	**2.32 (H)**
Eos Abs	0 - 0.47 x10E9/L	0.30		0.12	0.04
Baso Abs	0 - 0.08 x10E9/L	**0.10 (H)**		**0.09 (H)**	0.06
Immature Gran Abs	0.00 - 0.06 x10E9/L	**0.16 (H)**		**0.27 (H)**	**0.26 (H)**
NRBC Auto	/100 WBC	9		3	3

Labs: CMP

Component	Latest Ref Rng & Units	1/18/2018	1/17/2018 1:38 PM	1/17/2018 1:38 PM	1/15/2018
Glucose	74 - 106 mg/dL	79		87	99
Sodium	136 - 145 mmol/L	140		138	140
Potassium	3.5 - 5.1 mmol/L	3.5		3.7	3.9
Chloride	98 - 107 mmol/L	104		104	109 (H)
Carbon Dioxide	22 - 31 mmol/L	29		29	26
Calcium	8.5 - 10.1 mg/dL	9.3		8.7	8.3 (L)
Anion Gap	8 - 16 mmol/L	7 (L)		5 (L)	5 (L)
BUN	7 - 21 mg/dL	6 (L)		5 (L)	8
Creatinine	0.50 - 1.30 mg/dL	0.30 (L)		0.29 (L)	0.34 (L)
eGFR MDRD	>60 mL/min/1.73m2	>60		>60	>60
eGFR MDRD AFR AMR	>60 mL/min/1.73m2	>60		>60	>60
ALK PHOSPHATASE	38 - 126 U/L			92	76
ALT	13 - 61 U/L			38	20
AST	5 - 40 U/L			58 (H)	23
Protein Total	6.4 - 8.2 gm/dL			7.3	7.6
Albumin	3.4 - 5.0 gm/dL			3.8	4.3
BILIRUBIN TOTAL	0.2 - 1.0 mg/dL		9.1 (H)	9.1 (H)	6.4 (H)
Conjugated bilirubin	0 - 0.3 mg/dL		2.4 (H)		
Unconjugated bilirubin	mg/dL		6.7		

Labs: Urinalysis

URINALYSIS ROUTINE W/REFLEX TO CULTURE

Order:

Status: **Final result** Visible to patient: **No (Not Released)**

	Ref Range & Units	2mo ago
Color UA	Straw, Yellow	Yellow
Clarity UA	Clear	Clear
Glucose UA	Negative	Negative
Bili UA	Negative	Negative
Ketone UA	Negative	Negative
Specific Gravity UA	1.005 - 1.030	1.008
Blood UA	Negative	Negative
pH UA	5.0 - 8.0 pH	6.0
Protein UA	Negative	Negative
Urobilinogen UA	Negative mg/dL	**4.0 (Abnormal)**
Nitrite UA	Negative	Negative
Leukocyte UA	Negative	Negative
Urine Microscopy		Urine microscopy not indicated:R
Reflex Status		Culture not indicated

Blood Bank

Type and Cross ordered for transfusion of 1 pRBC unit

Hospital performed a type and screen

pan reactive (including auto control)

Sample referred to reference lab

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ABO/Rh

Anti-A	Anti-B	Anti-D	Rh control	A1 cell	A2 cell	B cell	Auto	ABO Interp
0	0	4+	NT	4+	NT	4+	NT	O positive
0	0	4+						

DAT

	Result	Method
IgG	2+	Gel
C_3	Neg	Tube

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	D	C	c	E	e	Cw	K	k	Kpb	Jsb	Fya	Fyb	Jka	Jkb	Lea	Leb	P1	M	N	S	s	Lub	Gel	Gel
1	+	+	0	0	+	0	0	+	+	+	+	+	+	+	+	0	+	0	+	0	+	+	2+	3+
2	+	+	0	0	+	+	0	+	+	+	+	0	0	+	0	0	+	+	+	0	+	+	2+	3+
3	+	0	+	+	0	0	0	+	+	+	+	+	+	0	0	+	+	+	0	+	0	+	2+	3+
4	+	0	+	0	+	0	0	+	+	+	0	+	+	+	0	+	+	0	+	+	+	+	2+	3+
5	0	+	+	0	+	+	0	+	+	+	+	+	+	0	0	+	0	+	0	0	+	+	2+	3+
6	0	0	+	+	+	0	0	+	+	+	0	+	0	+	0	+	+	+	0	0	+	+	2+	3+
7	0	0	+	0	+	0	+	+	+	+	0	+	0	+	0	+	0	+	0	+	0	+	2+	3+
8	0	0	+	0	+	0	0	+	+	+	+	0	0	+	0	+	+	+	0	0	+	+	2+	3+
9	0	0	+	0	+	0	0	+	+	+	+	+	+	+	0	+	0	0	+	0	+	+	2+	3+
10	0	0	+	0	+	0	+	+	+	+	+	+	+	0	+	0	+	+	+	+	+	+	2+	3+
TC	+	0	+	0	+	0	0	+	+	+	0	0	+	+	0	0	+	0	+	+	0	+	2+	3+
AC																							1+	

Plasma Eluate

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	+	+	0	0	+		0				+	0	0	+	0	+	+	0	+	0	+		Gel
	D	C	c	E	e	Cw	K	k	Kpb	Jsb	Fya	Fyb	Jka	Jkb	Lea	Leb	P1	M	N	S	s	Lub	
1	+	+	0	0	+	0	0	+	+	+	+	0	+	0	+	0	+	+	0	+	0		0
2	+	+	0	0	+	+	0	+	+	+	+	0	0	+	0	0	+	+	+	0	+	+	0
3	+	0	+	+	0	0	0	+	+	+	+	+	+	0	0	+	+	+	0	+	0	+	0
4	+	0	+	0	+	0	0	+	+	+	0	+	+	+	0	+	+	0	+	+	+	+	0
5	0	+	+	0	+	+	0	+	+	+	+	+	+	0	0	+	0	+	0	0	+	+	0
6	0	0	+	+	+	0	0	+	+	+	0	+	0	+	0	+	+	+	0	0	+	+	0
7	0	0	+	0	+	0	+	+	+	+	0	+	0	+	0	+	0	+	0	+	0	+	0
8	0	0	+	0	+	0	0	+	+	+	+	0	0	+	0	+	+	+	0	0	+	+	0
9	0	0	+	0	+	0	0	+	+	+	+	+	+	+	0	+	0	0	+	0	+	+	0
10	0	0	+	0	+	0	+	+	+	+	+	+	+	0	+	0	+	+	+	+	+	+	0
TC	+	0	+	0	+	0	0	+	+	+	0	0	+	+	0	0	+	0	+	+	0	+	0

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Adsorbed Plasma- R2

	+	0	+	+	0		0				+	+	+	+	0	0	+	+	+	0	+		Gel
	D	C	c	E	e	Cw	K	k	Kpb	Jsb	Fya	Fyb	Jka	Jkb	Lea	Leb	P1	M	N	S	s	Lub	
1	+	+	o	o	+	o	o	+	+	+	+	o	+	o	+	o	+	+	o	+	o		2+
2	+	+	o	o	+	+	o	+	+	+	+	o	o	+	o	o	+	+	+	o	+	+	2+
3	+	o	+	+	o	o	o	+	+	+	+	+	+	o	o	+	+	+	o	+	o	+	0
4	+	o	+	o	+	o	o	+	+	+	o	+	+	+	o	+	+	o	+	+	+	+	2+
5	o	+	+	o	+	+	o	+	+	+	+	+	+	o	o	+	o	+	o	o	+	+	2+
6	o	o	+	+	+	o	o	+	+	+	o	+	o	+	o	+	+	+	o	o	+	+	2+
7	o	o	+	o	+	o	+	+	+	+	o	+	o	+	o	+	o	+	o	+	o	+	2+
8	o	o	+	o	+	o	o	+	+	+	+	o	o	+	o	+	+	+	o	o	+	+	2+
9	o	o	+	o	+	o	o	+	+	+	+	+	+	+	o	+	o	o	+	o	+	+	2+
10	o	o	+	o	+	o	+	+	+	+	+	+	+	o	+	o	+	+	+	+	+	+	2+
TC	+	o	+	o	+	o	o	+	+	+	o	o	+	+	o	o	+	o	+	+	o	+	2+
sel cell	+	o	+	+	o	o	+	o	+	+	+	+	o	+	o	+	o	+	o	+	+	+	0

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Adsorbed Plasma- R2

	+	0	+	+	0		0				+	+	+	+	0	0	+	+	+	0	+		Gel
	D	C	c	E	e	Cw	K	k	Kpb	Jsb	Fya	Fyb	Jka	Jkb	Lea	Leb	P1	M	N	S	s	Lub	
1	+	+	o	o	+	o	o	+	+	+	+	o	+	o	+	o	+	+	o	+	o		2+
2	+	+	o	o	+	+	o	+	+	+	+	o	o	+	o	o	+	+	+	o	+	+	2+
3	+	o	+	+	o	o	o	+	+	+	+	+	+	o	o	+	+	+	o	+	o	+	o
4	+	o	+	o	+	o	o	+	+	+	o	+	+	+	o	+	+	o	+	+	+	+	2+
5	o	+	+	o	+	+	o	+	+	+	+	+	+	o	o	+	o	+	o	o	+	+	2+
6	o	o	+	+	+	o	o	+	+	+	o	+	o	+	o	+	+	+	o	o	+	+	2+
7	o	o	+	o	+	o	+	+	+	+	o	+	o	+	o	+	o	+	o	+	o	+	2+
8	o	o	+	o	+	o	o	+	+	+	+	o	o	+	o	+	+	+	o	o	+	+	2+
9	o	o	+	o	+	o	o	+	+	+	+	+	+	+	o	+	o	o	+	o	+	+	2+
10	o	o	+	o	+	o	+	+	+	+	+	+	+	o	+	o	+	+	+	+	+	+	2+
TC	+	o	+	o	+	o	o	+	+	+	o	o	+	+	o	o	+	o	+	+	o	+	2+
sel cell	+	o	+	+	o	o	+	o	+	+	+	+	o	+	o	+	o	+	o	+	+	+	o

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Adsorbed Plasma- rr

	0	0	+	0	+		0				0	+	+	0	0	0	+	+	0	+	0		Ge
	~~D~~	C	c	E	e	Cw	K	k	Kpb	Jsb	~~Fya~~	Fyb	Jka	~~Jkb~~	Lea	Leb	P1	M	~~N~~	S	~~s~~	Lub	
1	+	+	o	o	+	o	o	+	+	+	+	o	+	o	+	o	+	+	o	+	o		2+
2	+	+	o	o	+	+	o	+	+	+	+	o	o	+	o	o	+	+	+	o	+	+	2+
3	~~+~~	o	+	+	o	o	o	+	+	+	+	+	+	o	o	+	+	+	o	+	o	+	0
4	+	o	+	o	+	o	o	+	+	+	o	+	+	+	o	+	+	o	~~+~~	+	+	+	0
5	o	+	+	o	+	+	o	+	+	+	+	+	+	o	o	+	o	+	o	o	+	+	1+
6	o	o	+	+	+	o	o	+	+	+	o	+	o	~~+~~	o	+	+	+	o	o	~~+~~	+	0
7	o	o	+	o	+	o	+	+	+	+	o	+	o	+	o	+	o	+	o	+	o	+	0
8	o	o	+	o	+	o	o	+	+	+	~~+~~	o	o	+	o	+	+	+	o	o	+	+	0
9	o	o	+	o	+	o	o	+	+	+	+	+	+	+	o	+	o	o	+	o	+	+	0
10	o	o	+	o	+	o	+	+	+	+	+	+	+	o	+	o	+	+	+	+	+	+	0
TC	+	o	+	o	+	o	o	+	+	+	o	o	+	+	o	o	+	o	+	+	o	+	0
AC																							

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Adsorbed plasma- rr

	0	0	+	0	+		0				0	+	+	0	0	0	+	+	0	+	0		Gel
	~~D~~	C	c	E	e	Cw	K	k	Kpb	Jsb	~~Fya~~	Fyb	Jka	~~Jkb~~	Lea	Leb	P1	M	~~N~~	S	~~s~~	Lub	
1	+	+	o	o	+	o	o	+	+	+	+	o	+	o	+	o	+	+	o	+	o		2+
2	+	+	o	o	+	+	o	+	+	+	+	o	o	+	o	o	+	+	+	o	+	+	2+
3	~~+~~	o	+	+	o	o	o	+	+	+	+	+	+	o	o	+	+	+	o	+	o	+	o
4	+	o	+	o	+	o	o	+	+	+	o	+	+	+	o	+	+	o	~~+~~	+	+	+	o
5	o	+	+	o	+	+	o	+	+	+	+	+	+	o	o	+	o	+	o	o	+	+	1+
6	o	o	+	+	+	o	o	+	+	+	o	+	o	~~+~~	o	+	+	+	o	o	~~+~~	+	o
7	o	o	+	o	+	o	+	+	+	+	o	+	o	+	o	+	o	+	o	+	o	+	o
8	o	o	+	o	+	o	o	+	+	+	~~+~~	o	o	+	o	+	+	+	o	o	+	+	o
9	o	o	+	o	+	o	o	+	+	+	+	+	+	+	o	+	o	o	+	o	+	+	o
10	o	o	+	o	+	o	+	+	+	+	+	+	+	o	+	o	+	+	+	+	+	+	o
TC	+	o	+	o	+	o	o	+	+	+	o	o	+	+	o	o	+	o	+	+	o	+	o
AC																							

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Phenotype (with sickle separated cells)

C	c	E	e	K	Fya	Fyb	Jka	Jkb	S	s
0	4+	4+	4+	0	0	0	3+	0	0	3+

Hmm
e+ ?? But the patient has anti-e

Maybe it's auto anti-e

Let's find out…….

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Adsorbed Plasma- R2R2

	+	0	+	+	0		0				+	+	+	+	0	0	+	+	+	0	+		Gel
	D	C	c	E	e	Cw	K	k	Kpb	Jsb	Fya	Fyb	Jka	Jkb	Lea	Leb	P1	M	N	S	s	Lub	
1	+	+	o	o	+	o	o	+	+	+	+	o	+	o	+	o	+	+	o	+	o		2+
2	+	+	o	o	+	+	o	+	+	+	+	o	o	+	o	o	+	+	+	o	+	+	2+
3	+	o	+	+	o	o	o	+	+	+	+	+	+	o	o	+	+	+	o	+	o	+	o
4	+	o	+	o	+	o	o	+	+	+	o	+	+	+	o	+	+	o	+	+	+	+	2+
5	o	+	+	o	+	+	o	+	+	+	+	+	+	o	o	+	o	+	o	o	+	+	2+
6	o	o	+	+	+	o	o	+	+	+	o	+	o	+	o	+	+	+	o	o	+	+	2+
7	o	o	+	o	+	o	+	+	+	+	o	+	o	+	o	+	o	+	o	+	o	+	2+
8	o	o	+	o	+	o	o	+	+	+	+	o	o	+	o	+	+	+	o	o	+	+	2+
9	o	o	+	o	+	o	o	+	+	+	+	+	+	+	o	+	o	o	+	o	+	+	2+
10	o	o	+	o	+	o	+	+	+	+	+	+	+	o	+	o	+	+	+	+	+	+	2+
TC	+	o	+	o	+	o	o	+	+	+	o	o	+	+	o	o	+	o	+	+	o	+	2+
AC	(tested with sickle separated DAT negative patient cells)																						o

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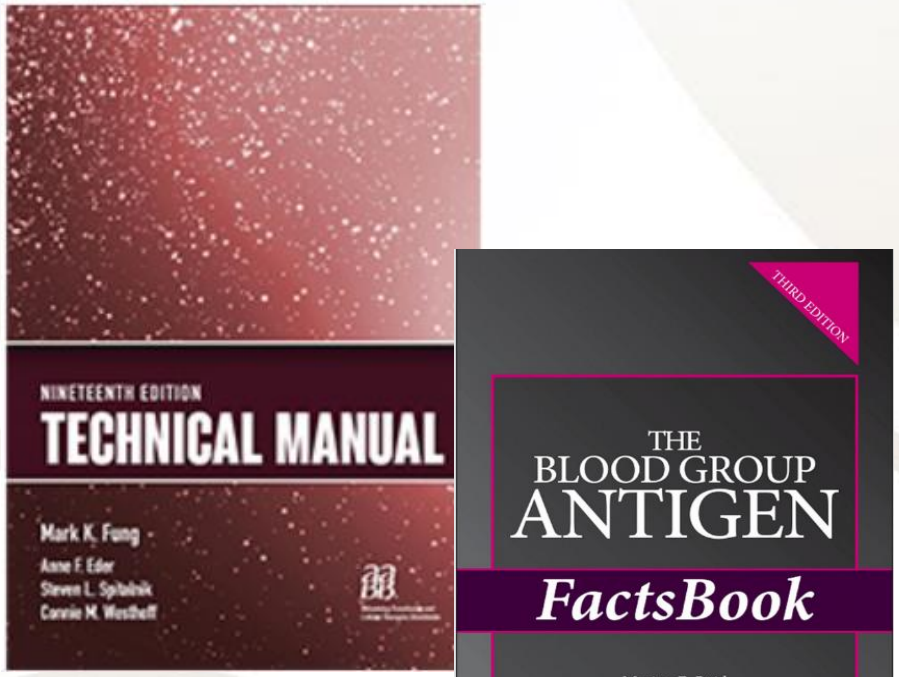
Is This e Variant?



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HEA Molecular

Blood Group	Antigen	Result
Rh	c	+
	C	0
	e	+
	E	+
	V	+
	VS	+
Kell	K	0
	k	+
	Kp^a	0
	Kp^b	+
	Js^a	0
	Js^b	+
Duffy	Fy^a	0
	Fy^b	(0)*
Kidd	Jk^a	0
	Jk^b	+
MNS	M	0
	N	+
	S	0
	s	+
	U	+
Lutheran	Lu^a	0
	Lu^b	+
Diego	Di^a	0
	Di^b	+
Colton	Co^a	+
	Co^b	0
Dombrock	Do^a	0
	Do^b	+
	Hy	+
	Jo^a	+
Landsteiner-Wiener	LW^a	+
	LW^b	0
Scianna	Sc1	+
	Sc2	0
Hemoglobin S	HbS	++

Patient was referred for RHCE variant testing

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RHCE Gene and RhCE Proteins

- RH locus is the most polymorphic of those encoding the antigens of the 30 BGS
  - antigens in the Rh BGS are the most immunogenic

- Two homologous genes RHD and RHCE, each spanning 10 exons, encode, respectively, the RhD and RhCE proteins
  - D, C, E, c, and e are the 5 major Rh antigens encoded by these genes

RHCE Gene and RhCE Proteins

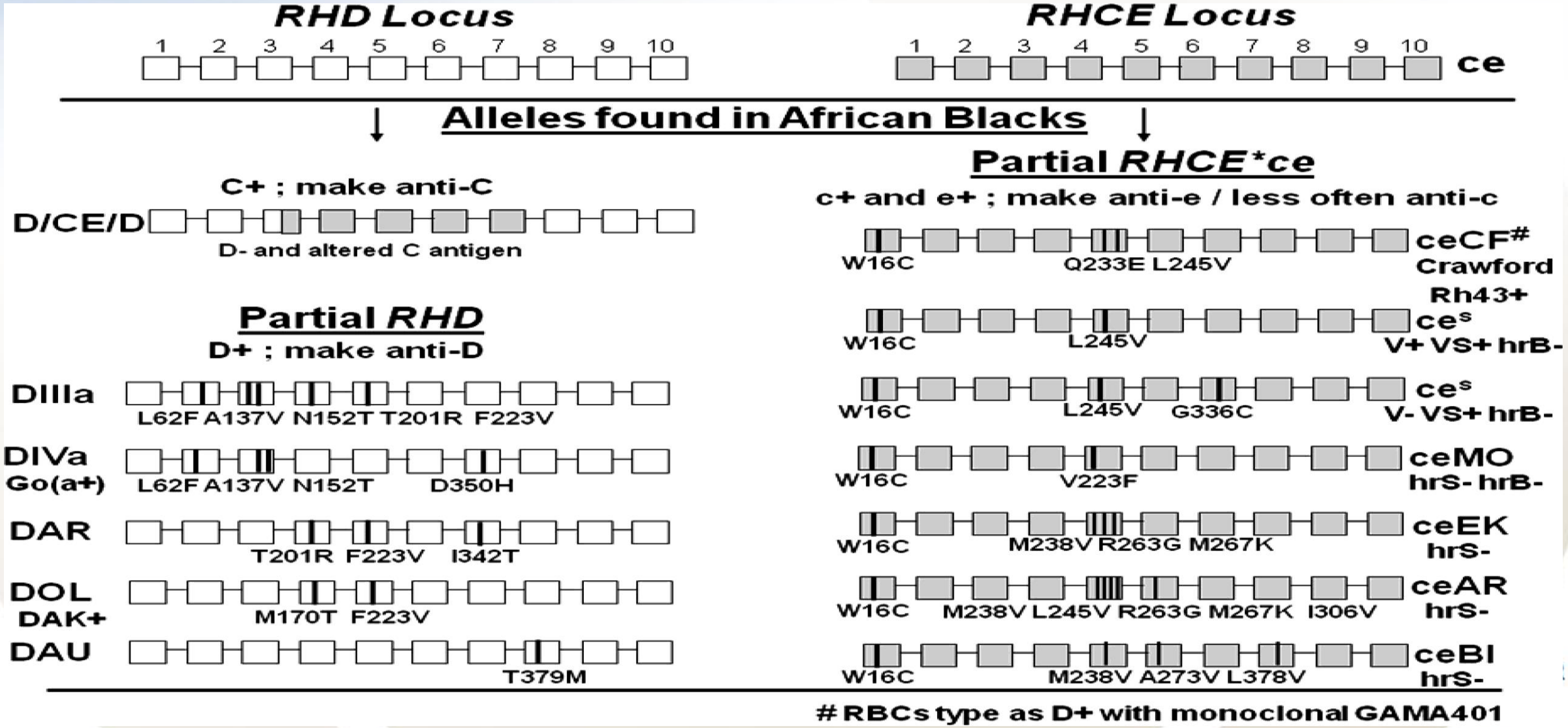
- Alteration in RHD and RHCE genes due to nucleotide changes
  - Cause gene rearrangement
  - May encode altered expression of antigens, aka “partial antigens”
  - present technical challenges

- Mutations in RHCE result in quantitative and qualitative changes in C/c or E/e antigen expression,
  - Patient antigen type as C+ and/or e+, but produce anti-C and/or anti-e.
  - Altered C and e encountered in African–Americans most frequently.

Genotyping

- Numerous partial e antigens have been described
  - Several partial e encoded by RHCE*ce alleles
- Many were classified as autoantibodies- prior to RH genotyping.
- Serologic methods do not detect variant C or e
  - *RH* genotyping can identify those patients who are at risk for alloimmunization if exposed to conventional C/c and E/e antigens.

Diagram of some altered RHD and RHCE alleles common in African Black ethnic groups that complicate transfusion in patients with sickle cell disease.



Back to our patient: Genotype Report

Molecular Analysis: RHCE Genotyping by DNA Analysis

Results **Sample ID:** 1802500001

Phenotype

C	0	c	+	E	+	e	+

Variant:

WT/ce(733G)

Genotype

	48 G>C (W16C)	106 G>A (A36T)	122 A>G (Q41R)	307 C>T (P103S)	109bp Intron 2 Ins (109Ins)	340 C>T (R114W)	344 T>G (L115R)	365 C>T (S122L)	455 C>A (T152N)	461 G>C (R154T)	500 T>A (M167K)	538 G>C (G180R)	602 G>C (R201T)	667 G>T (V223F)	676 G>C (A226P)	697 C>G (Q233E)	712 A>G (M238V)	733 C>G (L245V)	748 G>A (V250M)	744 T>C (dT744dC)	818 C>T (A273V)	916 A>G (I306V)	1006 G>T (G336C)	1025 C>T (T342I)	CdeS 5'UTR (Rh rs)	(IPC)	
	AA	AA	AA	AA	AA	AA	AA	AA	AA	AA	AA	AA	AA	AA	AB	AA	AA	AB	AA	AA	AA	AA	AA	AA	AA	AA	

How Do I Interpret That??

- *RHCE*cE/*ce(733G)*, with a predicted C-c+E+ and e+(partial) phenotype,
  - Partial e because of E *in trans* on the other allele.
  - Risk for allo anti-C and allo anti-e

- Recommended pheno-matched and e- units

  C- e- K- Fya- Jkb- S- SDN unit

High-Throughput Genotyping

Molecular DNA-based genetic methods provide an invaluable tool for improved transfusion therapy for patients with SCD.

Limitations:

- Multiple genetic variations will be found
  - May, or may not, be immunogenic or affect the phenotype.
  - The complexity of alleles encoding RBC antigens is complicated by geography, population diversity, and ethnicity, and new alleles continue to be found.

What does this all mean?

- Combine the molecular and serological methods to provide compatible blood and to avoid additional alloimmunization.

- High-throughput molecular methods may be cost-effective when screening large # of donor units.

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