# SVILUPPO DELLA RICERCA GENI E CANCRO

1990 progetto Genoma umano

Mary-Claire King 1993 gruppi familiari che esprimevano tumori della mammella prima dei 50 anni

1994 Myriad Genetics di Salt Lake City: scoperta di mutazioni a carico del cromosoma 17 individute alterazioni a carico di un gene oncosoppressore (BRCA1)

1997 scoperta di un altro gene mutato sul cromosoma 13 (BRCA2)

# Methods for Determining the Heritability of Cancer



**Cohort studies**

A traditional way of measuring the contribution of genes to a phenotypic trait is to examine the family histories of a cohort of individuals with that trait. The number of first-degree relatives who have the same trait is recorded. This rate is compared with the expected rate in a matched control group to obtain a ratio — often referred to as the family risk ratio or odds ratio — that provides a measure of familiality. This method eliminates the influence of phenocopies (cases in which the trait occurs in relatives by chance), but does not eliminate the effect of a shared environment.

**Twin studies**

Twin studies can minimize the effect of a shared environment. The effect of genes compared with that of the environment is thought to be adequately measured by comparing the concordance rate for the trait in monozygotic twins with that in dizygotic twins. The proportion of variance attributable to hereditary factors is one way of expressing heritability based on twin studies.

# Heritability of Selected Cancers

| Cancer type | Study 1 family risk ratios* | Study 2 family risk ratios* | Proportion of variance due to heritable factors‡ |
|---|---|---|---|
| Testicular | 8.57 | 8.50 | ND |
| Thyroid | 8.48 | 12.42 | ND |
| Laryngeal | 8.00 | ND | ND |
| Multiple myeloma | 4.29 | 5.62 | ND |
| Lung | 2.55 | 3.16 | 0.26 |
| Colorectal | 2.54 | 4.41 | 0.35 |
| Kidney | 2.46 | 5.26 | ND |
| Prostate | 2.21 | 9.41 | 0.42 |
| Melanoma | 2.10 | 3.41 | ND |
| Breast | 1.83 | 2.01 | 0.27 |

*The ratios shown here were in part recalculated by Risch[97]. Study 1 was carried out in Utah[98]. Ratios are based on all first-degree relatives; first-degree relatives of 35,228 probands with cancer were studied. Study 2 was carried out in Sweden[99]. Ratios are based on siblings; data comprised from 435,000 parents with cancer who had 5,520,756 offspring, 71,424 of whom had cancer. ‡Based on a twin study comprising 44,788 pairs[100]. ND, not determined.

| Syndrome | Associated genes | Predominant tumour types or abnormalities |
|---|---|---|
| Hereditary breast and ovarian cancer | *BRCA1*<br>*BRCA2* | Breast carcinomas, ovarian carcinomas |
| Carney complex | *PRKAR1A* | Skin pigment abnormalities, endocrine tumours, schwannomas |
| Cowden | *PTEN* | Breast carcinomas, thyroid carcinomas, endometrial carcinomas |
| Familial adenomatous polyposis | *APC* | Adenomatous polyps of the colon/rectum, gastrointestinal cancers, papillary thyroid carcinomas |
| Familial melanoma | *CDKN2A*<br>*CDK4* | Cutaneous malignant melanoma, pancreatic cancers |
| Hereditary papillary renal carcinoma | *MET* | Papillary renal-cell carcinomas |
| Hereditary non-polyposis colorectal cancer | *MSH2*<br>*MSH6*<br>*MLH1*<br>*PMS1*<br>*PMS2* | Colorectal and endometrial adenocarcinomas |
| Hereditary diffuse gastric cancer | *CDH1* | Diffuse adenocarcinomas of the stomach wall |
| Juvenile polyposis coli | *MADH4* | Multiple juvenile polyps in the gastrointestinal tract, colorectal and gastrointestinal malignancies |
| Li–Fraumeni brain | *TP53* | Breast cancers, soft-tissue sarcomas, tumours, adrenocortical tumours, leukaemia |
| Multiple endocrine neoplasia type 1 | *MEN1* | Primary hyperparathyroidism, pancreatic islet-cell tumours, anterior pituitary tumours |
| Multiple endocrine neoplasia type 2 | *RET* | Medullary thyroid carcinomas, phaeochromocytomas, mucosal neuromas |
| Nevoid basal-cell carcinoma | *PTCH* | Basal-cell carcinomas |
| Neurofibromatosis type 1 | *NF1* | Neurofibrosarcomas, astrocytomas, melanomas, rhabdomyosarcomas, chronic myeloid leukaemia |
| Neurofibromatosis type 2 | *NF2* | Bilateral vestibular schwannomas, meningiomas, spinal tumours, skin tumours |
| Peutz–Jeghers | *STK11* | Gastrointestinal-tract carcinomas, breast carcinomas, testicular cancers, gynaecological malignancies |
| Phaeochromocytoma | *SDHB*, *SDHC*, *SDHD* | Phaeochromocytomas, glomus tumours |
| Retinoblastoma | *RB* | Paediatric retinal tumours |
| Tuberous sclerosis complex | *TSC1*<br>*TSC2* | Multiple hamartomas, renal-cell carcinoma, astrocytomas |
| von Hippel–Lindau | *VHL* | Renal-cell carcinomas, retinal and central nervous system haemangioblastomas, phaeochromocytomas |

*APC*, adenomatosis polyposis coli; *CDH1*, cadherin 1 (E-cadherin); *CDK4*, cyclin-dependent kinase 4; *CDKN2A*, cyclin-dependent kinase inhibitor 2A; *MEN1*, multiple endocrine neoplasia 1; *RB*, retinoblastoma; *STK11*, serine/threonine kinase 11; *TSC*, tuberous sclerosis.

# INDIVIDUAZIONE DEI GENI ANOMALI

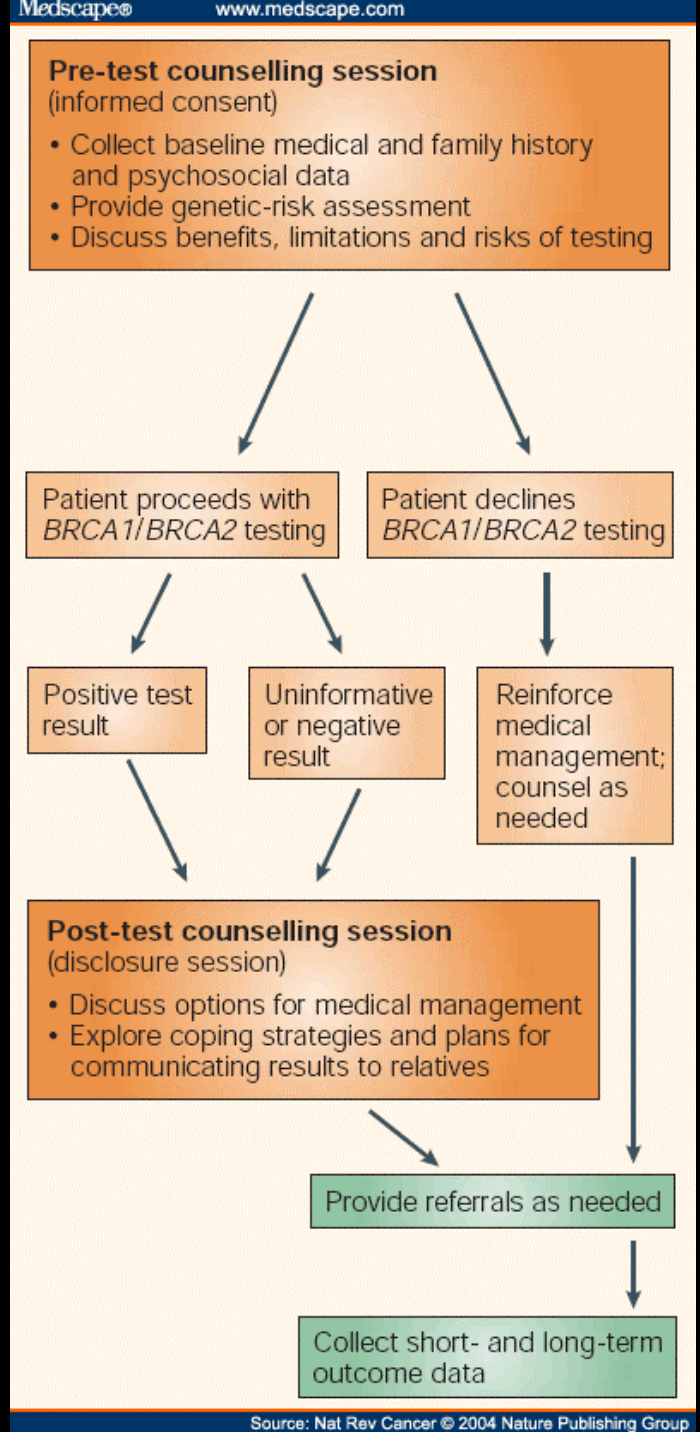
## ONCOGENOMICS SECTION DEL NCI

Nell' "Archivio genetico" sono conservate le sequenze di 18.927 geni sani. Con la tecnica 'microarray' si possono 'sovrapporre' le varie sequenze di Dna sospette confrontandole con quelle dell'archivio evidenziando le anomalie associate alle forme tumorali.

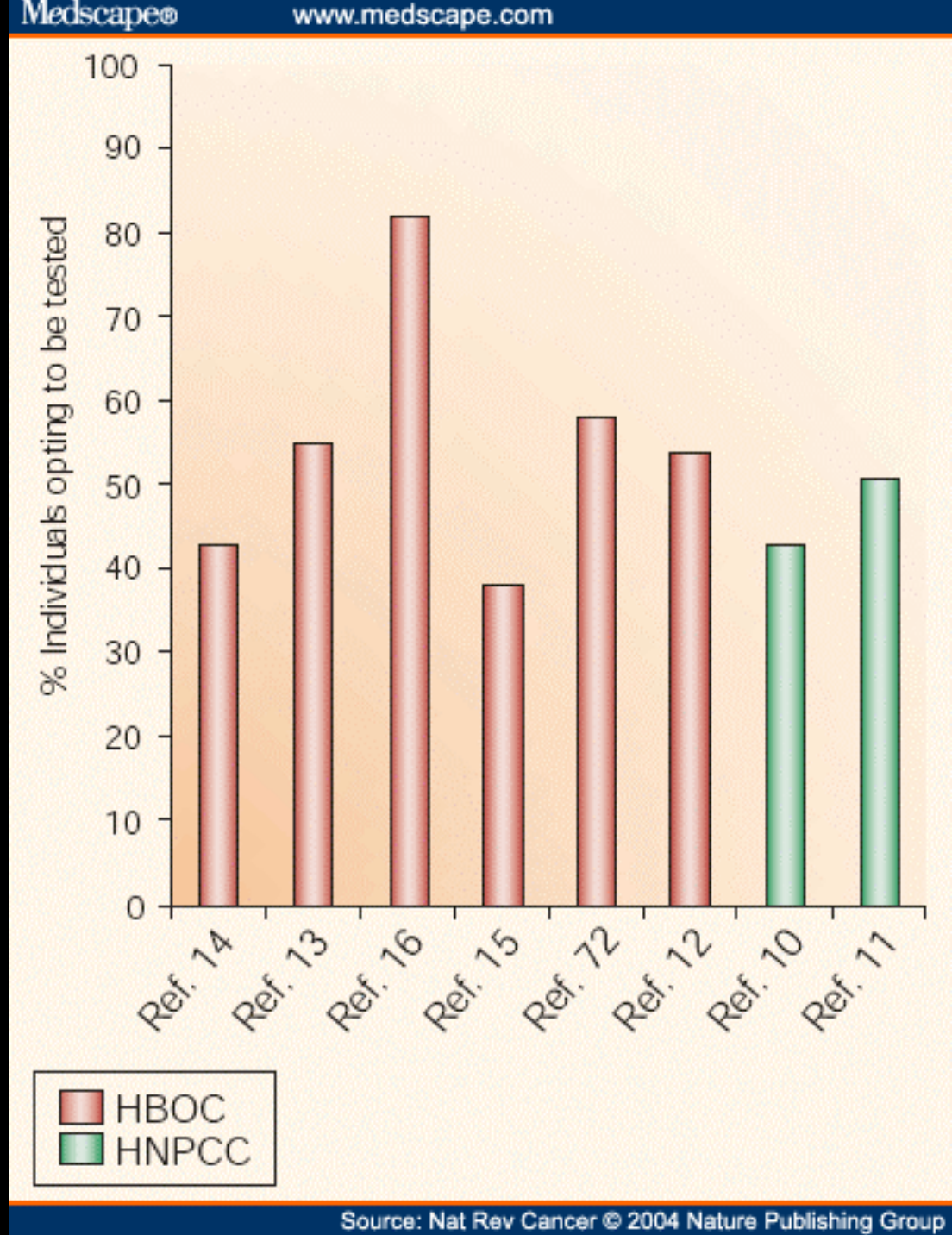
Metodica: si estrae dalle cellule il Dna-copia (cDna) che viene marcato con una sostanza fluorescente e confrontato con la sequenza dell'archivio.
Se il gene è regolare le due catene aderiranno in maniera perfetta, come due pezzi di velcro, se alterato le due catene mostreranno dei distaccamenti'.

**Genome Research Javed Khan 2005**

Process of genetic testing and counselling for hereditary breast and ovarian cancer.

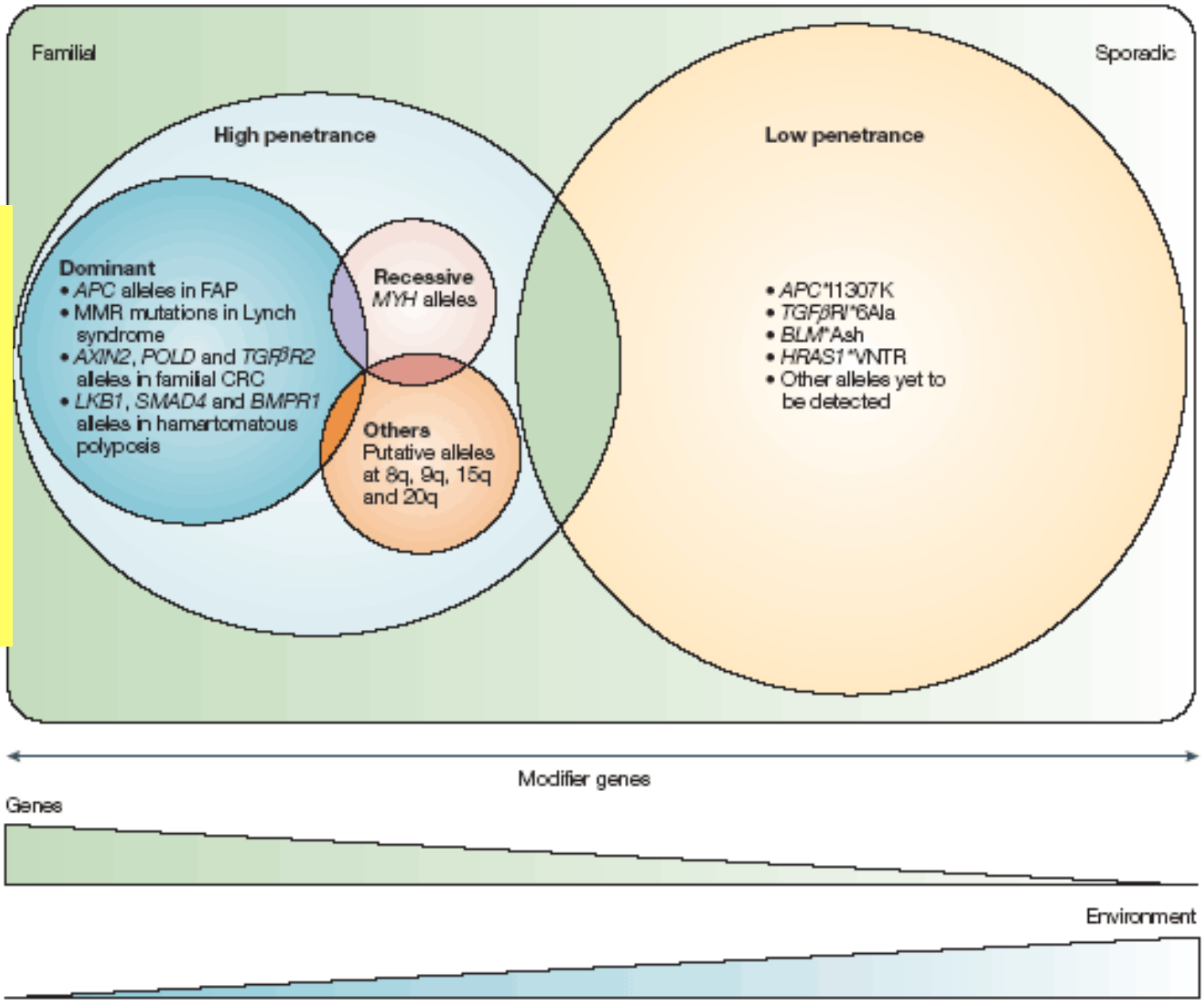


COMPARING UPTAKE RATES OF GENETIC TESTING IN FAMILIES WITH HEREDITARY BREAST AND OVARIAN CANCER OR HEREDITARY NON-POLYPOSIS COLON CANCER



# A global view of the genetic contribution to colorectal cancer





# CANCER-PREDISPOSING GENES VERSUS COMMON GENETIC VARIANTS

| Characteristic | Genetic mutations in key cancer-susceptibilitity genes (such as *BRCA1* and *APC*) | Genetic variants associated with cancer-risk behaviours/complex traits |
|---|---|---|
| Prevalence | Rare | Common |
| Relative risk (penetrance) | High | Low |
| Attributable (population) risk | Small | Moderate to large |
| Aetiological heterogeneity* | Sometimes | Always |
| Pleiotropy‡ | Rare | Often |
| Gene–gene interactions | Possible | Likely |
| Gene–environment interactions | Possible | Likely |

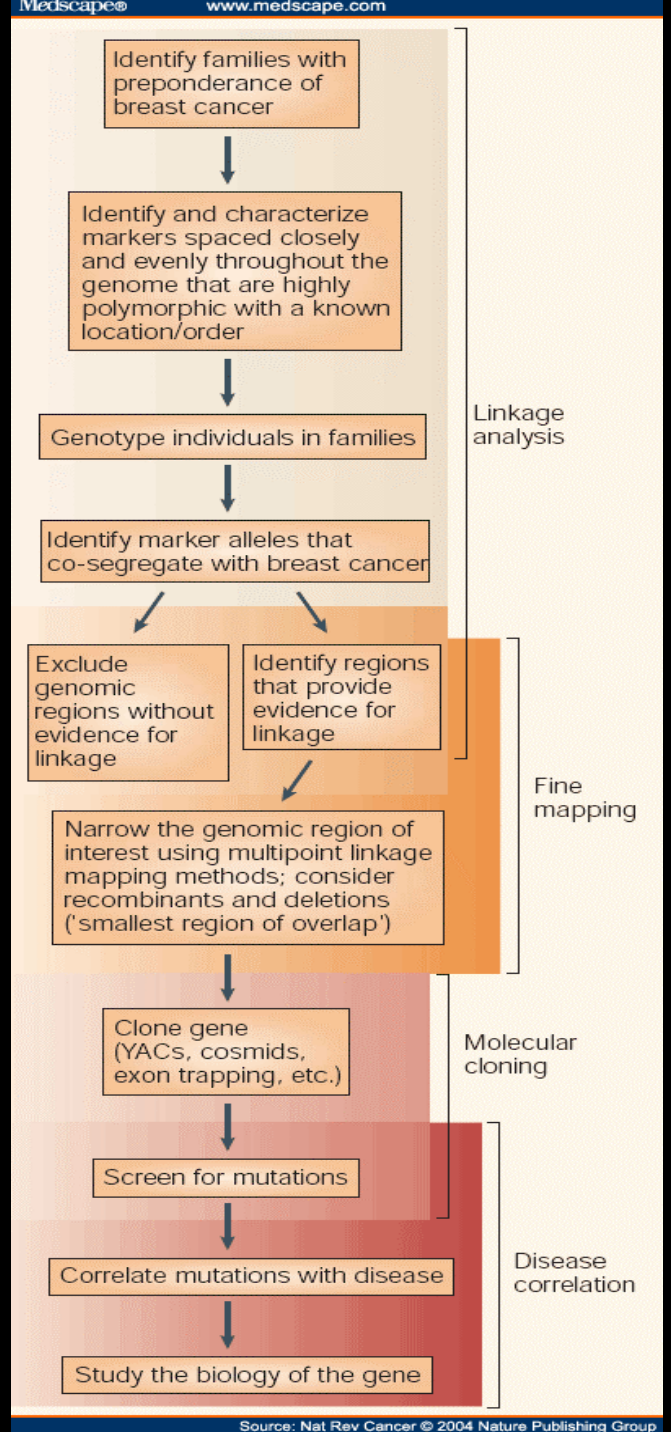
*Refers to multiple causal factors in disease aetiology. ‡Refers to multiple effects of a particular susceptibility mutation. *APC*, adenomatosis polyposis coli.

# FOUNDER MUTATIONS ASSOCIATED WITH LYNCH SYNDROME

Medscape® www.medscape.com

| Gene | Mutation | Estimated age of mutation in founder population (years) | Population | Proportion of all Lynch syndrome in population accounted for | References |
|---|---|---|---|---|---|
| *MLH1* | Deletion of exon 16 | 400–1,075 | Finns | > 50% | 101 |
| *MLH1* | Splice acceptor site for exon 6 disrupted | 125–525 | Finns | ~5% | 102 |
| *MLH1* | Stop codon introduced at Trp714 (truncated protein) | > 200 | Swiss | Not known | 103 |
| *MSH2* | Splice donor site for intron 5 disrupted | > 300 | Newfoundlanders | 20–25% | 43,104,105 |
| *MSH2* | Ala636Pro substitution | 200–500 | Ashkenazi Jews | ~20% | 106 |
| *MSH2* | Deletion of exons 1–6 | ~300 | North Americans | Not known | 107–109 |

# IDENTIFYING GENES ASSOCIATED WITH CANCER



**Distribution of mismatch repair mutations in Lynch syndrome**