which expressed myogenin protein under the control of the Myf5 promoter, had normal ribs[5], suggesting that the proteins were functionally equivalent, and that gene duplication served to provide expression of the transcription factor in the different tissues[6]. Apparently, the value of the gene duplication is to provide expression of one family member in rib primordia.

Likewise, the different tenascins may serve similar functions, with the different family members serving primarily to expand expression. Although *TNC* and *TNX* are both expressed in skin, tendons and ligaments, their more detailed expression pattern is frequently reciprocal, rather than overlapping[7]. This is certainly the case in skin, where *TNC* expression is found at the dermal-epidermal junction, and strong *TNX* expression, deeper in the dermis. The finer distribution of the tenascins in tendons and ligaments has yet to be elucidated. However, the tenascins here have more complicated structures than small transcription factors. Each tenascin has multiple domains, sometimes in different numbers, so it is quite possible that some of these domains have acquired functions specific to each family member. Knock-in experiments should eventually determine whether TN-X protein could be replaced by TN-C protein, if it were expressed under control of the *TNX* promoter. Analogous experiments to those described above should help to elucidate their functional relationships.

It has frequently been found that deletion of one member of a gene family may produce no apparent phenotype, while deletion of another yields a pronounced phenotype. This seems to be the case with the tenascin family. Recent reports of the *TNC*-knockout mouse suggest altered dopamine transport and behavioural deficits, but only in certain genetic backgrounds[8]. No detectable change was found in matrix structure, healing of skin wounds or severed nerves[2,9]. A preliminary analysis of $TNR^{-/-}$ mice revealed no obvious phenotype[10], and $TNC^{-/-}TNR^{-/-}$ double-mutants also showed no immediately obvious effect (R. Faessler, pers. comm.). TN-X deficiency in humans appears to have a more significant consequence. But one should not, of course, conclude that TN-X is the only important tenascin. TN-C, -R and -X are conserved in all vertebrates, suggesting that each subserves a critical function[11]. This may be subtle rather than vital, but nonetheless contributes to survival of the organism.

As to the future? Obviously, more patients will be sought with similar genetic deletions of *TNX*, but a *TNX* mouse knockout is also an item for Santa's list. Then the real quest can begin—for information that allows us to pin down the role of tenascin X at the cellular and molecular level; information that may also provide insight into the elusive phenotypes of the *TNC* and *TNR* knockout mice. □


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# *Mom1* leads the pack


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The cloning of genes whose germ-line mutations confer an inherited predisposition to cancer represents a quantum leap in facilitating our ability to explore the molecular events that lead to tumour formation. They also open the door to improved genetic counselling, early diagnosis and prevention strategies.

Confounding our understanding of gene action, however, is the wide spectrum of disease phenotypes observed in individuals with the same mutation of the same gene. Examples abound. A large variety of colonic and extracolonic lesions have been observed in related APC patients with the same mutation[1]. A family study has revealed that there is no correlation beween the type of mutation in *BRCA1* and age at diagnosis[2]; furthermore, the disease phenotype varies considerably between families carrying the same *BRCA1* mutation[3]. In families with neurofibromatosis, a disorder resulting from mutations in one of two genes, the high phenotypic correlation observed between monozygotic twin pairs decreases by degree of relationship within the same family[4]. Clearly, the clinical outcomes of several familial cancer syndromes cannot be explained solely in terms of the disease-gene mutation. Accruing evidence indicates that in addition to environmental and epigenetic factors, phenotypic variation is also due to the expression of genes that modify the cancerous phenotype— cancer modifier genes. Without candidate loci to test, however, identification of cancer modifier loci in humans is an extremely difficult task, requiring linkage studies of large and fully phenotyped pedigrees of individuals who carry specified disease mutations. Suitable animal models represent a means by which to identify such cancer modifier genes, the first of which is convincingly underscored by Robert Cormier and colleagues on page 88 of this issue[5].

Evidence for the existence of cancer modifier loci had previously been obtained in rodent models, characterized for their genetic susceptibility to spontaneous and induced tumour formation. Crosses between susceptible and resistant strains led to the conclusion that susceptibility is a dominant, or a co-dominant trait. However, in a few cases, this kind of cross resulted in tumour-resistant progeny, as was the case in a pioneering study published in 1942 (ref. 6). This phenomenon

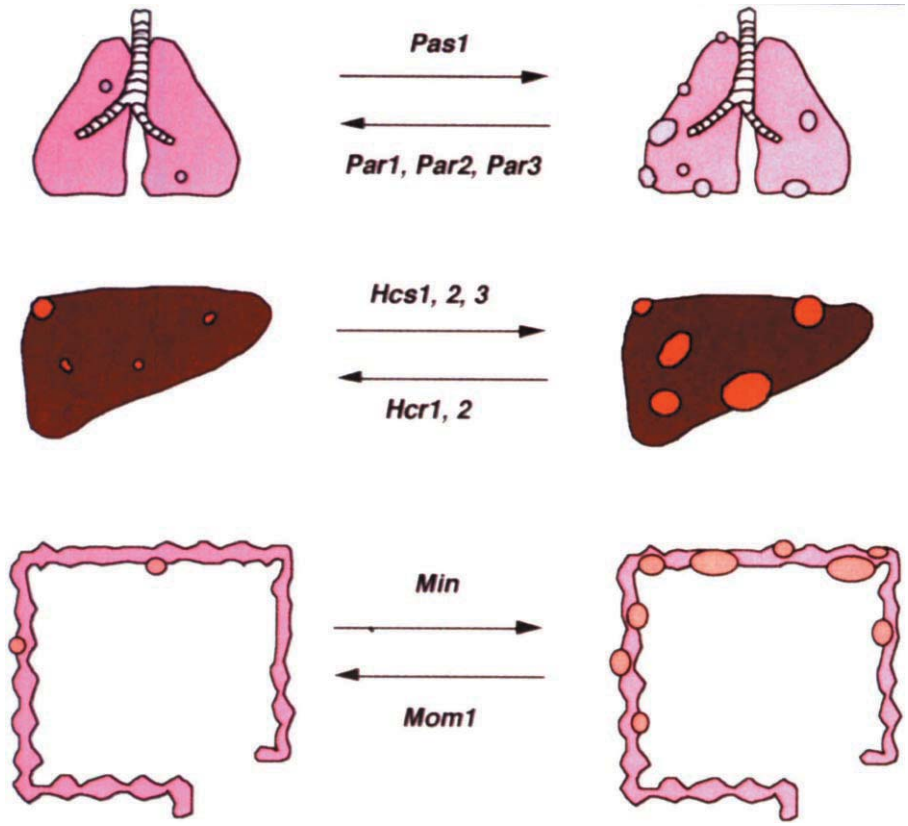


**Fig. 1** Tumour resistance genes act as modifiers of genes that predispose towards tumour multiplicity, and/or growth, partially suppressing their effects.

is also observed in mouse models of lung carcinoma, where the tumour-promoting effect of the *Pas1* locus[7] is down-regulated by the presence of the *Par* resistance loci[8,9] (Fig. 1). Loci that modify each other in a reciprocal, counteracting fashion have been reported to impact the incidence of mouse lung tumours[10].

Modifier loci also affect tumour growth. For example, the COP rat is resistant to mammary tumour growth; it carries a dominant locus[11] that confers resistance to tumour growth, rather than interfering with the initiation step[12]. A similar situation is observed in the liver, where tumours presumed to arise as a consequence of the hepatocarcinogen sensitivity locus, *Hcs*, are discouraged from growing by coincident presence of resistance (*Hcr*) loci (Fig. 1).

Tumours of the alimentary tract are rare in untreated stocks of laboratory rats and mice. However, mice who inherit the *Min1* locus (that is, a mutation in *Apc*) have a gut reaction; they spontaneously develop intestinal tumours. Inheritance of the *Mom1* (*Modifier Of Min1*) locus, however, decreases multiplicity and size of *Min1*-induced intestinal tumours[13,14] (Fig. 1). Linkage between a frameshift mutation and increased susceptibility in the B6 mouse strain suggested that the '*Mom1*' gene may be *Pla2g2a* (refs 15,5), a gene that encodes secretory phospholipase A2, the latter of which is involved in synthesising prostaglandins, hormone-like fatty acids that are believed to promote colon tumour cell proliferation and growth[16]. Other proposed mechanisms by which Pla2g2a may bring about tumorigenesis—for example, by bacteriocidal activity—seem unlikely. It is therefore counterintuitive that mice resistant to colon cancer (*Mom1*+) carry functional *Pla2g2a*, while susceptible, *Mom1*/- mice carry a stop mutation in *Pla2g2a* (ref. 15). Another conundrum is that inhibition of prostaglandin biosynthesis decreases both the rate of incidence and the size of colorectal tumours in rats, mice and humans, including patients with the APC syndrome[16,17]. Furthermore, no mutations in *PLA2G2A* and the related *PLA2G2C* and *PLA2G5* genes were detected in patients with different degrees of polyposis-disease severity[18].

In exploring the hypothesis that *Pla2g2a* is the '*Mom1*' gene, Cormier and colleagues introduced the *Mom1*/+ allele ($Pla2g2a^{AKR}$) into a B6 (*Mom1*/-) background. Mice who overexpressed $Pla2g2a^{AKR}$ showed a twofold reduction in tumour load and a significant reduction in tumour size, when compared with those carrying only a single copy of the resistance allele of $Pla2g2a^{AKR}$. Without replication of these results in additional transgenic lines, it remains a formal, although remote, possibility that the modified phenotype could result from the presence of another gene in the transgene construct, or from the interruption of an endogenous tumour supressor gene involved in colorectal carcinogenesis. Nonetheless, these results should signal a renaissance in the search for variations in human *PLA2G2A* that associate with intestinal cancer risk, and in experiments that explore the way in which *Pla2g2a* mediates risk reduction.

Cancer modifier loci are not limited to a few experimental models—they have been observed in a variety of strains and species, and for many tumour types. We predict that they may be much more common than is presently conceived, and that through modifying loci, animals maintain a system that can counteract any inherited predisposition to cancer. The identification of *Pla2g2a* as the *Mom1* gene provides salutary encouragement for those seeking to clone genes that underlie quantitative traits. As Cormier *et al.* insinuate, however, it would be naive to assume that the identification of other modifying genes will be as easy; serendipitous observations that recommend focused scrutiny on a candidate gene in the midst of a 15-cM interval are likely to be rare. Their eventual identification—using congenic strains and progeny testing to hone down the loci, followed by transgenic tests of candidate genes—will permit an understanding of biochemical mechanisms and the complex genetics of cancer, both in experimental models and humans. It is only then, that we can seriously contemplate a molecular approach to preventing and curing cancer. □


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