

Medical genetics: advances in brief

Invited editorial. Inherited predisposition to breast and ovarian cancer
Rowell S, Newman B, Boyd J, King MC.
Am J Hum Genet 1994;55:861-5.

Familial site-specific ovarian cancer is linked to BRCA1 on 17q12-21
Steichen-Gersdorf E, Gallion HH, Ford D,
et al. Am J Hum Genet 1994;55:870-5.

In some families the BRCA1 gene is responsible for an inherited predisposition to breast and ovarian cancer, and possibly also prostatic cancer. BRCA1 appears to explain most inherited breast cancers. A woman who inherits this susceptibility to breast cancer has a disease risk of >50% by 50 years, and >80% by 65 years. Her risk of ovarian cancer is 10% by 60 years. (In a recent consortium study among families with both breast and ovarian cancer, the proportion thought to be linked to BRCA1 was 1.0 although subsequently a few families with both malignancies which are not linked to BRCA1 have been reported. In the same consortium study, BRCA1 was linked to breast cancer in 67% of families with breast cancer diagnosed <45 years in the absence of ovarian cancer.) BRCA1 may also be responsible for an inherited susceptibility to epithelial ovarian cancer in families with multiple affected relatives with this disease, but with no breast cancers under the age of 50 years. It remains to be seen whether this latter group of families has a different spectrum of mutations in BRCA1 from families with combined ovarian and breast cancer.

The nine families studied by Steichen-Gersdorf *et al* all had three or more cases of epithelial ovarian cancer at any age, and no cases of breast cancer diagnosed at <50 years. In these families, if the disease gene confers a risk of ovarian cancer only (model 1) the proportion of linked families is 0.78. If the gene confers a risk of breast cancer as well (there were some cases in older women), then the proportion linked to BRCA1 is 1.0. Now that the gene has been cloned, many outstanding questions can be addressed. What are the normal and mutant products of the gene? What proportion of breast and ovarian cancers in the general population involve somatic mutations in BRCA1? What are the interactions with other genes? Can therapy be influenced by knowledge of the genotype? Will gene therapy ever be possible? Meanwhile, the other significant contributor to the risk of developing breast cancer appears to be the increasing interval between menarche and the first pregnancy (an average of eight years at the beginning of the century, and two to three times longer now).

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Parent-of-origin effects in multiple endocrine neoplasia type 2B
Carlson KM, Bracamontes J, Jackson CE, *et al. Am J Hum Genet* 1994;55:1076-82.

Multiple endocrine neoplasia type 2B (MEN 2B) is characterised by medullary thyroid carcinomas, pheochromocytomas, mucosal neuromas, ganglioneuromas, and skeletal and ophthalmological abnormalities. Fifty percent of cases occur as the result of spontaneous mutations. A single point mutation in the catalytic core regions of the receptor tyrosinase kinase (RET) proto-oncogene on chromosome 10 has been observed in the germline DNA of MEN 2B patients. In this study 25 de novo cases were analysed at a molecular level in order to determine the parental origin of the mutated RET allele, and in all cases the new mutation was of paternal origin. This suggests that a RET allele may be more susceptible to mutation when inherited from a father as opposed to a mother, and similar findings have been reported for Wilms's tumours, rhabdomyosarcomas, bilateral retinoblastomas, and neurofibromatosis type 1. In the MEN 2B study, the mean paternal age was 33 years (mean maternal age 29.5 years), and the authors postulate that one contributory factor could be that males may be exposed to a greater number of mutagens than females. The authors also noted a distortion of the sex ratio in the de novo MEN 2B patients (with 28 female to 15 male patients, out of a total of 43).

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Background statement. Genetic testing and insurance

Ad Hoc Committee on Genetic Testing/Insurance Issues. *Am J Hum Genet* 1995;56:327-31.

This report was drafted by the American Society of Human Genetics Ad Hoc Committee on Genetic Testing/Insurance Issues, and is a preliminary paper designed to identify the issues raised by the rapid expansion of genetic technology which affect relationships between patients, doctors, and insurers. Ultimately further discussion will lead to an ASHG position paper. Insurance products are developed to provide financial protection against unanticipated loss, and standard premiums are calculated on the expected outcome for large numbers of people with similar risks, and are expected to spread the cost of the loss among a group. Before issuing a policy, however, insurers must determine the risk that an individual client presents, and must adjust their premiums to acknowledge that risk. This process is called underwriting. The commercial insurance industry traditionally provides citizens with an opportunity to spread their risks in a large community, while allowing legitimate businesses to earn a profit. When insurance policies rely more on risks of only a few people, this social function is lost; but the ability to identify

and exclude high risk people can result in a paradoxical situation of insurance being most easily available to those who need it least. In the United States this presents a particular problem with health insurance policies in cases where the cost is borne by employers in small businesses, whose profits and even survival may be threatened by serious illness in a few employees. It can be difficult just defining "genetic" tests, as there is sometimes no clear boundary between genetic and non-genetic conditions and tests, which may complicate the drafting of new laws designed to regulate matters. With health insurance policies, it is becoming apparent that although the cost of the molecular tests is likely to be covered, the practice of insurers regarding reimbursement for the counselling required to support genetic testing may be inadequate. Distinguishing and classifying people at different risks is at the heart of commercial insurance, and differentiation of applicants on the basis of health risks is legal, but the extent of such legal discrimination is unclear, and its future course is uncertain. In the United States, information may be obtained from the Medical Information Bureau (MIB), a non-profit making cooperative agency formed by member insurance companies to combat fraud. It consists of a large database of identifiable insurance applicants, and provides a service to underwriters which can be used during the underwriting of new applications, only with the consent of the applicant. Insurers can access the database to confirm that they have received the same information on an applicant as has been collected by their competitors. Thus people refused insurance by one company because of an increased genetic risk may find themselves effectively uninsurable. Concealment of medical information is an important issue as well. If the insurer finds the physician has not disclosed all relevant information, a claim may be denied, and ultimately the insured person may be able to sue the physician, if the former had originally signed a waiver requesting that "all pertinent information" be sent to the insurance company. Another problem arising in the United States is one of "adverse rejection", whereby a client who has been paying regular premiums may have his policy cancelled by the insurance company if he is found to have a serious condition. It is to be hoped that health care reform legislation will eliminate this inequity. Another issue raised, which is very relevant in the United Kingdom, includes the complex question of whether a geneticist has a right or a duty to disclose genetic information to a relative without the consent of the patient. For Americans, however, the biggest challenge to be faced is the possibility of providing universal access to health care, without regard to past, present, or future risk of disease, which could eliminate risk oriented underwriting in health care cover.

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