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EPIGENETICS

Patterns of inheritance

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URLs

MLH1
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=gene&cmd=Retrieve&dopt=full_report&list_uids=4292

HNPCC
http://www.ncbi.nlm.nih.gov/entrez/dispomim.cgi?id=120435

MSH2
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=gene&cmd=Retrieve&dopt=full_report&list_uids=4436

Hypermethylation of a gene, a common epigenetic modification (epimutation), is associated with transcriptional silencing and can predispose to cancer or other diseases. Robyn Ward and colleagues have found evidence of the germ-line transmission of an *MLH1* (a mismatch repair gene) epimutation that causes cancer susceptibility. However, the inheritance pattern is non-Mendelian.

Both epimutations and germ-line sequence mutations in *MLH1* cause susceptibility to hereditary nonpolyposis colorectal cancer (HNPCC). Although epimutations usually arise somatically, eight cases of germ-line *MLH1* epimutations have been reported previously, but in these cases there was no evidence of intergenerational transmission. However, because germ-line *MLH1* epimutations exist, it implies that they could be inherited.

To test this possibility, Ward and colleagues identified two other individuals with *MLH1* epimutations and studied their families. To find these individuals, the authors examined the methylation of the *MLH1* promoter in 24 patients who had colorectal or endometrial cancer before the age of 50 years and who lacked *MLH1* and *MSH2* (another mismatch repair gene implicated in HNPCC) sequence mutations. They identified two unrelated women, Patient A and Patient B, who had dense methylation, and therefore transcriptional silencing, of one *MLH1* allele in all somatic cells. An analysis of nine first-degree relatives of these patients showed that one of Patient A's four sons had methylation of *MLH1* consistent with germ-line transmission. However, his sperm did not carry *MLH1* methylation, indicating that the inherited *MLH1* epimutation had reverted to normal during spermatogenesis. To complicate matters further, haplotype mapping of the methylated allele carried by Patient A showed that two of her other sons and her sister also carried the same allele, but it was not methylated.

There are several possibilities for why this pattern of inheritance might have occurred. Epimutations might be more efficiently erased during spermatogenesis than during oogenesis. Another possibility is that epimutations are erased during gametogenesis, but re-established owing to *cis*- or *trans*-acting genetic factors. Regardless, these data imply that the inheritance of epigenetic mutations can predispose to cancer risk.

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ORIGINAL RESEARCH PAPER Hitchins, M. P. *et al.* Inheritance of a cancer-associated MLH1 germ-line epimutation. *N. Engl. J. Med.* **356**, 697–705 (2007)
FURTHER READING Gosden, R. G. & Feinberg, A. P. Genetics and epigenetics — nature's pen-and-pencil set. *N. Engl. J. Med.* **356**, 731–733 (2007)