An Intronic CR2 Polymorphism Associated with Systemic Lupus Erythematosus Alters CTCF Binding and CRI Expression

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Complement Receptor 2

- Expressed primarily on B cells and follicular dendritic cells
- Known ligands
  - C3 degradation products: iC3b, C3d(g)
  - CD23
  - IFN-α
  - EBV gp350
- Important for humoral immunity
  - Target antigen/immune complexes to the germinal center
  - Functions with CD19 to augment BCR mediated signals

Role of CR2 in SLE

- Levels decreased by 50-60% on B cells of lupus patients and in mouse models (Wilson, et al., 1986; Levy, et al., 1992; Marquart, et al., 1995; Takahashi, et al., 1997)
- Earlier onset and more aggressive disease in Cr2 deficient mice (Prodeus, et al., 1998; Wu, et al., 2002)
- Candidate gene in the murine Sle1c lupus susceptibility interval (Boackle, et al., 2001)
- Genetic associations of CR2 haplotypes with SLE
  - Major allele haplotype associated with increased risk of disease \( \left[ P=1 \times 10^{-5}; \text{OR} 1.45 \right] \) (Wu, et al., 2007)
  - Minor allele haplotype associated with decreased risk of disease \( \left[ P=0.016; \text{OR} 0.90 \right] \) (Douglas et al., 2009)
- Causal variants remain elusive

Methodology

- Large Lupus Association Study 2 (LLAS2)
  - 15,750 unrelated case-control subjects
    - European American (EA): 3,872 cases vs. 3,449 controls
    - African American (AA): 1,676 cases vs. 1,929 controls
    - Asian (AS): 1,265 cases vs. 1,260 controls
    - Hispanic (HS): 1,492 cases vs. 807 controls
    - Fine-mapped 57.6kb region spanning ~10kb upstream of CR2 to intron 1 of CR1.
  - Variants subjected to association testing and trans-ancestral meta-analysis

Aims of Current Study

- Fine-map CR2 and surrounding region to identify causal variants.
- Investigate the specific contributions of CR2 to disease development by exploring the association of CR2 polymorphisms with clinical manifestations of lupus.

Disclosures

- Nothing to disclose
**Association of rs1876453 with SLE**

- EA
- AA
- HS
- AS
- Meta

\[ P = 4.2 \times 10^{-4}; OR 0.85 \]

**Strongest Association is with dsDNA Autoantibodies**

- EA
- AA
- HS
- AS
- Meta

\[ P = 7.6 \times 10^{-7}; OR 0.71 \]

**rs1876453 is Located in a Transcription Factor Hot-Spot**

- ENCODE Project: [http://genome.ucsc.edu/encode/](http://genome.ucsc.edu/encode/)

**CCCTC-Binding Factor (CTCF)**

- 11 zinc finger protein
- Multiple functions
  - Regulates transcription
  - Enhancer insulating
  - Multi-protein complexes
  - Long range effects
    - Intra- and inter-chromosome

**Minor (A) Allele Decreases Transcription Factor Binding Affinity**

**Complex C Includes CTCF**

- [Rhonda Mason and Daniela Ulgiati](#)
rs1876453 Alters CTCF Binding

rs1876453 Alters CR1 Expression on Primary B cells

Potential Protective Mechanisms

- CR2-mediated
  - Increased ligand generation
    - Chakravarty et al., 2001
    - Lee et al., 2005
- CR1-mediated
  - Inhibitory receptor
    - Jozsi et al., 2002
    - Kremlitzka et al., 2012

Summary

- rs1876453 is associated with decreased risk of SLE and dsDNA autoantibodies
  - Develop prior to clinical onset
  - Fluctuate with disease activity
  - Directly pathogenic
- rs1876453 is in a transcription factor hot spot
  - Minor allele reduces transcription factor binding affinity, including reduced CTCF occupancy
  - Other transcriptional changes?
- Minor allele is associated with increased CR1 mRNA and protein levels in resting B cells
  - Transcriptional mechanism?
  - Effects on B cell function?

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