

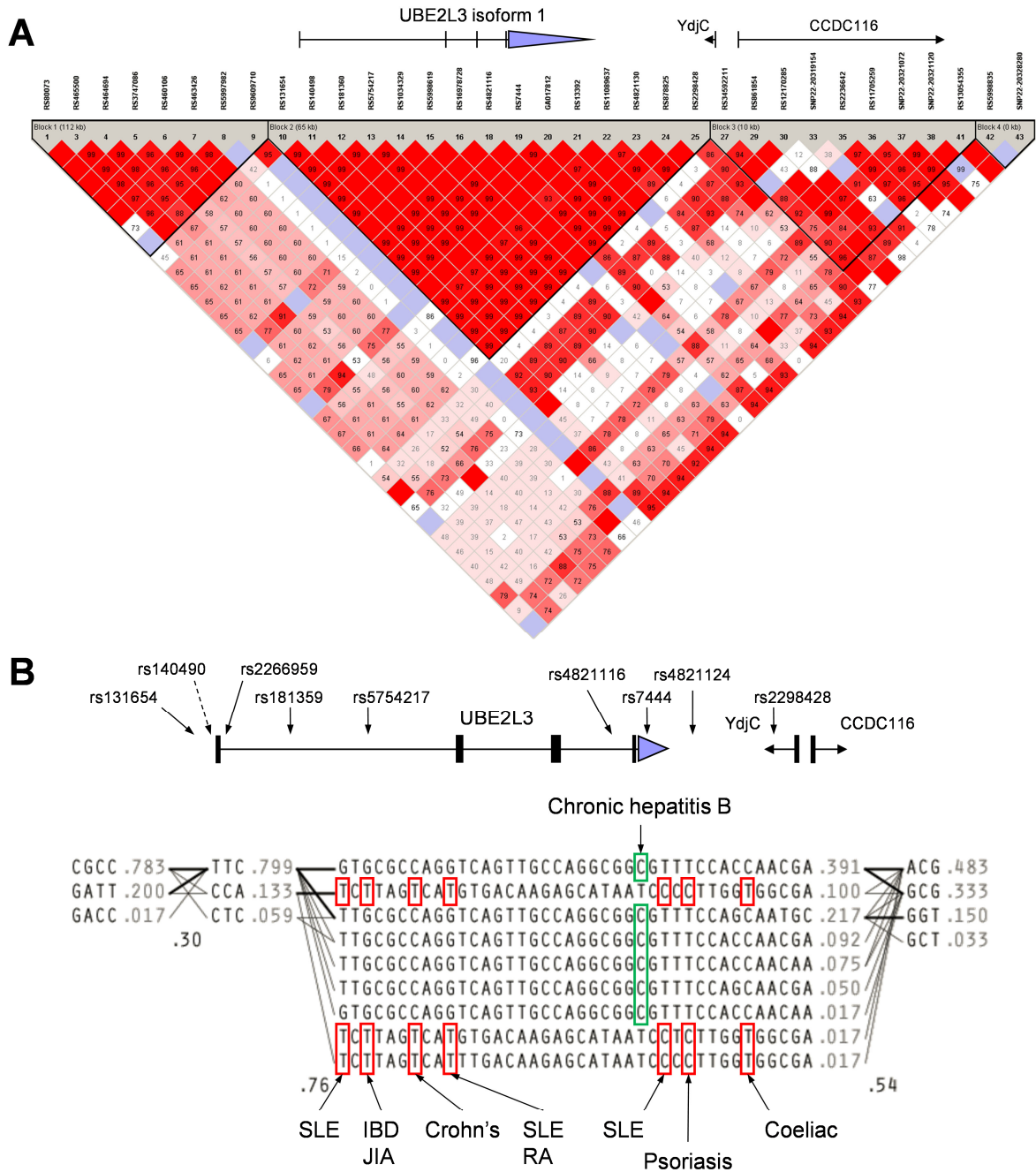
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Supplemental Data

***UBE2L3* Polymorphism Amplifies NF- $\kappa$ B Activation  
and Promotes Plasma Cell Development Linking  
Linear Ubiquitination to Multiple Autoimmune Diseases**

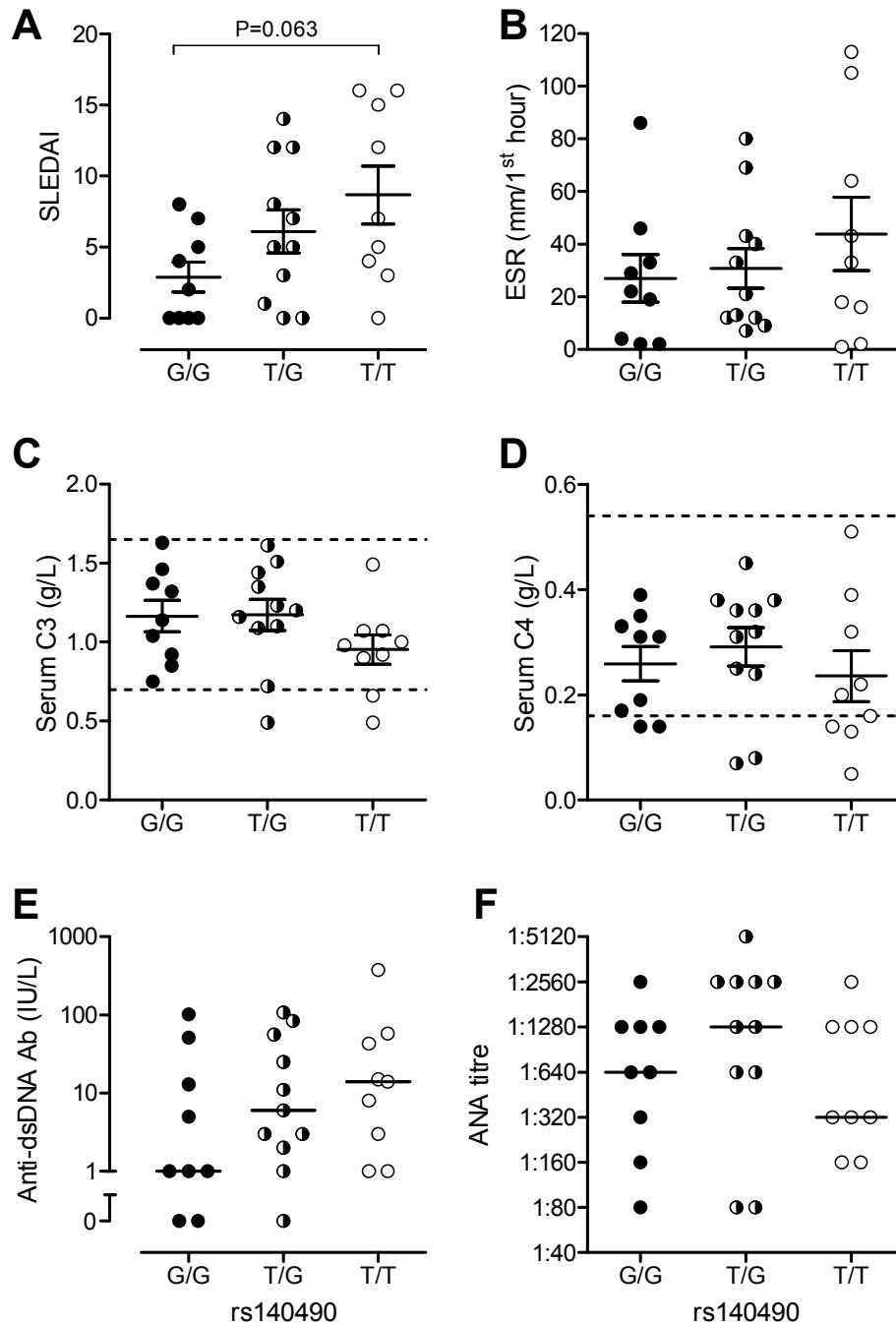
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Supplemental Data



**Figure S1.** Single haplotype at *UBE2L3* is associated with increased risk of multiple autoimmune diseases.

(A) Linkage disequilibrium (LD) plot from haplotype analysis of SLE GWAS SNPs performed in Haploview showing LD encompasses the whole of *UBE2L3*. Squares colored to represent linkage disequilibrium measured as  $D'$ . (B) Haplotype analysis in Haploview showing SNPs from GWAS in multiple autoimmune diseases segregate on the same *UBE2L3* risk haplotype, whereas risk of chronic Hepatitis B carriage is associated with a haplotype which protects against autoimmune disease (SNP highlighted in green).



**Figure S2.** SLE disease activity data in SLE individuals compared with *UBE2L3* genotype. (A) SLE Disease Activity Index (SLEDAI) was recorded for all SLE individuals on the same day that blood was drawn for flow cytometry analysis. (B-E) Blood markers of disease activity measured on the same day as blood samples were drawn for flow cytometry showing (B) Erythrocyte sedimentation rate (ESR), (C) serum complement C3 and (D) C4 levels and (E) anti-dsDNA antibody titer. Dotted lines in (C and D) represent laboratory normal range to show individuals with hypocomplementemia. (F) Maximum anti-nuclear antibody (ANA) titer recorded for each SLE individual as determined by case note review.

**Table S1.** Genetic studies showing an association between *UBE2L3* and autoimmune and infectious diseases.

| SNP        | Risk allele | Disease         | Study design                    | OR (95% CI)      | <i>P</i>               | Reference           |
|------------|-------------|-----------------|---------------------------------|------------------|------------------------|---------------------|
| rs5754217  | G→T         | SLE             | GWAS (SLEGEN)                   | 1.22 (1.14-1.32) | $7.53 \times 10^{-8}$  | Harley et al, 2008  |
| rs131654   | C→A         | SLE             | GWAS                            | 0.78 (0.74-0.83) | $2.99 \times 10^{-16}$ | Han et al, 2009     |
| rs5754217  | G→T         | SLE             | Replication study               | 1.20 (1.13-1.27) | $2.3 \times 10^{-6}$   | Gateva et al, 2009  |
| rs7444     | T→C         | SLE             | Multi-ethnic association study  | n/a              | $2.21 \times 10^{-14}$ | Wang et al, 2012    |
| rs140490   | G→C         | SLE             | GWAS                            | 1.30 (1.21-1.39) | $8.62 \times 10^{-14}$ | Lewis et al*        |
| rs5754217  | G→T         | RA              | GWAS meta-analysis              | 1.10             | $4.8 \times 10^{-5}$   | Stahl et al, 2010   |
| rs11089637 | T→C         | RA              | GWAS trans-ethnic meta-analysis | 1.08 (1.05-1.11) | $2.1 \times 10^{-9}$   | Okada et al, 2014   |
| rs2266959  | T→G         | JIA             | GWAS                            | 1.24 (1.15-1.33) | $6.20 \times 10^{-9}$  | Hinks et al, 2013   |
| rs181359   | G→A         | Crohn's disease | GWAS meta-analysis              | 1.10 (1.06-1.15) | $4.80 \times 10^{-16}$ | Franke et al, 2010  |
| rs2266959  | T→G         | IBD             | GWAS meta-analysis              | 1.11 (1.07-1.15) | $1.39 \times 10^{-16}$ | Jostins et al, 2012 |
| rs2298428  | G→A         | Celiac disease  | GWAS                            | 1.13 (1.08-1.19) | $1.84 \times 10^{-7}$  | Dubois et al, 2010  |
| rs4821124  | T→C         | Psoriasis       | GWAS (ImmunoChip)               | 1.13             | $3.8 \times 10^{-8}$   | Tsoi et al, 2012    |
| rs4821116  | G→A         | Hepatitis B     | GWAS                            | 0.82 (0.77-0.87) | $1.71 \times 10^{-12}$ | Hu et al, 2013      |

\*The present study

**Table S2.** Disease characteristics of SLE individuals analysed by flow cytometry.

| Individual number | Gender | Age | SLE disease characteristics                                 | Serological status                             | Medications           |
|-------------------|--------|-----|---|--|-----------------------|
| 1                 | F      | 41  | Nephritis, hematologic                                      | ANA 1:80, low C3, C4                           | HCQ                   |
| 2                 | F      | 50  | Arthritis, hematologic                                      | ANA 1:1280, RNP, dsDNA, RF                     | HCQ                   |
| 3                 | F      | 38  | Photosensitivity, mouth ulcers, polyarthralgia, lymphopenia | ANA 1:80, Ro                                   | Pred, MTX, HCQ        |
| 4                 | F      | 61  | Arthritis, ILD, lymphopenia, photosensitivity               | ANA 1:80, Ro                                   | Pred, Aza             |
| 5                 | F      | 50  | Arthritis, pleural effusion, ILD, lymphopenia               | ANA 1:160                                      | Pred, Aza             |
| 6                 | F      | 36  | Malar rash, photosensitivity, arthritis                     | ANA 1:640, RNP, dsDNA                          | Nil                   |
| 7                 | F      | 43  | Nephritis   | ANA 1:1280, dsDNA, low C3, C4                  | Ramipril              |
| 8                 | M      | 26  | Malar rash, nephritis                                       | ANA 1:1280, dsDNA, Ro, La, Sm, RNP, low C3, C4 | Pred, MMF, HCQ        |
| 9                 | F      | 51  | Discoid lupus, arthritis                                    | ANA 1:5120, Ro, La, RNP, RF                    | HCQ                   |
| 10                | F      | 51  | Discoid lupus, arthritis, ILD                               | ANA 1:160, Ro, Sm, RNP                         | Pred, MMF             |
| 11                | F      | 39  | Nephritis, alopecia   | ANA 1:2560, Sm, RNP, dsDNA, low C3, C4         | Pred, MMF, Everolimus |
| 12                | F      | 36  | Nephritis, fetal loss                                       | ANA 1:1280, Ro, La, RNP, low C3, C4            | Pred, Aza, HCQ        |
| 13                | F      | 61  | Nephritis   | ANA 1:160, Ro, RF                              | Aza, Pred, HCQ        |
| 14                | M      | 45  | Arthritis, nephritis  | ANA 1:2560, RNP, dsDNA, low C3, C4             | Depomedrone           |
| 15                | M      | 33  | Severe discoid lupus, alopecia, leukopenia                  | ANA 1:1280, dsDNA, Ro, Sm, RNP, low C3         | Pred                  |
| 16                | F      | 46  | TTP, ILD, AVN hip   | ANA 1:1280, RNP                                | Quinine               |
| 17                | F      | 33  | Nephritis   | ANA 1:320, Ro, La, dsDNA, low C3, C4           | Aza, Pred, HCQ        |
| 18                | F      | 52  | Discoid lupus, alopecia, arthritis                          | ANA 1:2560, dsDNA                              | Mepacrine, HCQ, Aza,  |
| 19                | F      | 44  | Malar rash, pleural effusion, pericarditis, ILD             | ANA 1:1280, Ro, RNP, dsDNA, low C3, C4         | Pred, MMF             |
| 20                | F      | 39  | Digital vasculitis with ulceration, retinal vasculitis, PE  | ANA 1:320, Ro, RNP, dsDNA, low C3, C4          | Pred, tacrolimus, MPA |
| 21                | F      | 31  | Discoid lupus, myositis                                     | ANA 1:2560, Ro, Sm, RNP, dsDNA, low C3, C4     | Pred, MMF, HCQ        |
| 22                | F      | 25  | SCLE, nephritis   | ANA 1:640, Ro, Sm, RNP, dsDNA, low C3, C4      | Pred, MTX, HCQ        |

| Individual number | Gender | Age | SLE disease characteristics                                      | Serological status                        | Medications                  |
|-------------------|--------|-----|--|---|------------------------------|
| 23                | F      | 29  | Polyarthritis, photosensitivity, malar rash, alopecia, Raynaud's | ANA 1:320, Ro, Sm, RNP, dsDNA, low C3, C4 | Pred, HCQ                    |
| 24                | F      | 37  | Nephritis  | ANA 1:2560, Ro, RNP, dsDNA, low C3, C4    | Pred, MTX, HCQ, rituximab    |
| 25                | F      | 45  | Autoimmune hepatitis, PHT  | ANA 1:2560, dsDNA                         | HCQ, warfarin, bosentan      |
| 26                | F      | 52  | Inflammatory arthritis   | ANA 1:640, Ro, RNP                        | Pred, MTX, HCQ               |
| 27                | F      | 54  | Thrombocytopenia, anaemia, neutropenia                           | ANA 1:1280, Sm, RNP                       | HCQ                          |
| 28                | F      | 63  | Arthritis, diffuse rash  | ANA 1:640, Ro, RNP                        | Pred, leflunomide, mepacrine |
| 29                | F      | 65  | Polyarthritis, neutropenia                                       | ANA 1:320, dsDNA                          | Pred, HCQ                    |

**Abbreviations:** ILD – interstitial lung disease; TTP – thrombotic thrombocytopenic purpura; AVN – avascular necrosis; PE – pulmonary embolus; SCLE – subacute cutaneous lupus erythematosus; PHT – pulmonary hypertension; Aza – azathioprine; Pred – prednisolone; HCQ – hydroxychloroquine; MTX – methotrexate; MMF – mycophenolate mofetil; MPA – mycophenolic acid.

Serological status was determined by case note review and reports maximal anti-nuclear antibody (ANA) titer, previously documented anti-dsDNA or extractable nuclear antigen (ENA) autoantibody positivity and whether C3 and/or C4 hypocomplementemia were ever observed for each individual.