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RNA editing underlies genetic risk of common inflammatory diseases

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A major challenge in human genetics is to identify the molecular mechanisms of trait-associated and disease-associated variants. To achieve this, quantitative trait locus (QTL) mapping of genetic variants with intermediate molecular phenotypes such as gene expression and splicing have been widely adopted[1,2]. However, despite successes, the molecular basis for a considerable fraction of trait-associated and disease-associated variants remains unclear[3,4]. Here we show that ADAR-mediated adenosine-to-inosine RNA editing, a post-transcriptional event vital for suppressing cellular double-stranded RNA (dsRNA)-mediated innate immune interferon responses[5–11], is an important potential mechanism underlying genetic variants associated with common inflammatory diseases. We identified and characterized 30,319 *cis*-RNA editing QTLs (edQTLs) across 49 human tissues. These edQTLs were significantly enriched in genome-wide association study signals for autoimmune and immune-mediated diseases. Colocalization analysis of edQTLs with disease risk loci further pinpointed key, putatively immunogenic dsRNAs formed by expected inverted repeat *Alu* elements as well as unexpected, highly over-represented *cis*-natural antisense transcripts. Furthermore, inflammatory disease risk variants, in aggregate, were associated with reduced editing of nearby dsRNAs and induced interferon responses in inflammatory diseases. This unique directional effect agrees with the established mechanism that lack of RNA editing by ADAR1 leads to the specific activation of the dsRNA sensor MDA5 and subsequent interferon responses and inflammation[7–9]. Our findings implicate cellular dsRNA editing and sensing as a previously underappreciated mechanism of common inflammatory diseases.

Genome-wide association studies (GWAS) have led to the discovery of hundreds of thousands of risk variants involved in trait and disease aetiology, but understanding their molecular function remains an ongoing challenge. QTL studies, best exemplified by gene expression QTLs (eQTLs), have been successful in bridging GWAS variants to their molecular mechanisms[1,2]. Alternative splicing QTLs (sQTLs) have further expanded discovery of these mechanisms[12]. However, other post-transcriptional processes, such as RNA editing, remain largely unexplored, despite the increasing appreciation of their important functions in health and disease[10,13,14].

One of the most abundant RNA modifications is adenosine-to-inosine (A-to-I) RNA editing catalysed by adenosine deaminases acting on RNA (ADARs) that bind to dsRNA substrates and convert adenosines to inosines[5]. As inosine is recognized as guanosine, RNA editing events can be accurately identified and quantified by standard RNA sequencing, unlike most other RNA modifications[15]. Previous studies have identified millions of RNA editing sites in humans, more than 99% of which are located in inverted repeat *Alu*s (IR*Alu*s) that form dsRNA substrates[16–18]. Key to editing in mammals are two enzymatically active ADAR proteins, ADAR1 and ADAR2, which have distinct physiological functions in vivo[19]. ADAR1, which is ubiquitously expressed across human tissues, has a critical role in suppressing dsRNA sensing that is mediated by MDA5, a cytosolic sensor of 'non-self' dsRNA[7–9] (Fig. 1a). Mice deficient in ADAR1 editing are embryonic lethal due to elevated innate immune responses indicated by the induction of interferon-stimulated genes (ISGs), but can be rescued to full life span when *Mda5* is knocked out[8]. In humans, *ADAR1* loss-of-function and *MDA5* gain-of-function mutations have been identified in rare autoimmune diseases such as Aicardi–Goutieres syndrome[6,20], further establishing the ADAR1–dsRNA–MDA5 axis as an underlying mechanism in immune disease (Fig. 1a). Protective, loss-of-function alleles in *MDA5* have also been found in GWAS of common inflammatory diseases such as type 1 diabetes[21,22], psoriasis[23], inflammatory bowel disease (IBD)[24], vitiligo[22,25], vitamin B_{12} deficiency anaemia[26], hypothyroidism[22] and coronary artery disease (CAD)[22,26]. Furthermore, aberrant editing has been reported in several common autoimmune diseases, including psoriasis, rheumatoid arthritis, systemic

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