CE-47 MOLECULAR IMAGING OF THE KIDNEY IN LUPUS NEPHRITIS TO CHARACTERISE RESPONSE TO TREATMENT

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Background The response of lupus nephritis (LN) to treatment is assessed by clinical criteria, usually proteinuria and renal function, alone. The consequences of treatment for the kidney at the molecular level have not been explored in human LN, but could have important implications for modifying therapy to improve renal outcomes in LN. In this investigation changes in intra-renal transcript expression were measured and correlated with response in a LN cohort that underwent serial kidney biopsies.
Methods SLE patients suspected of having LN had a kidney biopsy for diagnosis (Bx1) and patients with proliferative LN (n = 19) were induced with high-dose corticosteroids plus either MMF or cyclophosphamide. After completing induction therapy, approximately 6 months, patients had a second kidney biopsy (Bx2) to determine histologic response to therapy. Intra-renal transcript expression was measured in Bx1 and B × 2 using Nanostring technology and a panel of over 500 immune response genes. Patients were segregated by clinical response at 6 months into group of complete responders (n = 5, CR) and a group of non-responders (n = 4, NR). Changes in transcript expression were compared between Bx1 and B × 2 in each responder group and between responder groups.
Results Compared to healthy control kidneys (pre-implantation living donor transplant kidney biopsies, n = 4), the CR group had 21 differentially-expressed transcripts at B × 1 and 28 at B × 2. In contrast the NR had 45 and 103 differentially-expressed transcripts at B × 1 and B × 2, respectively, compared to controls. The profiles of these differentially-expressed genes indicated that the type 1 interferon, the alternative complement and T cell signalling pathways discriminated CR from NR. At B × 1 transcripts regulated by type 1 interferon were over-expressed in CR and NR. During induction therapy the expression of type 1 interferon-inducible genes declined in CR but increased in NR, and additional type 1 genes were activated. Similarly, complement component transcript expression was increased at B × 1 in CR and NR and transcripts for regulators of the alternative pathway were suppressed in NR. At B × 2, these complement transcripts normalised in CR, but increased expression in NR. Transcripts related to T cell signalling became overexpressed at B × 2 in NR; this occurred to a lesser extent in CR. To determine whether changes in intra-renal transcript expression translated to changes in protein expression that could be measured non-invasively, complement component C5a was measured in the urine of an independent cohort of LN patients (n = 34). Urine C5a concentration was significantly higher than normal in CR and NR at LN flare. After treatment urine C5a fell significantly in CR, but remained elevated in NR.
Conclusion These data demonstrate that activity of intra-renal inflammatory genes induced at LN flare begins to fall in patients who respond clinically to induction therapy, but increases in patients who do not respond. The functional profiles of the protein products of these transcripts suggest that non-responders may benefit from interventions targeted at the type 1 interferon, alternative complement and T cell signalling pathways.

CE-48 RESIDENTIAL PROXIMITY TO HIGHWAYS, DNA METHYLATION AND SYSTEMIC LUPUS ERYTHEMATOSUS

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Background Systemic lupus erythematosus (SLE) is a heterogeneous disease in which epigenetic and environmental risk factors have been implicated. DNA methylation can be influenced by environmental exposures. Exposure to motor vehicle emissions has been linked to increase in overall mortality, asthma and increase incidence of rheumatoid arthritis. The focus of this study was to evaluate methylation changes in relationship to residential proximity to highways in patients with SLE.
Materials and methods We studied 307 patients with SLE who were previously enrolled in a Lupus Genetics Project. As a replication cohort, 225 participants from a gene-environment study of asthma were studied. Residence at the time of blood draw was recorded and geocoded. The distance to the nearest roads from the geocoded locations were calculated for the four major Tele Atlas Feature Class Codes (FCC) road classes. The Geographic Data Technology, Inc. (GDT) road network data were used for these calculations. Genome-wide methylation profiling was performed using the Illumina Infinium HumanMethylation 450 BeadChip.
Results Patients residing within a 300 metre radius from a major highway were defined as at high risk for significant hazardous health outcomes[1]. Thirty-eight patients (12.4%) were residing in a high risk area. Multivariate analysis did not reveal any

Abstract CE-48 Table 1 Methylation differences between patients who resided in a high risk vs low risk area

Site	Chr	Gene	Pathway	P value
cg11167637	1	*UBE2U*	Ubiquitin-Conjugating Enzyme E2U	9.7 E-09
cg21204139	1	*UBE2U*	Class I MHC mediated antigen processing and presentation	1.6 E-08
cg26317111	1	*UBE2U*		1.8 E-07
cg02696670	1	*UBE2U*		2.2 E-07
cg11244180	1	*UBE2U*		3.2 E-07
cg12405788	17	*AMAC1L3;ZBTB4*	Acyl-malonyl condensing enzyme 1-like 3	4.3 E-07
cg07455318	14	*CCBC88C*	DAPLE	1.8 E −06
			Negative regulator of the Wnt signalling pathway	

statistically significant association between proximity to highways and disease phenotypes, however there was a trend for higher incidence of discoid rash (OR 1.5) neurological disorders (OR 1.4) and antiphospholipid antibodies (1.4). Analysis of genome-wide methylation data revealed 3 methylation sites that were significantly hypomethylated in patients who resided in a high risk zone (P value < 1.7 E-07, Table 1). These three sites belonged to a single gene, *UBE2U,* which encodes one of the E2 enzymes involved in the ubiquitination of proteins and histones, as well as DNA repair. To replicate these findings, CpG Sites for all the *UBE* gene family were analysed in a control group. Our 3 top hits were not replicated, however one CpG site (cg22352634) belonging to the first intron of the gene *UBE2U* was found hypomethylated in controls who resided in a high risk zone, with a p value of 0.0044.

Conclusions Hypomethylation of *UBE2U* was associated with residing close to a highway in our SLE patients, however this was not seen in a control cohort, and suggesting increased susceptibility for exposures in patients with SLE. Additional work is warranted to confirm these findings, examine other potentially relevant exposures, and determine whether these epigenetic changes are associated with increased UBE2U expression.

CE-49 RHEUMATIC AND NON-RHEUMATIC AUTOIMMUNE DISEASES IN SLE OFFSPRING

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Background Autoimmune diseases (AID) have familial aggregation and frequently share a common genetic predisposition. Only few small uncontrolled studies have evaluated the risk of AID in SLE offspring, with inconsistent results. In a large population-based study, we aimed to determine if children born to mothers with SLE have an increased risk of rheumatic and non-rheumatic AID compared to children born to mothers without SLE.

Materials and methods The "Offspring of SLE mothers Registry (OSLER)" includes all women who had ≥1 hospitalisation for delivery after SLE diagnosis, identified through Quebec's universal healthcare databases (1989–2009). OSLER also includes a randomly selected control group of women, matched at least 4:1 for age and year of delivery, who did not have a diagnosis of SLE prior to or at the time of delivery. We identified children born live to SLE mothers and their matched controls, and ascertained rheumatic (i.e. juvenile idiopathic arthritis, SLE, systemic sclerosis, Sjögren's disease, inflammatory myositis, systemic vasculitis) and non-rheumatic (i.e., type 1 diabetes, inflammatory bowel disease, psoriasis, celiac disease, autoimmune thyroid disease, myasthenia gravis, multiple sclerosis) AID based on ≥1 hospitalisation or ≥2 physician visits with a relevant diagnostic code, at least 2 months apart but within 24 months. The study interval spanned from birth to the first of the following: event of interest, age 18, death, or end of study. We performed multivariate analyses to adjust for maternal age, education, and ethnicity, as well as calendar year of birth and sex of the child.

Results 509 women with SLE had 719 children, while 5824 matched controls had 8493 children. Mean follow-up was 9.1 (SD 5.8) years. Compared to controls, children born to mothers with SLE had similar records of rheumatic diagnoses [0.14% (95% CI: 0.01, 0.90) vs 0.19% (95% CI: 0.11, 0.32)]. However, there was a trend towards more non-rheumatic AID in offspring of mothers with SLE versus controls [1.11% (95% CI: 0.52, 2.27) vs 0.48% (95% CI: 0.35, 0.66)]. The most frequently observed non-rheumatic AID were Crohn's disease (0.56% in SLE offspring, versus 0.19% in control children) and type 1 diabetes (0.42% in SLE offspring, versus 0.22% in control children).

In multivariate analyses, children born to mother with SLE had a substantially increased risk of non-rheumatic AID compared to controls (OR 2.62, 95% CI: 1.10, 6.24), while results were inconclusive for the risk of rheumatic AID (OR 0.78, 95% CI: 0.10, 5.92).

Conclusions Our novel data suggest that, compared to children from the general population, children born to women with SLE have an increased risk of non-rheumatic AID. Our effect estimate for the risk of rheumatic AID is inconclusive. Further study of these children, throughout late childhood, adolescence, and adulthood, would be additionally enlightening.

CE-50 NOVEL INFORMATICS APPROACHES TO AUTOMATE CASE-IDENTIFICATION OF LUPUS IN AN ELECTRONIC HEALTH RECORD

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Background Electronic health records (EHRs) can play an important role in generating data on the natural history, treatment, and outcomes of systemic lupus erythematosus (SLE). A key issue in using EHRs for SLE research is accurately identifying populations of patients with the disease. This is especially important because traditional definitions that rely on coding systems such as ICD9 have had poor specificity in previous studies. We aimed to develop and test disease classification algorithms to define a population with SLE in the EHR. We analysed both traditional definitions that used structured data (ICD-9 codes, medications, laboratories) and machine learning algorithms that used the entirety of information in the EHR, including unstructured data from clinical notes.

Materials and methods We created a repository of patients with possible SLE (based on relevant ICD-9 codes, positive auto-antibodies, and/or mention of "SLE" or "lupus" in the text of a clinical note). We combined 300 patients from that repository with 1000 randomly selected adult patients in our EHR as our training set. These patients were reviewed by domain experts for a diagnosis of SLE and confirmed cases were used as a gold standard for training our machine learning algorithms. We calculated the test characteristics for various definitions of SLE using only structured data. Finally, we compared this to a series of supervised machine learning algorithms based on support vector machines (SVMs) that used text features extracted from clinical notes in addition to structured fields. All SVM algorithms were trained and validated using 10-fold cross-validation.

Results One hundred thirty-seven patients met criteria for SLE. The test characteristics of both the structured and supervised ML algorithms are shown in the Table 1. A single ICD-9 code for 710.0 had a precision/positive predictive value of 79%. In contrast, machine learning algorithms greatly outperformed structured definitions in terms of precision, with precision/positive