Novel mutations in RHAG causing two new examples of the regulator type of Rh_{null}

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Introduction

- What is Rh_{null}?
- What is RhAG?
- How do mutations in RHAG cause Rh_{null}?
- 2 Novel mutations

What is Rh_{null}?

- A complete lack of all RhD and RhCE antigens
- Rh:-29 (total Rh)
- Very rare
- Anti-Rh29 is the immune response of Rh_{null} individuals
- Anti-Rh29 reacts with all cells that are D \ CE positive

2 mechanisms that cause Rh_{null} Amorph D neg due to no D gene AND CE neg due to a mutation causing a silent CE gene Regulator Normal D and CE genes mutations within RHAG that prevent expression/detection of D and CE

What is RhAG?

- Rh Associated Glycoprotein
- Shares 36% homology with Rh
- Identified as a blood group system by Tilley et al 2009
- RhAG forms a heterotrimer with RhD\CE
- The heterotrimer sits within a macrocomplex

Macro-complex



Mutations in *RHAG* that cause Rh_{null}

- NCBI database lists:
- 11 mutations in RHAG that cause Rh_{null}
- 6 are splice site or frame shift mutations
 Our abstract gives 1 further example
 - 154_157delCCTCinsGA
- 5 are SNPs
 - Our abstract gives 1 further example
 - A118E

Splice site \ Frame shift 154_157delCCTCinsGA Frame shift mutation → early STOP codon → improper formation of RhAG →

No RhAG → No detectable RhD RhCE RhAG expression

SNPs

 Even small changes appear to prevent expression\detection of RhAG\D\CE

A118E

SNP Ala118Glu



Alanine Non-polar



SNPs

- SNP mutations
 - change small amino acid for a larger one
 - commonly buried within the transmembrane region
 - commonly near the RhAG\D\CE interface

The heterotrimer



Ala118Glu Ser224Arg Gly279Glu Val270Iso Gly280Arg Gly380Val Asp399Tyr

Conclusion

- Rh_{null} = Rh:-29 = No Rh protein
- Rh_{null} regulator type due to mutations RHAG
- Frameshift mutations in RHAG →
 - prevent expression of RhAG \rightarrow
 - prevent expression of Rh
- SNP in RHAG →
 - prevent detection of RhAG
 - possibly correct stabilisation of Rh \rightarrow
 - prevent detection with Anti-D\CE

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The macro-complex

