BACKGROUND
Lupus nephritis affects more than one-half of patients with SLE and is the most common serious manifestation of the disease. Lupus nephritis is more common in Hispanic and African-American patients than in those of European ancestry, and class III and IV nephritis progresses to end-stage renal disease in 10%–15% of patients within 15 years of diagnosis. Identification of markers and mechanisms of lupus nephritis could provide new approaches to predict and treat disease.

METHODS
To identify blood cell transcriptome biomarkers that differentiate renal and non-renal disease we performed RNA sequencing on peripheral blood samples from 15 patients with lupus nephritis and 14 patients with non-nephritis manifestations of SLE (samples represented each patient during flaring and quiescent disease states) and from 5 healthy donors. To relate gene expression to activity of nephritis, 216 longitudinal samples from 30 patients with lupus nephritis covering a median time frame of 28 months were analyzed using the Illumina HT-V4 Bead array. Serum albumin levels were documented at the time of each visit.

RESULTS
Principal component analysis of RNA sequencing data clearly differentiated SLE patients with nephritis from those without nephritis, and linear models for microarray (limma) analysis identified 153 gene transcripts differentially expressed between the two patient groups (fold change >1.5; p<0.05). U1 and U3 RNA transcripts were increased in lupus nephritis samples, and the most highly expressed transcript based on fold change was TREML4, encoding a protein previously identified as amplifying TLR7 signaling and promoting type I interferon production. Analysis of longitudinal microarray data in relation to serum albumin identified 120 transcripts. Those most significantly correlated with lupus nephritis activity were pituitary tumor-transforming gene 1 (PTTG1), recently identified as polymorphic and associated with SLE, uridine cytosine kinase 2 (UCK2), thioredoxin (TXN), and RNASE2. Expression of PTTG1 fluctuated over time, with elevated levels preceding the time of peak renal disease activity.

CONCLUSIONS
Spliceosome-associated RNAs and TREML4, a TLR7-associated gene product, may represent biomarkers of lupus nephritis, and PTTG1, the product of a lupus-associated gene reported to be involved in epithelial-mesenchymal transition, may be a novel therapeutic target associated with active nephritis. These studies provide a rich data set stimulating new understanding of mechanisms contributing to lupus nephritis.

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