Journal of Zhejiang University SCIENCE B
ISSN 1673-1581 (Print); ISSN 1862-1783 (Online)
www.zju.edu.cn/jzus; www.springerlink.com
E-mail: jzus@zju.edu.cn

Review:

Mechanisms of inherited cancer susceptibility*

Shirley HODGSON
(*Department of Cancer Genetics, St Georges Hospital, University of London, London SW17 ORE, UK*)
E-mail: shodgson@sgul.ac.uk

Received Nov. 13, 2007; revision accepted Dec. 4, 2007

Abstract: A small proportion of many cancers are due to inherited mutations in genes, which result in a high risk to the individual of developing specific cancers. There are several classes of genes that may be involved: tumour suppressor genes, oncogenes, genes encoding proteins involved in DNA repair and cell cycle control, and genes involved in stimulating the angiogenic pathway. Alterations in susceptibility to cancer may also be due to variations in genes involved in carcinogen metabolism. This review discusses examples of some of these genes and the associated clinical conditions caused by the inheritance of mutations in such genes.

Key words: Cancer, Inherited mutations, DNA repair, Tumour suppressor gene, Oncogenes
doi:10.1631/jzus.B073001 **Document code:** A **CLC number:** R73; Q75

INTRODUCTION

Cancer is common, and it is a minority of cancers that arise as a result of inherited and highly penetrant cancer susceptibility gene alterations. However, familial clustering of cancer is relatively common, and is likely to be due to a combination of environmental factors, rare gene mutations with high penetrance, and commoner lower penetrant gene variants acting together to alter disease susceptibility.

TUMOUR SUPPRESSOR GENES

There are several types of genes which can cause inherited susceptibility to cancer if inherited in a faulty state. The paradigm of inherited alterations in tumour suppressor genes was first elucidated by Knudson and others in the 1970's (Knudson, 1971), and inherited faulty tumour suppressor genes (TSG) are a common cause of autosomal dominantly inherited susceptibility to specific cancers, for example inherited retinoblastoma (Huang *et al*., 1988), familial adenomatous polyposis (FAP), Gorlin and Cowden syndromes, and neurofibromatosis types 1 and 2 (Hodgson *et al*., 2007). A large number of inherited cancer susceptibility conditions are due to the inheritance of faulty TSG, and the inactivation of the normal allele in the susceptible tissue is usually the rate-limiting step to the initiation of a tumour in such individuals. Each condition is associated with an increased risk of a small spectrum of cancers. Many of these conditions are associated with phenotypic abnormalities, because the genes involved are often those with functions in developmental pathways. FAP is a good example of this type of condition, caused by germline mutations in the *APC* gene, where multiple adenomas begin to develop in the large bowel from the early teenage years, as the premalignant lesion, and these may develop into a cancer if the polyp is not removed. Polyps usually develop in the teens and penetrance is almost complete by the age of 40 years in classical cases. Progression to malignancy is inevitable, and colorectal carcinoma often develops in untreated cases by about the fourth decade or even in childhood, 20~30 years earlier than in non-familial colon cancer. Histologically, single crypt adenomas are a characteristic feature. Polyps also occur else-

* Project supported by the Cancer Research, UK

where in the gastrointestinal tract. Gastric polyps in FAP are of two types: benign hyperplastic fundic gland polyps occur in most patients, and adenomas may also occur, usually in the pyloric region of the stomach, but at a much lower frequency. It is usual to perform a total colectomy in affected individuals once the polyposis becomes established. The *APC* gene is large, and has 15 exons, of which exon 15 is much the largest. Currently, it is possible to detect mutations in the *APC* gene in up to 82% of families (Ilyas and Tomlinson, 1997). Most mutations in familial adenomatous polyposis patients are frameshift (2/3) or nonsense (1/3) mutations which result in the production of a truncated protein. The *APC* gene product appears to function as a tumour suppressor with subcellular location and interaction with catenins. Predictive genetic tests are available to the at-risk relatives of an affected individual once the mutation has been detected in an affected person in the family. Relatives of affected individuals should be ascertained with the help of a genetic register, and those at risk of inheriting the disease should be offered screening and genetic testing if possible. Screening of at-risk relatives is usually commenced between the ages of 11 and 13 years by annual sigmoidoscopy because the rectum is involved by adenomas at an early stage and polyps rarely develop before 11 years of age. However, annual colonoscopy is advisable for screening from 20 years of age, and upper gastrointestinal surveillance is needed in affected individuals later (Heiskanen *et al*., 2000).

Some mutations in the *APC* gene may cause attenuated polyposis, with a milder phenotype and fewer colonic polyps with a later onset of colorectal cancer risk. A similar polyposis syndrome (MutY human homologue-associated polyposis (MAP)) has recently been discovered to be due to inherited alterations in the MutY human homologue (*MYH*) gene, a DNA repair gene, and this condition is inherited as an autosomal recessive condition, so it is important to make a correct diagnosis for accurate genetic counselling (Sieber *et al*., 2003; Sampson *et al*., 2003).

ONCOGENES

Inherited mutations in oncogenes are a much less common cause of dominantly inherited cancer susceptibility, but some examples are recognised, including multiple endocrine neoplasia type 2 (MEN2), and a group of childhood dysmorphic syndromes such as Noonan's syndrome. The association with dysmorphic features is due to the fact that the normal functions of these oncogenes are in development. MEN2 is due to inherited mutations in the *RET* oncogene, and predisposes to medullary thyroid cancer with early onset, phaeochromocytomas and parathyroid hyperplasia. Management of mutation carriers includes prophylactic thyroidectomy in childhood, and annual screening for phaeochromocytoma (Eng *et al*., 1996).

DNA REPAIR GENES

DNA repair defects are a common cause of inherited cancer susceptibility, and many examples have now been recognised. Some of these are autosomal recessive conditions such as ataxia telangectasia, Fanconi anaemia and xeroderma pigmentosum, and MAP. Hereditary non-polyposis colon cancer and breast cancer susceptibility due to *BRCA1* and *BRCA2* mutations are examples of autosomal dominant cancer susceptibility syndromes due to inherited alterations in genes which are involved in DNA repair processes, and there are many other examples.

Hereditary non-polyposis colon cancer (HNPCC), also known as Lynch syndrome, is one of the commonest forms of inherited predisposition to colorectal cancer (CRC), accounting for 2%~5% of all CRC. CRC in individuals with HNPCC differs from sporadic CRC by an earlier age of diagnosis (mean age approximately 44 years), a predominance of proximally-sited colon cancers (60%~70%) and an increased propensity to synchronous or metachronous CRCs (25%). Individuals with HNPCC have an 80% probability of developing CRC by the age of 65 years. They are also at an increased risk of developing a second primary CRC, although the stage at diagnosis is reported to be lower in HNPCC families than in the general population (Watson and Riley, 2005). In addition, affected individuals are at increased risk of a number of extra-colonic malignancies, with women having a 50%~60% risk of endometrial cancer. An elevated risk of a number of other extra-colonic cancers has also been documented in the disease. These

include cancers of the stomach, small intestine, urological tract, ovary, brain and pancreas. Reports vary as to whether breast cancer is part of the Lynch syndrome spectrum. Multiple sebaceous skin tumours occur in a variant of HNPCC, the Muir-Torre syndrome (Mangold *et al*., 2004).

HNPCC arises as a result of germline mutation in one of the several DNA mismatch repair (MMR) genes. In most families the mutated gene is *MLH1* (50%), *MSH2* (39%) or *MSH6* (7%); *MLH3*, *PMS1* or *PMS2* genes are occasionally involved (Peltomaki and Vasen, 2004). There is some evidence for a relationship between the gene involved and the spectrum of cancer risks, carriers of mutations in *MSH2* appearing to have a higher risk of developing extra-colonic cancers than individuals with *MLH1* mutations (Vasen *et al*., 2001). Females carrying *MSH6* mutations have been reported to have a particularly high risk of endometrial cancer (71%), but only a 30% risk of CRC (Bandipalliam *et al*., 2004). Management of individuals with HNPCC and those at risk of the condition, is by colonoscopy every 1~2 years from 25 years of age, and endometrial ultrasound and biopsy from 35 years of age on an annual basis (Park *et al*., 2006).

Women with germline mutations in *BRCA1* or *BRCA2* have a high risk of developing breast and ovarian cancer, and such mutations account for about 5% of all breast cancers. A meta-analysis of 500 families with *BRCA1* and *BRCA2* mutations identified from population based studies has estimated the risks of breast and ovarian cancer in *BRCA1* carriers to be 65% (confidence interval (CI): 44%~78%) and 39% (CI: 18%~54%) by age of 70 years, respectively. For *BRCA2* the risk was 45% (CI: 31%~56%) for breast cancer and 11% (CI: 2.4%~19%) for ovarian cancer (Antoniou *et al*., 2003), respectively. Higher risk estimates are obtained from data using multiple case families as with the Breast Cancer Linkage Consortium, where the breast cancer risk for carriers of mutations in either gene approaches 80% over a lifetime, and the ovarian cancer risk is about 40% for *BRCA1* mutation carriers, and 20% for *BRCA2* mutation carriers. Ovarian cancer is, in particular, associated with mutations in the ovarian cluster regions of *BRCA1* and *BRCA2* (Thompson and Easton, 2002a). Carriers of *BRCA1* and *BRCA2* mutations also have a slightly increased risk of other malignancies. *BRCA1* carriers have a statistically significant increased relative risk of pancreatic cancer of 2.26, endometrial cancer of 2.65, cervical cancer of 3.72, prostate cancer diagnosed under the age of 65 years of 1.82. *BRCA2* mutation carriers have a statistically significant increased relative risk of stomach cancer of 2.59, malignant melanoma of 1.43, prostate of 4.65, gallbladder and bile duct of 4.97 and pancreas of 3.51 (Thompson and Easton, 2002b).

There is good evidence that salpingo-oophorectomy halves risk of breast cancer in women, both in the general population and in *BRCA1/2* mutation carriers and is thus a prophylactic option for women who carry *BRCA1/2* mutations (Meijers-Heijboer *et al*., 2001; Rebbeck *et al*., 1999). Prophylactic mastectomy decreases the risk of breast cancer in *BRCA1* mutation carrier by 89.5%~100% (Narod, 2001). It seems likely that poly (ADP-ribose) polymerase (PARP) inhibitors and cross-linking agents such as carboplatin may be particularly effective in treating cancers in women with *BRCA1* and *BRCA2* mutations because their tumours lack the ability to repair DNA damage by homologous recombination (Kennedy *et al*., 2002).

ANGIOGENESIS GENES

A further mechanism for inherited cancer susceptibility, exemplified by the autosomal dominant conditions von Hippel Lindau disease (VHL) and multiple paragangliomata, is due to alterations in genes which are involved in the vascular endothelial growth factor (VEGF) pathway, and such mutations lead to stimulation of angiogenesis. Individuals with VHL mutations are at high risk of developing cerebellar haemangioblastomas, renal cell cancers and phaeochromocytomas (Maher *et al*., 1990), and require careful monitoring at least annually. Treatment of these tumours with anti-angiogenic agents is being developed.

Other examples of inherited childhood cancer susceptibility are associated with overgrowth, such as Beckwith syndrome, and genetic imprinting may play a role in these. Many of the genes involved in these syndromes are growth promoters.

CONCLUSION

This overview shows that there are many different ways in which individuals can have an inherited predisposition to certain cancers, and understanding these mechanisms will help identify individuals at increased risk of developing cancer, and also should lead to improved treatment of cancer.

References

Antoniou, A., Pharoah, P.D.P., Narod, S., Risch, H.A., Eyfjord, J.E., Hopper, J.L., Loman, N., Olsson, H., Johannsson, O., Borg, A., *et al*., 2003. Average risks of breast and ovarian cancer associated with *BRCA1* and *BRCA2* mutations detected in case series unselected for family history: a combined analysis of 22 studies. *Am. J. Hum. Genet.*, **72**(5):1117-1130. [doi:10.1086/375033]

Bandipalliam, P., Garber, J., Kolodner, R.D., Syngal, S., 2004. Clinical presentation correlates with the type of mismatch repair gene involved in Hereditary Nonpolyposis Colon Cancer. *Gastroenterology*, **126**(3):936-937. [doi:10.1053/j.gastro.2004.01.038]

Eng, C., Mulligan, L.M., Healey, C.S., Houghton, C., Frilling, A., Raue, F., Thomas, G.A., Ponder, B.A.J., 1996. Heterogeneous mutation of the *RET* proto-oncogene in subpopulation of medullary thyroid carcinoma. *Cancer Res.*, **56**: 2167-2170.

Heiskanen, I., Luostarinen, T., Järvinen, H.J., 2000. Impact of screening examinations on survival in familial adenomatous polyposis. *Scand. J. Gastroenterol.*, **35**(12): 1284-1287. [doi:10.1080/003655200453638]

Hodgson, S.V., Foulkes, W., Eng, C., Maher, E.R., 2007. A Practical Guide to Inherited Cancer Susceptibility. Cambridge University Press, UK.

Huang, H.Y., Yeo, J.K., Shaw, J.Y., Chen, P.L., Bookstein, R., Friedmann, T., Lee, E.Y., Lee, W.H., 1988. Suppression of neoplastic phenotype by replacement of the *RB* gene in human cancer cells. *Science*, **242**(4885):1563-1566. [doi:10.1126/science.3201247]

Ilyas, M., Tomlinson, I.P., 1997. The interactions of *APC*, E-cadherin and beta-catenin in tumour development and progression. *J. Pathol.*, **182**(2):128-132. [doi:10.1002/(SICI)1096-9896(199706)182:2<128::AID-PATH839>3.0.CO;2-Q]

Kennedy, R.K., Quinn, J.E., Johnston, P.G., Harkin, D., 2002. *BRCA1*: mechanisms of inactivation and implications for management of patients. *Lancet*, **360**(9338):1007-1014. [doi:10.1016/S0140-6736(02)11087-7]

Knudson, A.G., 1971. Mutation and human cancer: statistical study of retinoblastoma. *Proc. Natl. Acad. Sci. USA*, **68**(4):820-823. [doi:10.1073/pnas.68.4.820]

Maher, E.R., Yates, J.R.W., Harries, R., Benjamin, C., Harris, R., Moore, A.T., Ferguson-Smith, M.A., 1990. Clinical features and natural history of von Hippel Lindau disease. *Q. J. Med.*, **77**(283):1151-1163.

Mangold, E., Pagenstecher, C., Leister, M., Mathiak, M., Rutten, A., Friedl, W., Propping, P., Ruzicka, T., Kruse, R., 2004. A genotype-phenotype correlation in HNPCC: strong predominance of *MSH2* mutations in 41 patients with Muir-Torre syndrome. *J. Med. Genet.*, **41**(7): 567-572. [doi:10.1136/jmg.2003.012997]

Meijers-Heijboer, H., van Geel, B., van Putten, W.L., Henzen-Logmans, S.C., Seynaeve, C., Menke-Pluymers, M.B.E., Bartels, C.C.M., Verhoog, L.C., van den Ouweland, A.M.W., Niermeijer, M.F., *et al*., 2001. Breast cancer after prophylactic bilateral mastectomy in women with a *BRCA1* or *BRCA2* mutation. *N. Engl. J. Med.*, **345**(3):159-164. [doi:10.1056/NEJM200107193450301]

Narod, S., 2001. Prophylactic mastectomy in carriers of *BRCA* mutations. *N. Engl. J. Med.*, **345**(20):1498. [doi:10.1056/NEJM200111153452014]

Park, J.G., Kim, D.W., Hong, C.W., Nam, B.H., Shin, Y.K., Hong, S.H., Kim, I.J., Lim, S.B., Aronson, M., Bisgaard, M.L., *et al*., 2006. International Society for Gastrointestinal Hereditary Tumours. Germ line mutations of mismatch repair genes in Hereditary Nonpolyposis Colorectal Cancer patients with small bowel cancer: International Society for Gastrointestinal Hereditary Tumours Collaborative Study. *Clin. Cancer Res.*, **12**(11 Pt 1): 3389-3393. [doi:10.1158/1078-0432.CCR-05-2452]

Peltomaki, P., Vasen, H., 2004. Mutations associated with HNPCC predisposition—update of *ICG-HNPCC/INSiGHT* mutation database. *Dis. Markers*, **20**(4-5):269-276.

Rebbeck, T.R., Levin, A.M., Eisen, A., Snyder, C., Watson, P., Cannon-Albright, L., Isaacs, C., Olopade, O., Garber, J.E., Godwin, A.K., *et al*., 1999. Breast cancer risk after bilateral prophylactic oophorectomy in *BRCA1* mutation carriers. *J. Natl. Cancer Inst.*, **91**(17):1475-1479. [doi:10.1093/jnci/91.17.1475]

Sampson, J.R., Dolwani, S., Jones, S., Eccles, D., Ellis, A., Evans, D., Frayling, I., Jordan, S., Maher, E., Mak, T., 2003. Autosomal recessive colorectal adenomatous polyposis due to inherited mutations of *MYH*. *Lancet*, **362**(9377):39-41. [doi:10.1016/S0140-6736(03)13805-6]

Sieber, O.M., Heinimann, K., Tomlinson, I.P., 2003. Genomic instability: the engine of tumourigenesis? *Nat. Rev. Cancer*, **3**(9):701-708. [doi:10.1038/nrc1170]

Thompson, D., Easton, D.F., 2002a. Breast cancer linkage consortium: variation in *BRCA1* cancer risks by mutation position. *Cancer Epidemiology, Biomarkers and Prevention*, **11**:326-329.

Thompson, D., Easton, D.F., 2002b. Breast Cancer Linkage Consortium. Cancer incidence in *BRCA1* mutation carriers. *J. Natl. Cancer Inst.*, **94**(18):1358-1365.

Vasen, H.F., Stormorken, A., Menko, F.H., Nagengast, F.M., Kleibeuker, J.H., Griffioen, G., Taal, B.G., Moller, P., Wijnen, J.T., 2001. *MSH2* mutation carriers are at higher risk of cancer than *MLH1* mutation carriers: a study of Hereditary Nonpolyposis Colorectal Cancer families. *J. Clin. Oncol.*, **19**(20):4074-4080.

Watson, P., Riley, B., 2005. The tumor spectrum in the Lynch syndrome. *Fam. Cancer*, **4**(3):245-248. [doi:10.1007/s10689-004-7994-z]