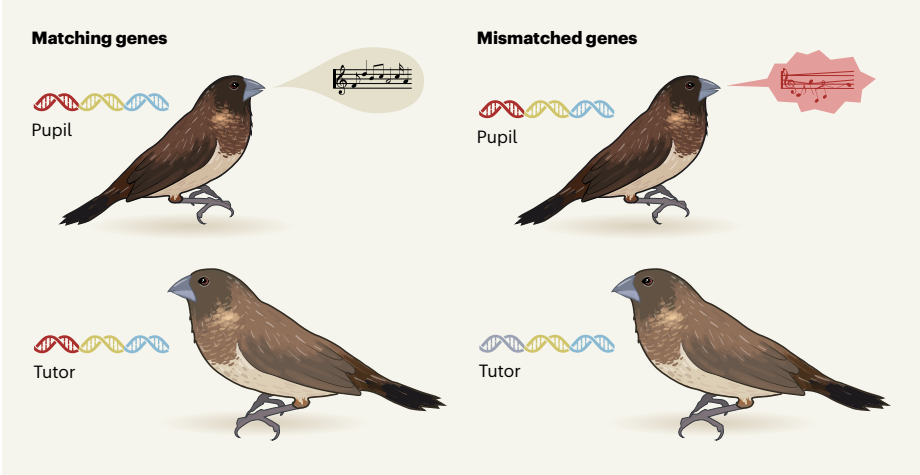

Figure 1 | How genetics and teaching style intersect. Mets and Brainard[1] show that a songbird's ability to learn depends on whether its genetic propensity for learning matches that of its tutor. Birds genetically predisposed to sing at a fast tempo (DNA beginning with the red section) learn best from birds that also have a genetic propensity to sing fast, and birds predisposed to sing at a slow tempo learn best from slow-singing birds (not shown). Poor singers are the result of a mismatch between the gene sets that determine singing speeds in the tutor and pupil.

genes and experience explains much of the variation in learning outcomes. It seems that certain birds are genetically tuned to learn and produce slow songs, whereas others are wired for fast songs. Giving a 'slow' bird a fast tutor does him or her no favours; the same is true in reverse (Fig. 1).

To rule out the possibility that the results reflected a difference in how fathers behaved towards their own offspring as opposed to their fostered tutees, Mets and Brainard reran the experiment using a computer-based tutoring system. As shown previously, when all birds were tutored with a standard synthetic song, there was a strong genetic variability in learning propensity. The authors demonstrated that those genetically predisposed to acquire a song with a tempo similar to that of the synthetic song learnt much better than 'faster' and 'slower' birds. Varying the tempo to match the tempo characteristic of the bird's biological father improved learning.

It might be imagined that the most brilliant birds would be able to learn at any tempo, whereas others would learn well only when tutored at a slow tempo. But Mets and Brainards' results demonstrate that this is not the case. Most remarkably, birds that were genetically tuned to sing slowly were not inherently worse learners. In fact, they often learnt better than the fast birds once the tutoring tempo 'resonated' with them.

The authors' results indicate that, if we can work out how to match genetic predisposition and 'tutoring' style among humans, we might be able to enhance learning for children. Indeed, some observational results in humans suggest that there is an interaction between the polygenic score for education of a child and that of their mother[7] — high polygenic scores for both mother and child are associated with higher educational achievement than is a high score for the child or the mother alone. Of course, in extreme cases, some children (and birds) might be inherently worse learners, no matter to whom they are matched.

It is difficult to be a child in today's super-competitive world. Mets and Brainard's results raise the possibility that even a modest mismatch between tutoring pace and genetics can hamper learning. Of course, we do not yet have a good way to discover how interactions between a person's genes and their environment will affect learning[8,9]. But it is imperative to ensure that human genetics studies of learning are sufficiently nuanced, and acknowledge the huge effect of the environment — including the possibility that a child might be in the wrong learning environment for their genes.

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Immunology

One ring to rule them all

Ferenc Livak & André Nussenzweig

Distant DNA regions are juxtaposed and joined to form diverse immune-system genes encoding antibodies and T-cell receptors. It seems that both types of gene form by relying on DNA extrusion through a protein ring called cohesin. **See p.385**

Our ability to fight the multitude of potential disease-causing agents that we encounter depends on a process called recombination, which can occur in different ways. Recombination manipulates DNA sequences to enable our bodies to generate an enormous diversity of the immune system's recognition components: antibodies and T-cell receptors (TCRs). Two papers in *Nature* from the same laboratory, by Zhang *et al.*[1] and Zhang *et al.*[2] (page 385), reveal an unexpected similarity in how these types of recombination event occur.

In developing immune-system cells, a process called V(D)J recombination rearranges DNA sequences to assemble genes that will encode either an antibody or a TCR, using a large pool of three classes of gene segments, termed V, D and J. These gene segments are flanked by evolutionarily conserved DNA sequences called recombination signal sequences (RSSs), which direct the enzyme RAG to join together one V segment and one J segment, and sometimes also one D segment, in an astonishing variety of combinations. The intervening DNA between these joined segments is usually deleted, although in rare instances it is instead inverted and retained when two gene segments are joined. This recombination process enables antibodies and

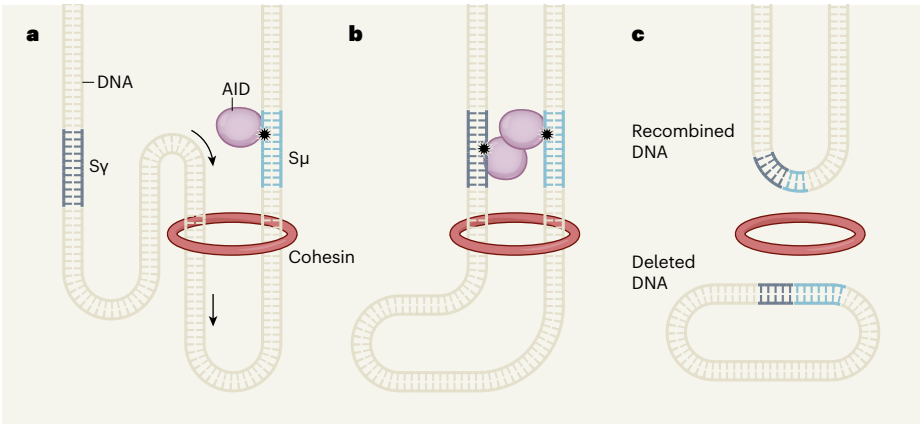

Figure 1 | DNA-loop extrusion aids a process called class-switch recombination. Zhang *et al.*[2] report that a DNA rearrangement called class-switch recombination (CSR), which helps to generate antibodies that have different functions, depends on DNA extrusion through a ring formed by the cohesin protein complex (the extruded DNA is in the form of a DNA–protein complex called chromatin, which is not shown). **a**, During this process, the enzyme AID binds to an antibody-encoding DNA segment called a switch region (Sμ) to drive the mutation and subsequent breakage (black star) of part of the DNA. Motor components of cohesin drive DNA extrusion (arrows) through the cohesin ring. **b**, This enables the alignment of two antibody switch regions (Sμ and Sγ) that undergo AID-mediated DNA mutation and breakage. **c**, This is followed by the joining (recombination) of the two switch regions, which switches the encoded antibody's class. The intervening DNA is deleted from the chromosome during the recombination process. DNA extrusion through a ring of cohesin also underlies the regulation of gene expression and, as reported by Zhang *et al.*[1], another type of recombination process in immune-system cells called V(D)J recombination.

TCRs to have diverse protein domains called variable domains, which recognize protein fragments called antigens. It is this diversity in antigen-recognition domains that allows the immune system to respond effectively to a variety of disease-causing agents.

The genes encoding antibodies can sometimes undergo further refinements that change single DNA nucleotide bases (generating what are known as somatic point mutations) to boost an antibody's ability to recognize antigens. The DNA in these genes can also go through a series of alterations, called antibody class-switch recombination (CSR), that do not affect antigen recognition – instead, they endow the antibody with diverse effector functions, such as the ability to bind to mucosal surfaces or to help other immune cells tackle the infection.

V(D)J recombination is initiated by RAG, whereas somatic point mutations and CSR in antibody-encoding sequences are initiated by a DNA-mutating enzyme called AID. The potential power of RAG and AID to cause widespread alterations to the genome is dangerous, so their action needs to be limited to the target sequences at which DNA alterations can be exploited for host defences.

The DNA–protein complex chromatin, which is tightly packaged inside the nucleus of human cells, forms thousands of loops of varying size that are anchored at their base by the ring-like structure of a protein complex called cohesin[3]. These loops form when a molecular-motor component of cohesin actively extrudes chromatin through the cohesin ring until chromatin hits a 'roadblock'. This probably forms before or when chromatin enters the ring, and typically if DNA has bound to the protein CTCF. Cohesin-dependent extrusion of large loops partitions chromatin into discrete regions known as topologically associated domains, and smaller loops enable regulatory DNA sequences, such as enhancers and promoters that are located far apart in the linear DNA sequence, to be placed next to each other to drive gene expression. Zhang and colleagues' work[1,2] shows that chromatin-loop extrusion also underlies the control of both V(D)J recombination and CSR (Fig. 1).

During V(D)J recombination, RAG is recruited to modified DNA-binding histone proteins that accumulate at high levels in a small region of the chromosome containing antibody- or TCR-encoding J genes. This generates a VDJ recombination centre[4], at which RAG binds the RSS motifs that flank the J gene segments. RAG then scans the rest of the chromosome in a linear fashion to locate the RSS of another, more distant gene segment[5]. Once compatible RSSs are aligned, RAG introduces DNA breaks to initiate recombination between these two RSSs. RAG is anchored in the VDJ recombination centre, which raises the question of how DNA moves during this scanning process.

Zhang *et al.*[1] realized that chromatin-loop extrusion might explain this DNA movement. In this model, after cohesin has assembled in the VDJ recombination centre with an RSS-bound RAG, cohesin 'reels' DNA through its ring, enabling the RSSs in the loop to possibly find a compatible RSS bound to RAG with which to recombine (see Supplementary Video 1 in ref. 1). This model is supported by the authors' experiments, including their demonstration that blocking DNA movement through the cohesin ring biases recombination events to favour recombination targeting RSSs near the site where DNA movement was impeded. Importantly, the directional DNA-scanning mechanism in this model also explains the overwhelming predominance of deletion rather than inversion events during V(D)J recombination, which has long been an unexplained conundrum. Together with earlier studies[6] demonstrating that cohesin-binding elements (DNA motifs next to certain antibody V gene segments) are major determinants of DNA-rearrangement patterns, and the resulting antibody repertoires, a convincing model emerges that chromatin-loop extrusion aids V(D)J recombination.

CSR is a conceptually similar, although enzymatically distinct, process to V(D)J recombination. Zhang *et al.*[2] investigated whether cohesin-driven extrusion of DNA loops also underlies CSR. During CSR, AID introduces multiple point mutations of DNA nucleotide bases in specific 'switch regions' in antibody-encoding genes, which eventually leads to DNA breaks[7]. Unlike V(D)J recombination – in which RAG-mediated cleavage of DNA depends on the assembly of a pair of compatible RSSs – AID causes mutations at individual DNA sites that can lead to DNA breakages before or after the alignment of the switch regions that will subsequently join together[7].

The authors propose that, analogous to events that occur in a VDJ recombination centre, a CSR centre forms over one particular switch region (called Sμ) in an antibody-encoding gene. Previous studies[7] favoured diffusion as the mechanism leading to the alignment of DNA during class switching, whereas Zhang and colleagues' work supports the idea that cohesin-based loop extrusion aligns the two switch regions to enable their recombination (Fig. 1). These two studies thus offer compelling evidence for a unified model for V(D)J recombination and CSR. It also links these processes to gene-expression regulation, on the basis of the dynamic modulation of chromatin architecture.

This model offers testable predictions and raises numerous questions. For example, how is cohesin recruited to VDJ and CSR recombination centres? Cohesin depletion from particular cellular lineages causes defective V(D)J recombination[8], and cohesin loss eliminates all loops across chromosomes[9]. However, the effect of such alterations on CSR remains to be determined.

Loop extrusion generates torsional stress in DNA[10], and cohesin recruits the enzyme topoisomerase IIB to relieve this stress by transiently breaking DNA[10]. Therefore, reeling in DNA to regulate gene expression or

to enable recombination-based immune diversification might drive a type of chromosomal abnormality known as a chromosomal translocation, which could lead to cancer. Much like the DNA loops themselves, these insights into the role of chromosomal architecture might help to reveal connections between areas that were previously considered to be separate.

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High-energy physics

Link between antimatter and dark matter probed

Gianpaolo Carosi

Ultrasensitive experiments on trapped antiprotons provide a window onto possible differences between matter and antimatter. Now they could also shed light on the identity of dark matter — the 'missing' mass in the Universe. **See p.310**

Two of the most intriguing mysteries in modern cosmology are the apparent preponderance of ordinary matter over antimatter and the nature of dark matter, which accounts for about 85% of the mass in the Universe[1]. Dark matter has made its presence known only through its gravitational effects on astrophysical objects. Therefore, whatever type of particle it is made of must have feeble interactions with other matter. One leading candidate is the axion — a light neutral particle that was originally postulated to explain why the neutron lacks a measurable electric dipole moment[2]. Until now, researchers have looked for evidence of couplings between axion dark matter and only ordinary particles such as photons, electrons and nuclei[3,4]. On page 310, Smorra *et al.*[5] report a search for a coupling between axion dark matter and antimatter (specifically, antiprotons).

Every known particle can be classified as either a boson or a fermion. Bosons have integer spin (intrinsic angular momentum), and include the (spin-1) photon and the (spin-0) Higgs boson. By contrast, fermions have half-integer spin, and include the (spin-1/2) electron. The axion is expected to be a spin-0 boson that has odd parity, which means that its wavefunction changes sign if spatial coordinates are flipped.

Unlike fermionic dark matter (such as dark-matter candidates called weakly interacting massive particles, WIMPs), there is no limit to the number of axions that can exist in a certain volume of space. As a result, axion dark matter has an extremely wide range of potential masses. Astrophysical measurements place an upper limit[6] on the mass of about 10^{-2} electronvolts (eV). This value is expressed in units of energy, in which the electron mass is 511 kiloelectronvolts and the proton mass is 938 megaelectronvolts (see go.nature.com/2bwkrqz). And a lower limit[7] of about 10^{-22} eV comes from the fact that, when these particles are described as waves in quantum mechanics, their wavelengths cannot be larger than the size of a dwarf galaxy — otherwise, such galaxies would show deviations from their observed structure.

The particles associated with axion dark matter can be thought of as classical waves that have an oscillation frequency directly proportional to the axion mass. There are several techniques that can be used to look for such waves, and the most appropriate one depends mainly on the frequency range that is being considered. For axions that have masses below 10^{-17} eV (corresponding to a frequency of tens of millihertz), the waves oscillate extremely slowly. If antiprotons are held in the strong magnetic field of a device known as a Penning trap, these waves will produce changes in the frequency at which the spins of the antiprotons precess.

The Baryon Antibaryon Symmetry Experiment[8] (BASE) at the European particle-physics laboratory CERN near Geneva, Switzerland, uses this technique. The BASE collaboration relies on ultrasensitive Penning traps, which use specialized configurations of magnetic and electric fields to trap antiprotons in a high-vacuum environment. This set-up allows the antiprotons to be measured continuously for long periods of time, and to be shuttled back and forth between different measurement chambers without running into ordinary matter and being annihilated. One of the main

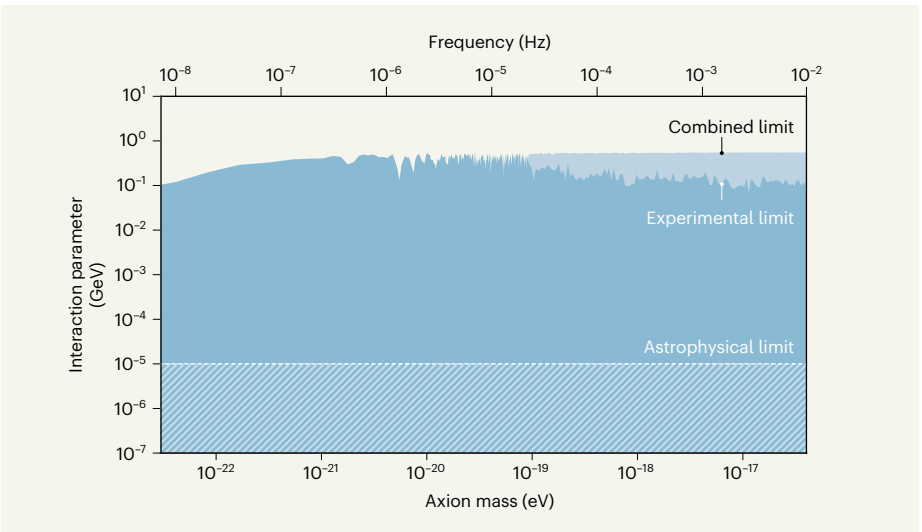

Figure 1 | Constraining axion–antiproton interactions. Particles called axions could account for the elusive dark matter that pervades the Universe. Smorra *et al.*[5] present experimental limits on the coupling between axion dark matter and antiprotons. These bounds are expressed in terms of an axion–antiproton interaction parameter and vary with the axion mass or the frequency of the axion if the particle is represented as a wave (eV, electronvolts; GeV, gigaelectronvolts; Hz, hertz). The combined limit represents the strongest constraint that could be set by the experimental data. An astrophysical limit, as estimated by the authors, is included for comparison. The coloured and hatched areas show the parameter space that is excluded.