Objectives: To explore potential mechanisms for the SLE related IRF7 SNP on type I IFN production, which might indicate new theoretical basis for genetic therapeutic strategy.

Methods: We constructed different genotypes of SLE relevant SNP cell lines by Crispr/Cas9 technology, and confirmed them by sequencing. After TLR-ligand stimulation, the mRNA expression of IFN α was detected by real-time qPCR. The levels of IFN α , TNF α and IL-6 were detected by ELISA kit. The protein expression of IRF7/p-IRF7 was detected by western blot. The binding ability of endogenous IRF7 with type I IFN promoter was studied by chromatin immunoprecipitation.

Results: We got IRF7 SNP rs1131665 GG/AA cell lines by gene editing technique. After TLR-ligand stimulation, IRF7 SNP rs1131665 AA cell line showed higher IFN α expression than GG, which indicated statistical significance. IRF7 SNP rs1131665 AA cell line showed higher p-IRF7 expression than GG detected with western blot. Endogenous IRF7 in IRF7 SNP rs1131665 AA cell line showed stronger binding ability with IFN α promoter than GG, which indicated statistical significance.

Conclusion: The missense variant of G to A in IRF7 SNP rs1131665, increased the production of type I IFN, which indicated that IRF7 G to A missense variant increased the susceptibility of type I IFN associated diseases.

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analysis demonstrated how a SNP highly correlated with the PsA lead variant is found within an open, active region of chromatin in the HaCaT cell line, shifting the priority from the (statistical) lead variant (rs11121129) to rs11121131 – demonstrating the value of this type of analysis (fig 2).

Conclusion: A region associated with PsA on chromosome 1p36, previously annotated with the TNFSF9/ERF1/SLC45A1 gene, makes robust interactions with the PARK7 and ERF1 genes, both strong candidates for causality in disease. An associated variant, within a cell type relevant enhancer, is currently being targeted with genome editing technology (CRISPR) to assess its potential for causality and possible mechanism.

Fig1

Fig2

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FRI0004

CHROMATIN INTERACTIONS IN NOVEL CELL TYPES REVEAL PARK7 AND ERRF1 AS PUTATIVE CAUSAL GENES IN THE SUSCEPTIBILITY TO PSORIATIC ARTHRITIS

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Background: One of the major tasks post-GWAS is to link disease associated single nucleotide polymorphisms (SNPs) to their causal genes. Unexpectedly the vast majority of disease associated SNPs lay outside protein coding regions of the genome, often in gene regulatory regions, known as enhancers. These enhancers operate by physically interacting with their target genes, often over long distance, and often skipping genes. We, and others, have demonstrated how these enhancer interactions can change with different cell type and stimulatory conditions. In psoriatic arthritis, as with all complex diseases, there are a large number of genetic loci implicated in susceptibility to disease, but relatively few of these regions have confirmed causal genes.

Objectives: Map disease associated enhancers to potential causal genes through physical chromatin interactions in relevant, novel cell types.

Methods: We used Capture HiC (Chi-C) technology to map enhancer to promoter interactions in both a keratinocyte cell line (HaCaT) and a T cell line (MyLa) in biological duplicate. We generated Hi-C libraries and enriched them for autoimmune-associated GWAS loci using RNA baits. The resultant Chi-C libraries underwent high-throughput sequencing generating 75 bp paired-ends. Significant interactions were detected using CHICAGO.

Results: A region on chromosome 1p36 demonstrated markedly differential interactions between the T cell line (MyLa) and the skin cell line (HaCat). Here the enhancer region containing SNPs associated with PSA demonstrated a strong interaction with both the PARK7 and ERF1 genes in HaCaT cells, absent in the MyLa cell line (fig 1). These interactions were contained within a functionally relevant topological activation domain (TAD) boundary, enriched for enhancer to promoter links. Bioinformatic

FRI0005

CHROMATIN CONTACTS AND TRANSCRIPTOMICS IN CD4+ T-CELLS REVEAL GENES IMPLICATED IN RHEUMATOID ARTHRITIS

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Background: Rheumatoid arthritis (RA) is a chronic autoimmune disease characterized by inflammation of synovial joints. RA is a clinically heterogeneous disease and treatment response varies between individuals. The pathogenesis of RA is not completely understood yet, but it has been