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Genomics

# Genetic variants that edit risk of immune disease

**Kaur Alasoo**

A process called A-to-I RNA editing helps to prevent unwanted immune responses. Associations between genetic variants and this type of RNA editing now provide mechanistic insights into the genetic basis of autoimmune diseases. **See p.569**

The genetic variants that increase the risk of disease do so by exerting effects on RNA. Variants can alter the amount of RNA produced from a given gene. They can alter the transcribed RNA sequence itself, leading to changes either in the amino-acid sequence of the encoded protein or in how much of the RNA is removed through 'splicing' before it is translated into protein. Finally, variants can influence whether RNA molecules undergo A-to-I RNA editing[1] — a process in which a subunit of RNA is changed from adenosine (A) to inosine (I). On page 569, Li *et al.*[2] present a comprehensive analysis of the effects of genetic variants on A-to-I RNA editing. Their work provides new insights into the mechanisms by which genetic variants mediate the risk of some immune-related diseases.

A-to-I RNA editing disrupts the formation of double-stranded RNA molecules. These molecules occur naturally, either when both a protein-coding gene and its complementary DNA are transcribed and the transcripts form a duplex, or when non-coding, repetitive transcripts form duplexes with themselves. Conversion of A to I by the enzyme ADAR disrupts the RNA duplex. But unedited RNA duplexes are bound by the sensor protein MDA5 which, by mistaking them for viral RNA, triggers an immune reaction against the body's own cells that can lead to autoimmune disease (Fig. 1).

The extent to which variation in RNA editing, mediated by genetic variation, affects the risk of autoimmune diseases has been unclear. Although this question has been touched on before[3], Li and colleagues took a broader approach, studying genomes and RNA sequences from 49 human tissues from 838 people, using data from a project called GTEx (ref. 4). The authors analysed how patterns of RNA editing varied between individuals, to identify *cis* genetic variants (those located close to editing sites) that are associated with RNA editing. These variants are dubbed editing quantitative trait loci (edQTLs).

**"The study highlights the importance of considering all possible mechanisms by which a genetic variant might influence disease risk."**

The researchers found that the edQTLs are largely different from the variants that regulate gene expression or splicing. They are clustered in specific genomic features, such as regions that encode A-to-I editing sites, and the authors provide evidence that the variants might alter the strength with which ADAR can bind to RNA.

Li *et al.* next examined the overlap between their edQTLs and variants that other studies have associated with autoimmune and immune-mediated diseases. They found that, in general, edQTLs associated with decreased levels of RNA editing confer a higher-than-average risk of autoimmune and immune-mediated diseases. This directionality contrasts with the behaviour of risk variants for these diseases that alter gene expression and splicing. Such variants can either increase or decrease protein function, depending on the part that the protein plays in the disease.

Finally, the authors zoomed in to identify specific edQTLs that bring about disease-associated changes in editing, and found that 33% of these genomic regions encode proteins. It is intriguing to think that, at these loci, it might not be changes in the function of the protein that contributes to disease risk (as is often assumed to be the case), but rather the formation of double-stranded RNA that leads to activation of the innate immune system. The function of the encoded protein might even be completely irrelevant for the disease.

However, individual genetic variants often have effects on multiple genes, as well as on different layers of regulation (that is, on expression, splicing and editing). Although the authors used careful analysis to try to reduce such confounding factors, they cannot be completely avoided. For example, around 20% of the genetic variants associated with changes in RNA editing were also associated with altered gene-expression levels or splicing. This means that, for any given locus, it is difficult

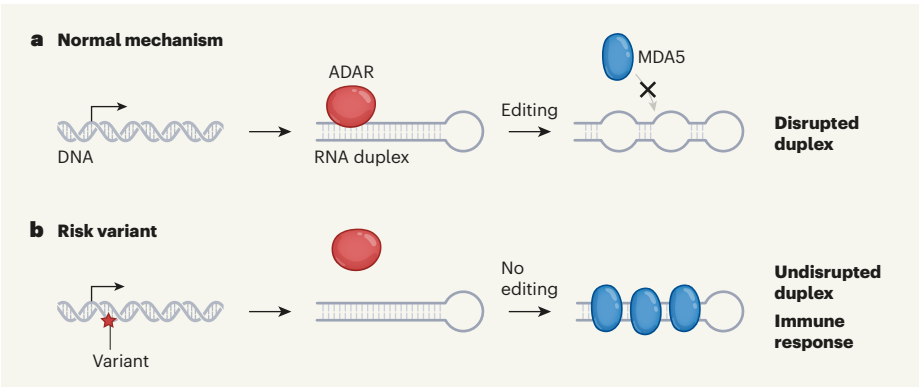


**Figure 1 | Varying risk for autoimmune disease. a**, Some regions of the genome give rise to RNA that forms a double-stranded duplex. This RNA can be edited by the enzyme ADAR, which converts a subunit of the RNA called adenosine into inosine (not shown), disrupting the duplex and preventing the viral-sensor protein MDA5 from binding. **b**, Li *et al.*[2] provide evidence that some genetic variants are associated with lower levels of this type of RNA editing, perhaps because ADAR does not bind the RNA so strongly. Unedited RNA duplexes are bound by MDA5, which wrongly recognizes the RNA as 'non-self' and triggers immune responses. Thus, these genetic variants are also associated with a higher risk of developing some immune-related diseases.

to demonstrate with certainty that disease risk is mediated through one specific type of regulation. Further complicating matters, many genetic effects on gene expression or splicing are restricted to highly specific cell types or cell states[5]. Consequently, variants that seem to be specifically associated with RNA editing in the GTEx data set might turn out to control gene expression or splicing in cell types not included in GTEx, such as immune cells.

Because Li and colleagues focused on *cis* variants, a key next question is whether *trans* variants, which have broad effects on RNA editing across the genome, might also have a part to play in the risk of autoimmune disease. If so, does this effect involve innate immune activation triggered by the formation of double-stranded RNA, as the authors propose for *cis* edQTLs? Perhaps large-scale meta-analyses of genomes and RNA sequences such as those conducted by the eQTLGen consortium[6] could help to provide an answer.

Li and colleagues' study reaffirms the value of open data sharing — this work would not have been possible without publicly available data sets. At the same time, it highlights the limitations of current data-sharing systems. Although smaller data sets covering immune cell types exist (for example, those documented in refs 7 and 8), obtaining access to many smaller studies is a bureaucratic maze that few are willing to navigate. To increase the pace of science, researchers need to come up with mechanisms to reduce these administrative hurdles while protecting the privacy of study participants.

Li and colleagues' study highlights the importance of considering all possible mechanisms by which a genetic variant might influence disease risk, and raises the intriguing prospect that at some loci, the genetic effect might be entirely mediated by RNA. Although these individual loci probably have small effects on disease risk, more loci are likely to be discovered as autoimmune genetic studies increase in scale. Thus, researchers and clinicians should be mindful of this possibility when prioritizing new therapeutic targets for autoimmune disease.

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Palaeoceanography

# Plate tectonics lets the ocean breathe

**Katrin J. Meissner & Andreas Oschlies**

Variations in ocean oxygen levels during Earth's history have been linked to evolution and mass extinctions. Simulations now suggest that the configuration of the continents has a substantial impact on ocean oxygenation. **See p.523**

On page 523, Pohl *et al.*[1] present simulations of ocean states spanning the past 540 million years — the first study to systematically investigate ocean circulation and oxygenation changes over such a long time frame. They find that changes in the configuration of the continents alone can generate large variations in deep-ocean (benthic) oxygenation through changes in ocean circulation. The simulations were conducted using present-day levels of atmospheric oxygen, and demonstrate that benthic oxygen records of the past are not a reliable proxy for ancient atmospheric oxygen concentrations. Moreover, under certain continental arrangements, the authors' simulations produce self-sustained oscillations of ocean oxygen levels on timescales of several thousand years.

Oxygen is a prerequisite for the evolution of complex organisms, and essential for those that have aerobic metabolisms. Although today's atmospheric oxygen levels are more than sufficient to sustain multicellular life on land, many regions in the present-day ocean are starved of oxygen. Global warming will lead to further ocean oxygen loss, a situation that has precedence in Earth's history — there is evidence for previous large-scale deoxygenation events[2,3], some of which are thought to have caused mass extinctions[4].

**"The study highlights the complexity of the processes that can affect ocean oxygenation."**

Seawater oxygen levels depend on a series of complex biological, chemical and physical processes. The oxygen is supplied through photosynthesis and air–sea gas exchange in the surface layer, and consumed by the breakdown (respiration) of organic matter by microorganisms, both at the surface and in the dark ocean interior. Sea-surface oxygen concentrations are largely controlled by the temperature-dependent solubility of oxygen in seawater. Wherever sea-surface waters are carried to the deep ocean, they initially retain the oxygen levels associated with the surface temperature. In the ocean interior, oxygen concentrations then decline along the flow of the water, because the oxygen is increasingly consumed as a result of bacterial respiration of organic matter sinking from biomass produced at the surface.

Ocean circulation controls the period of time that waters spend in the deep ocean without contact with the atmosphere; during this time, they continuously lose oxygen through respiration. Circulation also controls the supply of nutrients to the surface ocean — and thus the productivity of marine phytoplankton and the amount of organic matter available for respiration. Changes in ocean circulation, and the resulting effects on oxygen supply and consumption, are thought to be a dominant mechanism for the ocean deoxygenation that has been observed during the past few decades[5,6].

Pohl *et al.* simulated the global ocean at 28 points in time, producing a snapshot every 20 million years. Two series of simulations were generated, one with constant global mean surface air temperatures and another with constant greenhouse-gas concentrations. In both series, the authors used the continental configuration appropriate for each time point, but kept solar luminosity, atmospheric oxygen levels and the ocean's nutrient inventory the same. Their approach was therefore not designed to reconstruct climate and ocean oxygen concentrations to match current best knowledge of the prevailing conditions, but to estimate the impact of ocean circulation on oxygen levels through time.

The simulations show that surface oxygen concentrations are mostly temperature-driven, with cold waters being more oxygenated than warm waters. Changes in oxygen concentrations in the subsurface (around 90–190 metres depth in their study) are influenced by biological activity, with high production rates at the