FOGSI Focus

Genetics for the Generalist

Series Editor
Hrishikesh D Pai

Editors
Seetha Ramamurthy Pal
Vandana Bansal

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Genetics and Inherited Cancers

Saswati Mukhopadhyay

INTRODUCTION

Hereditary cancer syndromes (HCSs) are a heterogeneous group of genetic diseases, with significantly increased risk of tumor development. Cancer susceptibility is found in multiple syndromes such as Bloom syndrome, Fanconi anemia, Nijmegen breakage syndrome, ataxia-telangiectasia, etc. In most of these syndromes, there is biallelic inactivation of deoxyribonucleic acid (DNA) repair genes. The "genuine" HCSs, however, have no phenotypic malfunctions, only an increased risk of development of organ-specific malignant disease.

Genes involved in cancer are of two types—tumor suppressor genes and oncogenes.

1. *Oncogenes:* They are mutated copies of certain normal cellular genes called proto-oncogenes. Proto-oncogenes regulate normal cellular growth, division, and apoptosis. Oncogenes may lead to uncontrolled cell growth and the escape from cell death, which may result in cancer development.

   Examples: HER2, RAS, EGFR, etc.
2. Tumor-suppressor genes normally inhibit cell proliferation and tumor development. If mutated or deleted, these genes cannot function as negative regulators of cell proliferation allowing abnormal proliferation of tumor cells.

   Examples: p53, Rb, PTEN, BRCA1, BRCA2, etc.

MECHANISMS OF HEREDITARY CANCER PREDISPOSITION

Most of the HCS genes are tumor-suppressor genes, requiring biallelic inactivation to manifest as cancer. When inactivating pathogenic variant (PV) is inherited in a single allele, the remaining copy of the gene retains its function; thereby the normal health status is preserved. The process of malignant transformation is usually triggered by the "second hit", i.e., the remaining allele is inactivated by a somatic mutation. *RB1, BRCA1, BRCA2, MLH1, MSH2*—these HCS genes work in this way[1] **(Fig. 1)**.

Sometimes, mutated suppressor genes, in monoallelic form, may cause malignancy by reduced gene dosage (haploinsufficiency). A few cancers are caused by the inheritance of activated oncogene, e.g., multiple endocrine neoplasia (MEN) type 2A and 2B, associated with gain-of-function PVs in *RET* gene.

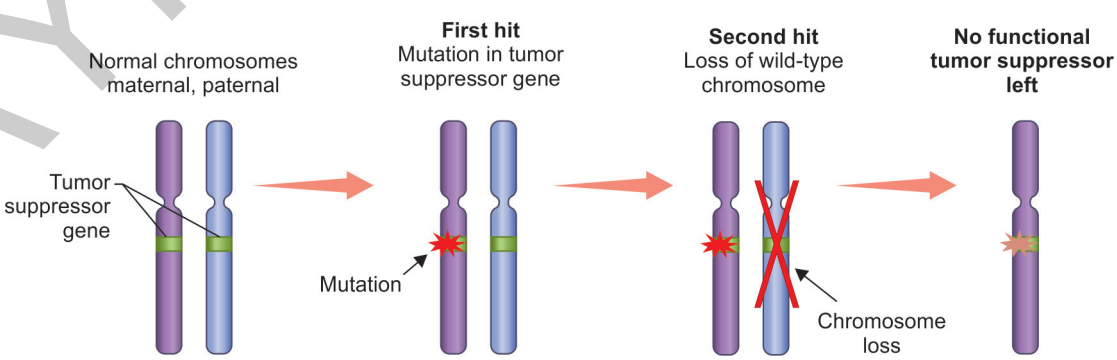

Fig. 1: Knudson's two-hit hypothesis for hereditary cancer syndrome (HCS).

MAJOR TYPES OF HEREDITARY CANCER SYNDROMES

Hereditary Breast and Ovarian Carcinomas

Families with a history of multiple breast or ovarian cancers approximately account for 15% of all patients with breast cancer.[2] Certain mutations in BRCA1 or 2 are responsible for most cases of hereditary breast and ovarian cancer (HBOC) syndrome. HBOC patients may also have an increased propensity for developing other types of cancer, such as melanoma, pancreatic, and prostate cancers. Hereditary breast cancer (BC) and hereditary ovarian cancer (OC) are represented by PVs located within the same genes, *BRCA1* and *BRCA2*, both of which are involved in double-strand DNA repair by homologous recombination. BC may also be a part of multiorgan cancer syndrome like Li–Fraumeni syndrome, diffuse stomach cancer. More than 2,900 variants of *BRCA1* and more than 3,400 variants of *BRCA2* pathogenic germline mutations are registered in ClinVar, a public archive of human genetic variants and interpretations of their significance to disease.[3]

BRCA1-related breast cancer has the following features:

- Histopathologically resembling medullary carcinoma
- High histological nuclear grade
- No expression of either estrogen and progesterone receptors or HER2 overexpression.

BRCA2-mutated breast cancer has the following features:

- Almost similar to those with *BRCA1* mutations
- Histologically high nuclear grade

High-grade serous adenocarcinoma has been found as a pathological feature of *BRCA1/2* ovarian cancer. Small cell carcinomas of the ovary, hypercalcemic type are related to germline PV in the *SMARCA4* gene, associated with chromatin remodeling.

Colorectal Cancer

Lynch syndrome, also called hereditary nonpolyposis colorectal cancer (HNPCC), is the most common genetic risk for colorectal cancer (CRC). Besides CRC, there is increased risk of endometrial cancer, gastric, small bowel, biliary, urothelial, ovarian, brain malignancies in Lynch syndrome.[4]

Some germline PVs predispose to polyposis of gastrointestinal tract; these polyps are commonly found to become malignant. Adenomatous polyposis coli (APC) is a tumor-suppressor gene, its inactivation results in upregulation of the WNT signaling pathway. APC is associated with highly increased risk of malignancy in the gastrointestinal (GI) tract. The incidence of APC is around 1:10,000.

Gastric Cancer

Gastric cancer (GC) risk is significantly increased when there is *Helicobacter pylori* infection, low hygienic standard, high consumption of salt, "Northern" diet, excessive alcohol intake. The role of heredity is obtained only for diffuse GC. This type of GC is poorly differentiated, with presence of signet-ring cells. The causative gene, *CDH1*, is associated with severely increased incidence of diffuse GC.[5] Other genes involved in GCs include *PALB2*, and the Lynch syndrome genes. The lifetime GC risk in carrier of *MLH1* or *MSH2* PVs is ~7–8%.

Other hereditary cancers include pancreatic cancer, prostate cancer, lung cancer, renal cancer, melanoma and the MEN1 and MEN2 syndromes **(Table 1)**.

Hereditary Cancer Syndromes

Li–Fraumeni syndrome: In the pediatric population, Li–Fraumeni syndrome is associated with adrenal cortical

TABLE 1: Genes involved with different types of hereditary cancers.

Malignancy	***Genes involved***
Breast and ovarian cancer	*BRCA1, BRCA2, PALB2, ATM, and CHEK2, NBN (NBS1), BLM, RECQL, FANCM, BARD1*
Ovarian cancer	*ANKRD1, POLE, ERCC3, and SMARCA4*
Lynch syndrome (HNPCC)	*MLH1, MSH2, MSH6, PMS2, and EPCAM*
Polyposis syndrome (polyposis in GIT)	*APC, POLE, POLD1, STK11, SMAD4, BMPR1A, PTEN, GREM1, RNF43* (autosomal dominant) *MUTYH, NTHL1, MSH3, and MBD4* (autosomal recessive)
Diffuse gastric cancer	*CDH1*
Renal cancer	*VHL, FH, and FLCN*
Lung cancer	*EGFR*
Prostate cancer	*HOXB3, BRCA2, and ATM*
Pancreatic cancer	*PALB2 and BRCA2*
Melanoma	*CDKN2A, CDK4, POT1, and TERT*

(HNPCC: hereditary nonpolyposis colorectal cancer)
Source: Imyanitov EN, Kuligina ES, Sokolenko AP, Suspitsin EN, Yanus GA, Iyevleva AG, et al. Hereditary cancer syndromes. World J Clin Oncol. 2023;14(2):40-68.

carcinomas, choroid plexus carcinomas, rhabdomyosarcomas, and medulloblastomas. In adults, Li–Fraumeni syndrome involves very young-onset BC in females, lung carcinomas, osteosarcomas, soft-tissue sarcomas, and brain tumors.

PTEN hamartoma tumor syndrome (Cowden syndrome): *PTEN* hamartoma tumor syndrome (PHTS) features multiple benign and malignant tumors of breast, thyroid, endometrium, skin, kidney, and colon.

Peutz–Jeghers syndrome (PJS): PJS is an autosomal dominant disease shows characteristic mucocutaneous pigmentations in the lips, eyes, nostrils, perianal area, mouth and of the buccal mucosa, and various polyps.

Multiple gastrointestinal hamartomatous polyps in the affected patients are located mainly in the small bowel, most commonly in jejunum and ileum. Stomach and colon polyps are also seen.

Gorlin syndrome: Gorlin syndrome, also called Gorlin–Goltz syndrome, basal cell nevus syndrome (BCNS), or nevoid basal cell carcinoma syndrome, is an autosomal dominant familial cancer syndrome. It is characterized by the appearance of BCCs and the development of odontogenic keratocysts. There is also increased risk of medulloblastoma.

Pediatric tumors: Retinoblastoma, Wilms' tumor (nephroblastoma), DICER1 syndrome

Hematological malignancies: Hereditary acute lymphoblastic leukemia, hereditary Hodgkin lymphoma.

The genes associated with hereditary cancer syndromes are listed in **Table 2**.

TABLE 2: Genes involved with different types of hereditary cancers syndromes.

Syndromes	*Genes*
Li–Fraumeni syndrome	*TP53*
Multiple endocrine neoplasia (MEN) • MEN1—affects parathyroid glands, pancreatic islet cells and the anterior pituitary • MEN2—medullary thyroid carcinoma (MTC), pheochromocytoma • MEN3—highly metastatic and potentially fatal MTC, pheochromocytomas	*MEN1* *RET* *RET M918T allele, A883F allele*
PTEN hamartoma tumor syndrome	*PTEN*
Peutz–Jeghers syndrome	*STK11/LKB1 PVs*
Gorlin syndrome	*PTCH1, SUFU or PTCH2*
Retinoblastoma	*Rb*
Neurofibromatosis	*NF1*
Wilms' tumor (nephroblastoma, WT)	*WT1*
DICER1 syndrome (pleuropulmonary blastomas, gynandroblastomas, sarcomas, Sertoli–Leydig cell tumors)	*DICER1*

Source: Imyanitov EN, Kuligina ES, Sokolenko AP, Suspitsin EN, Yanus GA, Iyevleva AG, et al. Hereditary cancer syndromes. World J Clin Oncol. 2023;14(2):40-68.

MANAGEMENT OF HEREDITARY TUMORS

Cancer Detection and Prevention

Female carriers of BRCA1, BRCA2:

- Breast self-examination, starting from 18 years of age
- Clinical breast examination annually
- Magnetic resonance imaging, starting from 25 years,
- Annual mammography between 30 and 75 years

Ovarian cancer screening:

- Transvaginal ultrasound examination annually to detect ovarian tumors
- CA-125 serum marker measurement yearly, starting at 30–35 years

Patients with lynch syndrome:

- Colonoscopy should be performed every 1–2 years beginning from 20–25 years of age to detect suspicious ulcer
- Upper GI endoscopy every 3–5 years starting at 30–35 years
- Endometrial cancer screening by dilation and curettage (D&C) and endometrial sampling from 35 years, annually.

Carriers of highly-penetrant BC-predisposing pathogenic variants (*BRCA1*, *BRCA2*, *PALB2*, *TP53*, *etc.*) are encouraged to undergo:

- Mastectomy
- Prophylactic salpingo-oophorectomy at the age of 35–45 years (or after the completion of childbearing).

Advances in cytotoxic and targeted therapy: Several discoveries, made within the past 10–15 years have helped recognize specific drug vulnerabilities in hereditary cancers. Thus targeted therapies, aimed to the susceptible

TABLE 3: Cytotoxic and targeted therapy for tumors arising in carriers for cancer—predisposing alleles.

Tumor type	*Target*	*Drugs*
BRCA1/2-driven carcinomas	Deficiency of DNA repair by homologous recombination	Platinum derivatives, mitomycin C, bifunctional alkylating agents, PARPi
Microsatellite-unstable cancers, including tumors arising due to Lynch syndrome, *POLE/POLD1*, and *MUTYH*-related malignancies	Excessive number of somatic mutations and consequently, high tumor antigenicity	Immune checkpoint inhibitor—pembrolizumab
RET associated malignancies	*RET* tyrosine kinase	*RET* inhibitors—selpercatinib and pralsetinib
Neurofibromatosis, type 1	Upregulation of RAS/RAF/MEK pathway due to NF1 inactivation	MEK inhibitor—selumetinib
Gorlin syndrome	Hedgehog pathway	Smoothened (SMO) inhibitor—vismodegib
Tumors arising in patients with tuberous sclerosis	mTOR pathway	mTOR inhibitors
Renal cell carcinomas associated with Von Hippel–Lindau syndrome	Upregulation of HIF-2α due to *VHL* gene inactivation	HIF-2α inhibitor—belzutifan

(mTOR: mammalian target of rapamycin; PARPi: poly (ADP-ribose) polymerase inhibitor)
Source: Imyanitov EN, Kuligina ES, Sokolenko AP, Suspitsin EN, Yanus GA, Iyevleva AG, et al. Hereditary cancer syndromes. World J Clin Oncol. 2023;14(2):40-68.

pathways of the genetic mutations, are the new line of medical management of cancers[4] **(Table 3)**.

CONCLUSION

In those families in which multiple members have cancers in different/same target organs, genetic testing by whole exome or multigene sequencing should be offered to at-risk family members, after careful pretest counseling. Identifying the mutations in specific genes will help to screen at-risk family members, plan specific drug therapy for the patients and keep a strict vigilance on the target organs so that the cancer detection happens at the earliest stage. However, carrying the mutation does not mean developing the malignancy in the target organ, only the risk is increased, compared to the general population.

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FOGSI Focus

Genetics for the Generalist

Genes are the building blocks of life and genetics touches every aspect of health and disease. After the Human Genome Project, a lot has been discovered about our genetic make-up and its significance.

There are hundreds of genetic conditions that can affect every system, organ, tissue, and cell in the human body and added to it is the effect of multiple genetic variants and their interaction with the environment.

Considering this, genetics is too large a topic to be covered. However, this FOGSI Focus is a humble attempt to simplify genetics and make it user friendly to our FOGSIans to apply this in their clinical practice. The Focus covers all essential aspects of genetics in Obstetrics and Gynecology, starting from history taking, pedigree charting and basics of inheritance, both Mendelian and non-Mendelian.

Our genetic make-up increases or decreases our risk of certain diseases, and the presence of any pathogenic variant does not guarantee presence of disease or lack of it. The very important aspect of genetic counseling based on family history of diseases or hemoglobinopathies, abnormal screening or ultrasound features and the importance of selecting, ordering, and understanding genetic tests is very well dealt with.

Finally, aspects of genetics in subfertility, recurrent pregnancy losses, inherited cancers and the wide world of pre-implantation genetic diagnosis and gene therapy will give you a picture of how far science is advancing especially in the field of genetics.

We are sure this FOCUS will help you seek information on the common aspects of genetics, and we hope you will come away with more confidence incorporating the principle of genetics in your general or specialty practice.

Hrishikesh D Pai MD FRCOG (UK-HON) FCPS FICOG MSc (USA) is the President of FOGSI (2022–2023). He is the Medical Director of Bloom IVF Group and Administrator of FOGSI Manyata Initiative. He is the Director of Corporate Affairs, International Federation of Fertility Societies (IFFS), and adjunct Assistant Professor at Eastern Virginia Medical School, USA. He is a Postgraduate Teacher in gynecology at DNB Examination, India and a Visiting Professor in Obstetrics and Gynecology, Manipal University, India. He has been awarded with the esteemed Fellowship Ad Eundem of the RCOG (Royal College of Obstetricians and Gynaecologists, London, UK). He is the Past Secretary General, Senior Vice President, Deputy Secretary General, Treasurer, and Chairman of FOGSI. He is the Past President of ISAR, IAGE, and MOGS.

Seetha Ramamurthy Pal MBBS DGO MD MRCOG FICOG RCOG/RCR Diploma in Obst USG is Consultant, Department of Obstetrics and Fetal Medicine, Apollo Multispecialty Hospitals, Kolkata, West Bengal, India. She is Honorable Treasurer, Bengal Obstetric and Gynecologist Society (2023–2024); the Chairperson, Genetics and Fetal Medicine Committee, FOGSI (2023–2025); Fellow Representative, AICC RCOG Eastern zone. She is also Honorable Vice President, Society of Fetal Medicine, Kolkata Chapter; Clinical Secretary, ISOPARB, Kolkata Chapter; Examiner MRCOG Part 3; and Faculty, MRCOG Part 2/3 courses; She is Member, National Board Specialist Committee of Maternal and Fetal Medicine and Peer Reviewer JOGI and Journal of Fetal Medicine.

Vandana Bansal MD DGO DNB MNAMS FICOG FRCOG (UK) FNB (High Risk Pregnancy and Perinatology) is an Additional Professor, Nowrosjee Wadia Maternity Hospital and GS Medical College, Mumbai; the Director, Fetal Medicine Centre, Surya Mother and Child Hospital, Mumbai, Maharashtra, India. She is an Obstetrician with super-specialization in Fetal Medicine and Interventions. She is First Post-doctoral Fellow of National Board (FNB) in India qualified in High-risk Pregnancy and Perinatology. She has 28 years of experience in Obstetrics and Gynecology including 23 years in Fetal Medicine. She is an MUHS Approved Faculty for Fellowship program in Fetal Medicine and MD; and ICOG Course Coordinator and Faculty for Certificate course in Fetal Medicine. She is an Examiner for Part 3 MRCOG exams; the Vice President Society of Fetal Medicine, Mumbai Chapter; Member Secretary and Expert, Ethics Committee Nowrosjee Wadia Hospital; the Chairperson, Fetal Medicine Committee; AMOGS (2017–2019); National Co-ordinator, Imaging Science Committee, FOGSI (2018–2020), Member Management Committee, MOGS (2016–2022). She has 52 publications including 30 papers in national/international journals and 18 chapters in books in her credit. She has honored by NA Purandare Best Paper Award (MOGS), Best Paper Award (ISOPARB), Best Poster Award (ISOPARB), Kamala Achari Symposium Award, and Dr DK Tank Best Paper Award MOGS.

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