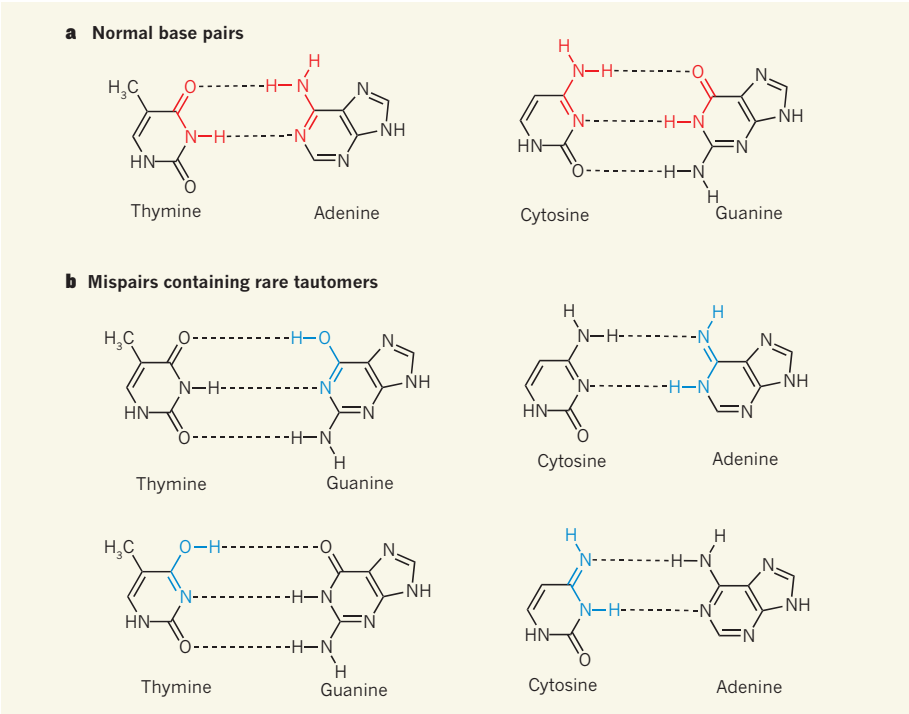

Figure 1 | Base-pair structures in DNA. **a**, The double-helix structure of DNA is held together by specific interactions (dotted lines) between pairs of bases: adenine (A) pairs with thymine (T), and guanine (G) pairs with cytosine (C). **b**, The DNA bases form rare isomeric structures known as tautomers, which can allow the formation of mispairs; bonds shown in blue are the tautomeric forms of the bonds shown in red in **a**. Kimsey *et al.*[1] have detected tautomeric G·T mispairs in DNA duplexes, and conclude from modelling studies that this explains the frequency with which G·T is misincorporated into DNA during DNA duplication by polymerase enzymes — as proposed[3] by Watson and Crick in 1953.

of manganese(II) ions, which are known to cause mutations. A second X-ray structure[10] reported that year identified an ionized G·T mismatch, also formed between substrates bound by DNA polymerase. In both cases, the mismatched pairs had the same geometry as Watson–Crick pairs.

In Watson and Crick's model for mutagenesis, the rare occurrence of disfavoured tautomeric bases could account for the observed frequency with which DNA polymerases produce mismatches (about one per thousand to one per million base pairs formed[11]). But such tautomers and the associated base pairs were thought to be almost impossible to detect in duplexes. Then, in 2015, 62 years after the mutagenesis model was proposed, researchers from the same group as Kimsey *et al.* reported a tour de force of experimental work: they used nuclear magnetic resonance (NMR) spectroscopy to identify[12] a long-lived wobble G·T structure that was in a dynamic equilibrium with transient, rarely formed G·T mispairs associated with disfavoured tautomers, and with ionized $G{\cdot}T^{-}$ structures, both of which have Watson–Crick geometry.

The first step of the DNA-synthesis process that forms a G·T pair is the binding of dGTP (a G-containing nucleotide) in the polymerase's active site. This is followed by the enzyme's catalytic step, in which the DNA is elongated through incorporation of a new G·T base pair. Once dGTP is bound in the active site, the base pair formed between dGTP and T on the complementary strand assumes a distorted wobble conformation, but seemingly cannot make the conformational transition needed for the catalytic step[10].

Kimsey and colleagues' current study goes straight to the heart of the mutagenesis model by integrating structural analysis of G·T base pairs in duplexes with measurements of the kinetics of DNA polymerase reactions and computer modelling to show that tautomerism does indeed account for the misincorporation of base pairs. To ensure efficient catalysis, DNA polymerases require optimal geometrical alignment of nucleotide substrates with amino-acid residues in their active site[13,14]. Such alignment can occur when G·T adopts one of its Watson–Crick-like structures (one of the disfavoured tautomeric forms, or the ionized structure[15]). Kimsey *et al.* deduced from their studies that, at neutral pH, at least 99% of G·T misincorporation is attributable to the formation of G·T tautomers — rather than of the ionized structure — from an initially bound G·T wobble pair.

By successfully identifying a role for the disfavoured tautomeric forms of G·T in base-pair misincorporation, Kimsey and colleagues have solved half of the mystery of spontaneous mutagenesis. A solution for the other half now requires the disfavoured tautomeric forms of C·A to be characterized in duplexes and correlated with the rate of C·A misincorporation. So far, NMR and X-ray data have identified only charged $C{\cdot}A^{+}$ wobble structures in a DNA duplex[7,8].

A related challenge would be to establish the mechanism by which 2-aminopurine, a base analogous to both adenine and guanine, induces mutagenesis. For example, 2-aminopurine is a potent mutagen of the virus bacteriophage T4, for which it increases the frequency of A·T to G·C mutations (and of the reverse G·C to A·T mutations) to 10–50 times the frequency of spontaneous mutation levels[16]. If 2-aminopurine was found to undergo a tautomeric shift much more frequently than A, it would implicate tautomerization in the mechanism, and thus provide the icing on the cake for the tautomerization model of mutagenesis. ■

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CORRECTION

The News & Views 'Strategy for making safer opioids bolstered' by Susruta Majumdar and Lakshmi A. Devi (*Nature* **553,** 286–288; 2018) incorrectly stated that more than 100,000 adults suffer from chronic pain in the United States. The correct figure is more than 100 million adults.