NEWS AND COMMENTARY

Modifier Genes and HNPCC

Variable phenotypic expression in HNPCC and the search for modifier genes

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Variance in disease expression in monogenetic disorders has been attributed to environmental and/or other genetic factors. This is especially true for inherited predispositions to malignancy where phenotypic expression cannot be adequately explained by a single causative genetic factor. In regard to inherited predispositions to malignancies such as breast cancer or colorectal cancer a growing body of evidence is accumulating that strongly suggests genetic modifiers of disease risk are important players when (or if) mutation carriers develop disease.^{1–5} The search for modifier genes continues as a result of inconsistencies between reports of the effect of the modifier on different cohorts of patients diagnosed with the same disease and the modifying effects of candidate genes being inconsistent in different inherited diseases. The selection of modifier genes has until recently been based on the candidate gene approach which is now to some extent being superseded by genome-wide association studies. Notwithstanding, the candidate gene approach has resulted in some significant insights into the role of genetic modifying factors. The choice of candidate gene to investigate can; however, be problematic and one approach is to investigate genes that have a plausible biological role in either the initiation or progression of disease.

One such interaction was reported by Niessen *et al.*⁶ which initiated a follow-up study on a larger cohort of patients by Steinke *et al.*⁷. Hereditary non-polyposis colorectal cancer (HNPCC) is

characterised by deficiencies in DNA mismatch repair (MMR) as a result of mutations in one of four genes *hMSH2*, *hMLH1*, *hPMS2* and *hMSH6*. The majority of HNPCC patients harbour mutations in either *hMSH2* or *hMLH1* and a smaller percentage are associated with mutations in either *hPMS2* or *hMSH6*.^{8,9} The identification of modifier genes that affect disease expression in *hMSH2* and *hMLH1* mutation carriers has revealed several candidates^{1,4,5,10,11} whereas little has been forthcoming in patients harbouring *hPMS2* or *hMSH6* mutations.

The work of Steinke *et al.*⁷ and Niessen *et al.*⁶ has been aimed at addressing the paucity of information about the potential role of modifier genes in *hMSH6* mutation carriers. There appears to be greater phenotypic variation in *hMSH6* mutation carriers compared to *hMSH2* or *hMLH1* mutation carriers. The greater variability in disease expression observed in *hMSH6* mutation carriers could be a result of altered functional activity of the encoded protein, the influence of proteins that interact with *hMSH6* or other downstream responses. The focus of the two reports by Niessen *et al.*⁶ and Steinke *et al.*⁷ has been on the reported interaction between *hMSH6* and *MUTYH*. *MUTYH* has recently been shown to be associated with a recessive form of intestinal polyposis with a carrier frequency estimated to be in the order of 1:100.¹² These findings in association with a physical and functional interaction between *hMSH6* and *MUTYH*¹³ suggest that *MUTYH* is a potential candidate

modifier of disease expression in HNPCC patients and in particular those harbouring *hMSH6* germline mutations. The report by Niessen *et al.*⁶ identified a higher frequency of *hMSH6* mutation carriers harbouring missense changes in *MUTYH* compared to any other mismatch repair gene mutation carrier. This result has not been substantiated in the report by Steinke *et al.*⁷ where a larger group of *hMSH6* mutation positive carriers were studied. This suggests that the association reported in the Dutch study may not be applicable to other populations or was a chance finding.

The reports by Niessen *et al.*⁶ and Steinke *et al.*⁷ highlight the problems associated with small sample numbers, so where to from here? The failure to corroborate the role of a modifier gene in one population compared to another is not new. There have been several studies reporting supposed associations that have not been substantiated in other reports. This does not necessarily imply that the basic premise is incorrect, rather that the testable hypothesis may not be adequately powered to provide a definitive answer. One of the major obstacles to be overcome in determining the influence of a potential modifier gene is publication bias (not a problem in this instance), which tends to only focus on positive associations and does not pay particular attention to findings that refute original claims. With regard to HNPCC and the role of modifying genes it is particularly complex as there are several genes predisposing to a clinical entity that is not precisely defined. Notwithstanding, modifier gene identification is proceeding and some inroads have been made. For more rapid advances in this field essentially two choices need to be made. First, it would be better if major collaborative efforts could be put in place so that there are sufficient numbers of cases and controls to ensure statistical rigour. Second, failing the creation of multi-centre studies the reporting of association studies of modifier genes ought to follow standardized reporting requirements. This should be insisted upon so that once sufficient studies have been reported appropriate meta-analyses can be performed, which will significantly improve our ability to precisely identify whether or not a

candidate modifier truly plays a role in disease penetrance.

Finally, what should we do with the information gained from studies that have unequivocally identified a modifier gene? Recently, a polymorphism in the RAD51 gene has been associated with a protective effect in women harbouring BRCA1 mutations.¹³ It is to be expected that in the near future similar data will appear that has a significant effect on the risk of developing malignancy in persons harbouring germline MMR gene mutations. At this stage clinical decision making is relatively comfortable about providing information concerning monogenetic disease risk; however, this may be tempered by the use of additional information which is less precise in its ability to predict disease likelihood. It is to be expected that there will be more than one modifier gene and that some may well cancel each other out. For this information to be incorporated into clinical practise all modifier genes will need to be identified and appropriate decision algorithms developed for the correct implementation and interpretation of this information ■

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Warfarin Pharmacogenomics

A big step forward for individualized medicine: enlightened dosing of warfarin

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Using genetic testing, a potential new face has been put on one of medicine's oldest, most commonly used and dreaded medications.

Warfarin is an anticoagulant medication prescribed worldwide to prevent stroke and venous thromboembolism. Its use is complex due to a narrow therapeutic

window, variability in dose–response, interactions with drugs and diet and risk of serious bleeding.¹ The optimal dose of warfarin is titrated to prolongation of the patient's blood test, the protime and international normalized ratio (PT/INR). Achieving and maintaining the target PT/INR and dose of warfarin is labor intensive and challenging. The importance of INR within the target range is critically important due to the risk of clinical bleeding with excessive prolongation and risk of thrombosis with inadequate prolongation. Many factors affect the metabolism of warfarin making adjustment of the drug dosage common. The traditionally understood clinical factors such as drug–drug interactions, dietary interactions, age and body surface area account for a significant portion of the variability in warfarin dosing.¹