908 THE ASSOCIATION BETWEEN SYSTEMIC LUPUS ERYTHEMATOSUS (SLE) AND BONE MINERAL DENSITY (BMD) POLYGENIC RISK SCORES WITH LUMBAR SPINE BMD Z-SCORE: A RETROSPECTIVE COHORT STUDY

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10.1136/lupus-2022-lupus21century.59

Background Systemic lupus erythematosus (SLE) is a chronic autoimmune disease. Genetics play a role in SLE susceptibility, with >100 risk single nucleotide polymorphisms (SNPs) from genome wide association studies (GWAS). Approximately 20% of SLE patients have childhood- onset SLE (cSLE) diagnosed <18 years. These patients are at risk for reduced bone mineral density (BMD) due to disease activity and chronic glucocorticoid exposure. Our aim was to assess the genetic contribution to bone mineral density among a multi-ethnic cohort of patients with cSLE.

Methods All patients were diagnosed and followed for cSLE at the SickKids Lupus Clinic. Patients were genotyped on the multiethnic Multiethnic Genotyping Array or the Infinium Global Screening Array. Those with baseline Lumbar Spine (LS) BMD dual-energy X-ray absorptiometry (DXA) scan were included in analysis. Baseline was defined as 1 month prior, or up to one year after cSLE diagnosis. Patients with bony abnormalities and with DXA scans due to medical conditions other than SLE were excluded. We extracted demographics, clinical features, and medication use from the Lupus database. The main outcome of interest was LS (L1-L4) BMD z scores. Two weighted polygenic risk scores (PRSs) were calculated. 1.) BMD PRS was calculated using alleles associated with low LS from the largest LS BMD meta-GWAS of BMD to date. 2.) SLE PRS was also calculated using one of the largest SLE GWAS. We regressed BMD and SLE PRSs with baseline BMD z-scores in linear models adjusted for sex, ancestry, glucocorticoid exposure, height percentile, and an indicator for lupus nephritis and/or neuropsychiatric lupus.

Results Our study included 285 patients, 82% female, 30% of European and 28% of East Asian ancestry. The median age of cSLE diagnosis was 13.3 years [IQR 10.8, 15.1]. In univariate and multivariate adjusted models, a higher BMD PRS was significantly associated with low BMD z- score (β: -0.73; 95% CI: -1.30, -0.16; P = 0.01, multivariable model). Using steroids prior to DXA was significantly associated with low BMD at a univariate level but was not significant in the adjusted model. Height percentile was significantly associated with BMD z-score (β: 0.01; 95%CI: 0.01, 0.02; P=5.09e-10), yet the presence of LN and/or NPSLE was not (β: 0.06; 95% CI: 0.21, 0.33; P=0.67).

Conclusions Our study found that a low-BMD PRS was significantly associated with lower LS BMD z-score in cSLE patients at baseline. BMD PRS may be used to stratify patients with cSLE who are at greatest risk of reduced BMD. We hope to expand this to long term LS BMD z-scores and explore BMD PRS predicts long term BMD z scores among cSLE patients.

Lay Summary Systemic lupus erythematosus, commonly known as lupus is chronic, life-threatening autoimmune disease. Up to 20% of all people with lupus are diagnosed during childhood. Treatment for lupus involves long-term steroids which can have devastating impacts on children's bones. However, different people respond differently to steroid treatment, with some patients having more severe negative side effects than others. We aimed to explore the genetic basis of bone mineral density (BMD) in children and adolescents diagnosed with SLE. We calculated genetic risk scores for: 1. low bone density (BMD); 2. Lupus risk. We tested the association between these genetic risk scores and BMD in a multiethnic group of children and adolescents with lupus. We found that genetics for low bone density was significantly associated with lower bone density in these lupus patients within 1 year of lupus diagnosis. This was true even when we accounted for steroid exposure and the presence of kidney and/or brain involvement. Our work has the potential to identify lupus patients at high risk of developing low bone density.

Genetics

909 HAPLOTYPE-SPECIFIC CHROMATIN LOOPING REVEALS GENETIC INTERACTIONS OF REGULATORY REGIONS MODULATING GENE EXPRESSION AT THE SLE SUSCEPTIBILITY LOCUS *FAM167A-BLK*

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10.1136/lupus-2022-lupus21century.60

A major goal of genetics research is to elucidate mechanisms explaining how genetic variation contributes to phenotypic variation. The genetic variants identified in genome-wide association studies (GWASs) generally explain only a small proportion of heritability of phenotypic traits, the so-called missing heritability problem. Recent evidence suggests that additional common variants beyond lead GWAS variants contribute to phenotypic variation; however, their mechanistic underpinnings generally remain unexplored.

Herein, we undertake a study of haplotype-specific mechanisms of gene regulation at 8p23.1 in the human genome, a region associated with a number of complex diseases. The *FAM167A-BLK* locus in this region has been consistently found in the genome wide association studies (GWASs) of systemic lupus erythematosus (SLE) in all major ancestries. Our haplotype-specific chromatin interaction experiments, allele-specific enhancer activity measurements, genetic analyses and epigenome editing experiments revealed that: (1) haplotype-specific long-range chromatin interactions are prevalent in 8p23.1; (2) *BLK* promoter and *cis*-regulatory elements cooperatively interact with haplotype-specificity; (3) genetic variants at distal regulatory elements are allele- specific modifiers of the promoter variants at *FAM167A-BLK*; (4) the *BLK* promoter interacts with and, as an enhancer-like promoter, regulates *FAM167A* expression and (5) local allele-specific enhancer activities are influenced by global haplotype structure due to chromatin looping.