UNIVERSITY OF LEEDS

Predictors of Response to Rituximab

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nhsa Northern Health Science Alliance
A Health Partnership for Northern England

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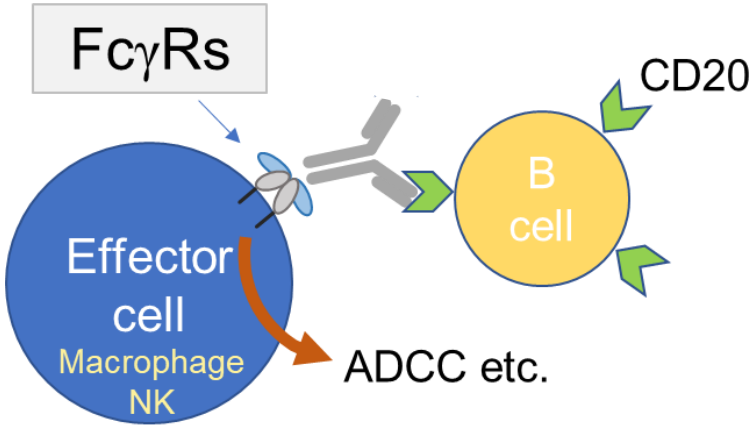
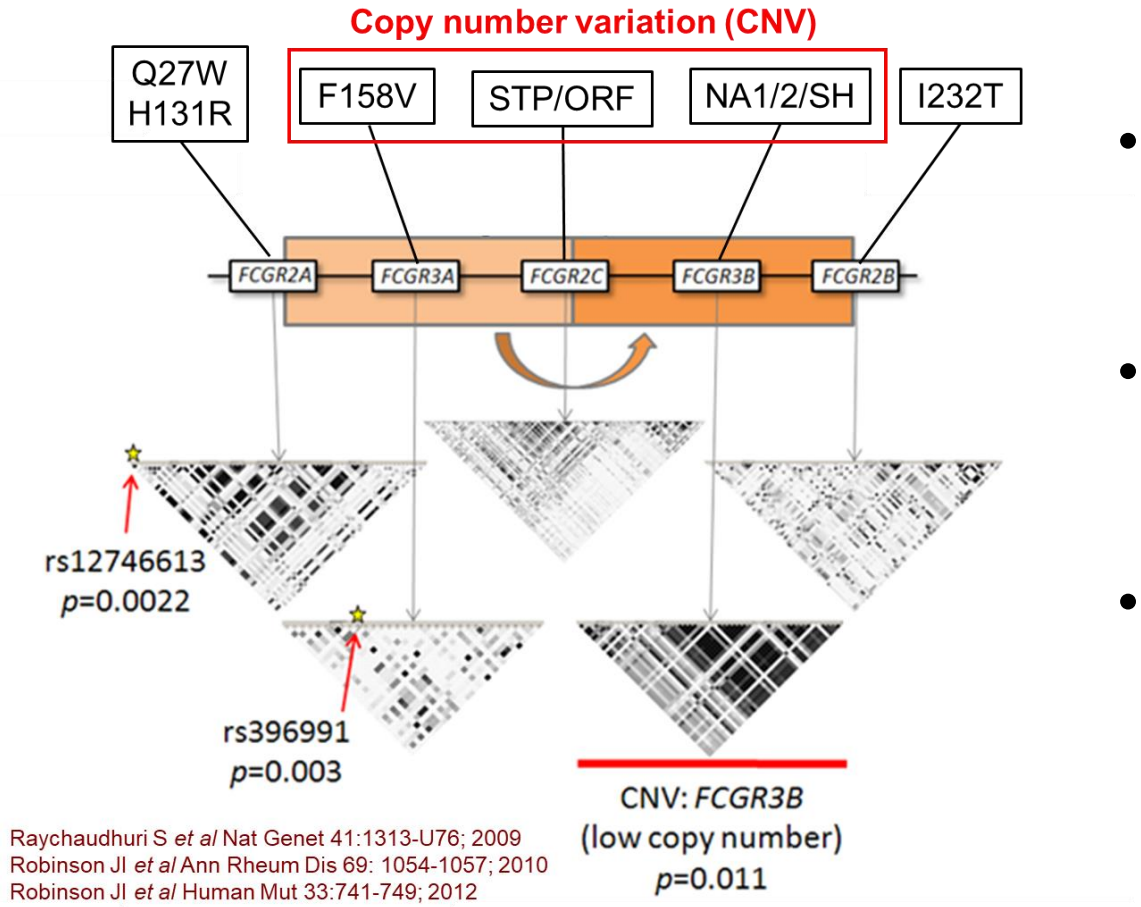
FcγR involvement in rituximab response

- Rituximab (RTX) is a monoclonal anti CD20 antibody (mAb) B cell depletion
- Approved for rheumatoid arthritis (RA) patients with severe active disease and inadequate response to disease-modifying anti-rheumatic drugs, including TNF inhibitors
- Clinical response to RTX is variable and unpredictable
- Our work for MATURA has focused on the role of the Fc gamma receptors in predicting response



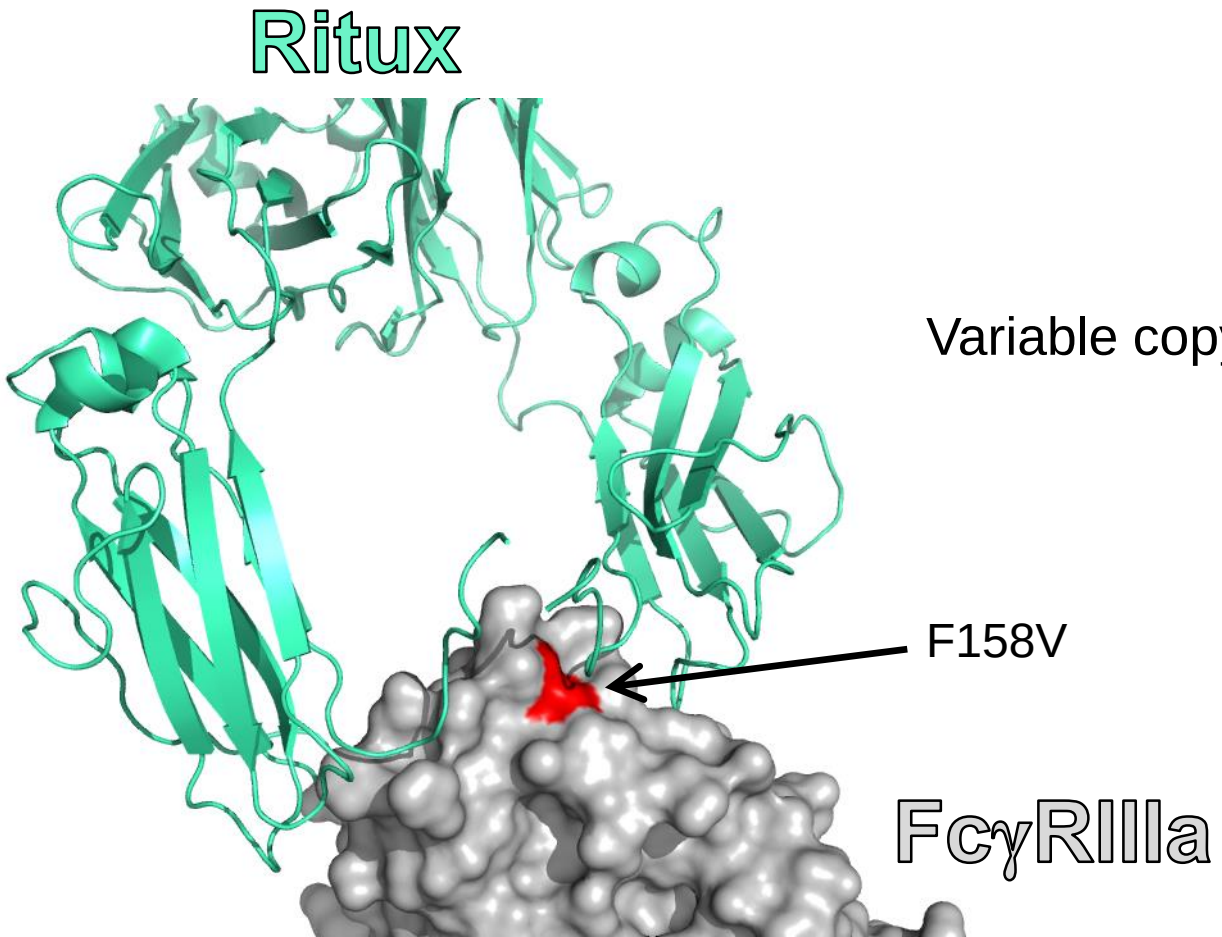
Human *FCGR* gene cluster



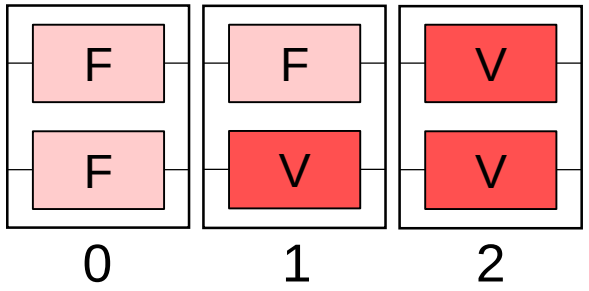
Raychaudhuri S *et al* Nat Genet 41:1313-U76; 2009
Robinson JI *et al* Ann Rheum Dis 69: 1054-1057; 2010
Robinson JI *et al* Human Mut 33:741-749; 2012

- Segmental duplication and structural variation (98% homology)
- Missed by standard genome-wide genotyping
- Multiplexed Ligation-dependent Probe Amplification (MLPA) is robust and reliable

Quantitative genotypes

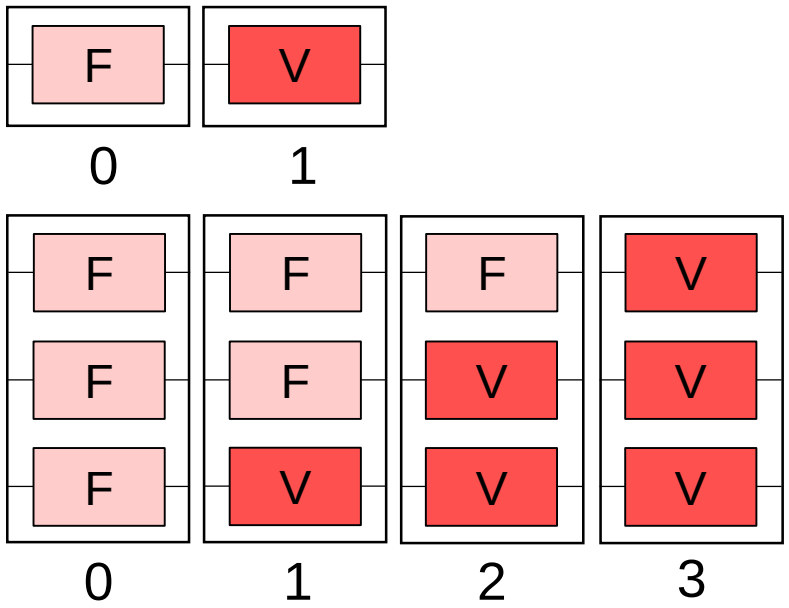


Single copy



"Normal" expression

Variable copy



Low expression

High expression

Response may be dependent of expression and affinity

Subjects and outcome measures

581 patients from BRAGGSS and Leeds NHS clinics

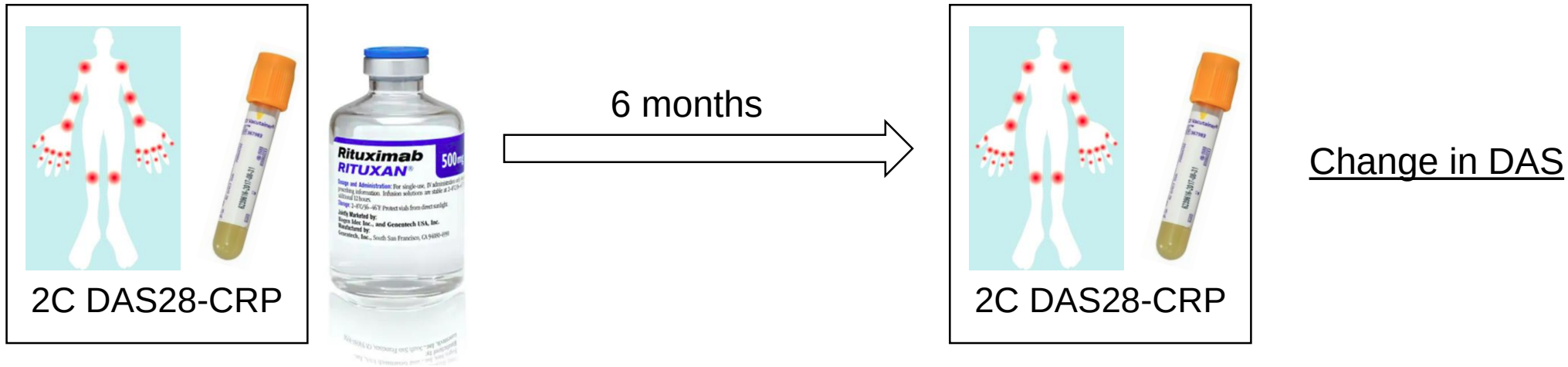
457 (79%) female

381/469 (81%) rheumatoid factor positive

Mean (SD) age at diagnosis 46.6 (14.2)

age at first cycle RTX 58.5 (12.3)

disease duration 12.3 years (10.0)



Statistical analysis *FCGR3A*-F158V

- (i) Disregard copy number: compare rare homozygotes, heterozygotes and common heterozygotes (as all other studies have)
- (ii) Effect of *FCGR3A* copy number alone
- (iii) Additive effect of each allele

(i) Treated as single copy gene

- Heterozygote effect seen for F158V polymorphism in SJC

Phenotype	SNP	Number	Coefficient	P-value
CRP	F only	204	-	
	FV	225	-0.03	0.73
	V only	52	-0.03	0.81
SJC	F only	190	-	
	FV	217	-0.25	**0.02**
	V only	50	-0.26	0.13
DAS-2C	F only	175	-	
	FV	193	-0.29	**0.03**
	V only	47	-0.28	0.17

(ii) *FCGR3A* copy number only

- Analysed relative to 2 copies, regardless of F158V genotype
- >2 copies significantly associated with response
- <2 copies borderline associated with poor response
- Effects mainly through SJC component

Phenotype	SNP	Number	Coefficient	P-value
CRP	2 copies	435	-	
	< 2 copies	10	0.18	0.52
	> 2 copies	36	-0.19	0.23
SJC	2 copies	413	-	
	< 2 copies	10	0.59	0.09
	> 2 copies	34	-0.42	**0.03**
DAS-2C	2 copies	376	-	
	< 2 copies	9	0.83	**0.05**
	> 2 copies	30	-0.58	**0.02**

(iii) Additive effect of V and F alleles

- Combined effect of gene copy number and the number of F and V alleles
- Number of V alleles most significant
- Number of F alleles weakly associated with response
- Effects mainly through SJC component

Phenotype	Number	SNP	Coefficient	P-value
CRP	481	V	-0.18	0.17
		F	-0.19	0.17
SJC	457	V	-0.50	**0.003**
		F	-0.36	0.04
DAS-2C	415	V	-0.68	**0.001**
		F	-0.55	0.01

Conclusions

- *FCGR3A*-F158V polymorphism associated with clinical response as measured by swollen joint count, and with the DAS28 measure based on SJC and CRP only
- Increasing number of copies of the V allele associated with better response; also some evidence that, conditional on number of V copies, additional copies of the F allele also associated

- Further work:
  - Currently finalising analysis of B-cell depletion in the RA Leeds cohort
  - Samples from patients with Systemic lupus erythematosus (SLE) from Leeds and from Tim Vyse are being analysed in a similar manner
  - NK cell functional data generated on the Leeds SLE samples

Acknowledgements

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Study subjects

- Well-characterised RA patients from
  - Biologics in Rheumatoid Arthritis Genetics and Genomics Study Syndicate (BRAGGSS)
  - Leeds biologics clinic (routine NHS)
- Inclusion criteria
  - Received RTX for active RA
  - Clinical and laboratory documentation of response to the first cycle of rituximab
- 581 patients
  - 457 (79%) female
  - 381/469 (81%) rheumatoid factor positive
  - Mean (SD) age at diagnosis 46.6 (14.2)

    age at first cycle RTX 58.5 (12.3)

    disease duration 12.3 years (10.0)

Association of *FCGR2A* and *FCGR2B* genotypes with clinical response

- No effect of polymorphism I123T in *FCGR2B* with clinical response

- Some weak evidence of association for *FCGR2A*

  H131R = rs1801274

  Q27W = rs9427399

Phenotype	SNP	Number	P-value
CRP	H131R	481	0.16
	Q27W	481	0.44
SJC	H131R	457	0.40
	Q27W	457	0.82
DAS-2C	H131R	415	0.25
	Q27W	415	0.74
DAS-3C	H131R	413	0.04
	Q27W	413	0.42

FcgRIIIa expression on NK cells in RA is associated with RTX response