Inherited epimutation or a haplotypic basis for the propensity to silence?

To the Editor:

Chan and colleagues report a kindred in which a specific haplotype at the *MSH2* locus is associated with mosaic promoter hypermethylation and cancers suggestive of hereditary nonpolyposis colorectal cancer (HNPCC)[1]; they describe this as an example of germline epimutation similar to that which we and others have reported in another DNA mismatch repair gene, *MLH1* (refs. 2–6). We have followed the terminology of Holliday[7] in defining epimutation as epigenetic (transcriptional) silencing of a gene that is normally active[3]; epimutation may occur in the soma or the germline and is often accompanied by hypermethylation (the term may also be applied to activation or hypomethylation of a normally silent sequence[8]). The phenomena described by us and by Chan *et al.* seem to share an association between promoter hypermethylation in normal tissues and the risk of developing cancers with defective DNA mismatch repair. However, we suggest that what Chan and colleagues have found is distinctly different from the germline epimutation of *MLH1*, although no less interesting. Our conclusion rests on two features of the *MSH2* epimutation: its mosaicism with prominent tissue specificity and its strong heritability.

In the *MLH1* germline epimutations reported thus far, the epimutation appears to be present in nearly all somatic cells; we described the epimutation as mosaic only because it was absent from occasional somatic alleles[3]. In the kindred reported by Chan and colleagues, however, the mosaicism is prominently tissue specific: only the rectal mucosa shows a high proportion of cells carrying the epimutation. The authors propose that the *MSH2* epimutation is a germline event and that somatic reversion has produced the tissue-specific pattern, but the evidence seems insufficient for this conclusion. It would be helpful to know more about the tissue distribution of the *MSH2* epimutation—in particular, whether it is found in cells derived from all three germ layers. The tissue specificity of the epimutation in this unusual kindred seems consistent with somatic acquisition of a mosaic epigenetic state.

It is striking that the *MSH2* epimutation appears to be inherited in a mendelian pattern: all individuals carrying the at-risk haplotype also have the epimutation. This is in sharp contrast to the *MLH1* epimutation, which has occurred on multiple haplotypic backgrounds and seems to be only weakly heritable[2–6]. In the ten cases known to us, there is only one example in which the epimutation was transmitted to a proband's child[6] (in another case, the epimutation was present in a low proportion of spermatozoa[3]). In all other cases where the affected allele was transmitted, it no longer carried the epimutation. Thus, whereas the *MLH1* epimutation is not linked to a specific genotype and is clearly prone to reversion in the germline, the *MSH2* epimutation appears to be inherited in lockstep with the underlying haplotype. We suggest that the *MSH2* haplotype in this kindred predisposes in *cis* to somatic hypermethylation; the pattern is mosaic and tissue specific perhaps because of specific chromatin characteristics of the *MSH2* locus in some tissues.

We have proposed that the *MLH1* epimutation is an accident conditioned by the presence of epigenetically silent material (heterochromatin) in the germline[3] and that any genomic sequence is potentially subject to this process, which can create the equivalent of a temporary loss-of-function mutation. The *MSH2* epimutation may be something quite different: a haplotype that is prone to somatic hypermethylation in certain cell types (quite likely not limited to rectal mucosa). In essence, Chan *et al.* may have found an allele prone to spontaneous somatic epigenetic silencing similar to that which occurs in the *FMR1* promoter when it carries an expanded triplet repeat[9] and similar to other examples such as position-effect variegation. This view explains the strong heritability and tissue variability of the effect: it may be conditioned by the genetic structure of the allele and also by tissue-specific chromatin structure at the *MSH2* locus.

The study of mammalian epigenetic inheritance is in its infancy (if it can be said to have been born at all). Compared with the routine predictability of mendelian inheritance, epigenetic effects are diverse, because epigenetics involves not only DNA sequence but also a variety of often unstable accretions to the DNA. We suggest that the phenomenon described by Chan *et al.* is distinct from germline epimutation as seen in *MLH1*. This does not make it any less significant, but the distinction illustrates the difficulties that will inevitably arise as we attempt to classify and analyze a complex and poorly understood system of inheritance.

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COMPETING INTERESTS STATEMENT
The authors declare no competing financial interests.

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Heritable germline epimutations in humans

To the Editor:

Epigenetic marks such as DNA methylation and histone modification allow the transmission of gene activity states from one cell to its daughter cells. A fundamental question in epigenetics is whether these marks can also be transmitted through the germline. If so, an aberrant epigenetic mark (epimutation) acquired in one generation could be inherited by the next generation. Although observations in other species suggest that transgenerational epigenetic inheritance might occur in humans as well, evidence for this is scanty. Two recent reports in *Nature Genetics* claim to have identified germline epimutations in humans. Suter *et al.*[1] describe two individuals with multiple cancers who have soma-wide, allele-specific, mosaic hypermethylation of the DNA mismatch repair gene *MLH1*. Chan *et al.*[2] describe a single three-generation family with hereditary colon cancer and soma-wide, allele-