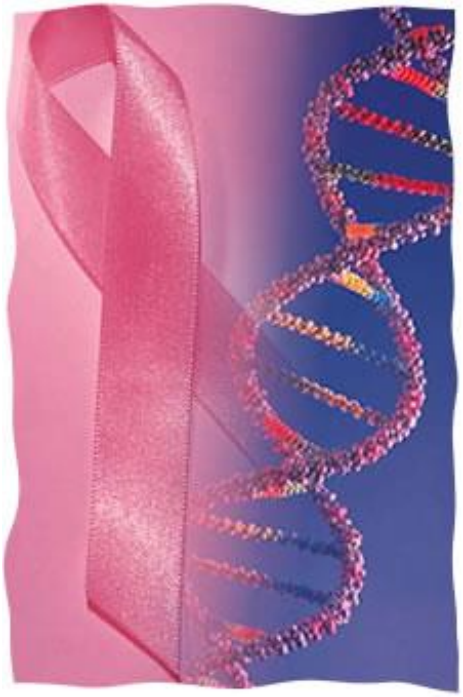
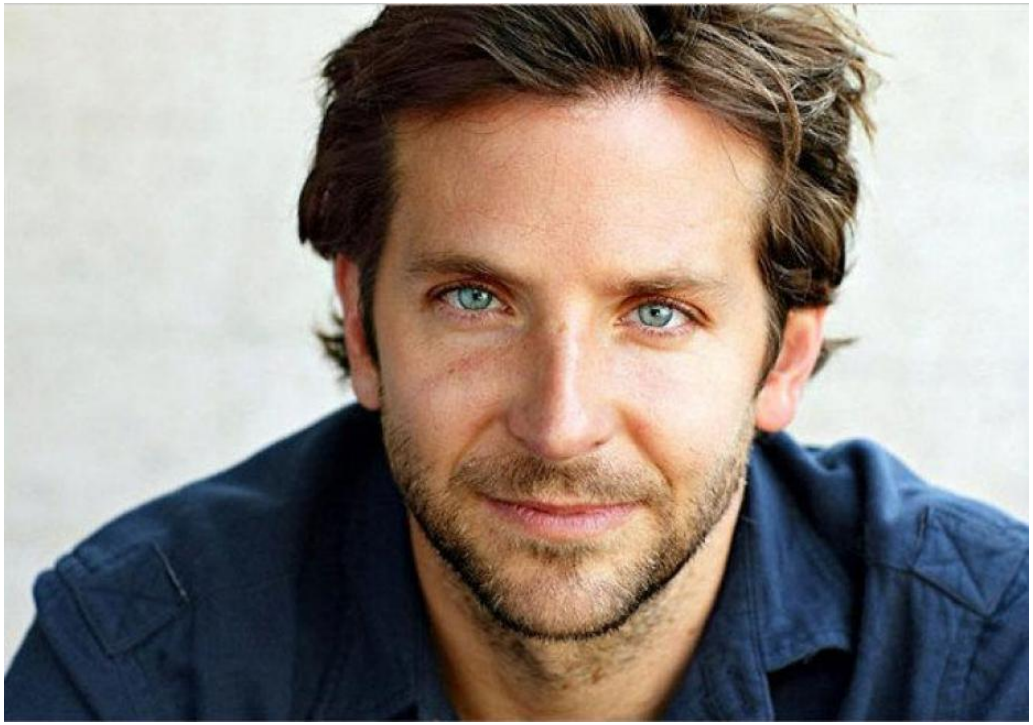


Kalıtsal Kanser Sendromları
(HBOC, HNPCC/FAP, Tiroid, Mide)

Doç.Dr.Hüseyin Onay

Ege Üniversitesi Tıp Fakültesi Tıbbi Genetik AD



BRCA1

RESEARCH ARTICLES

A Strong Candidate for the Breast and Ovarian Cancer Susceptibility Gene *BRCA1*

Yoshio Miki, Jeff Swensen, Donna Shattuck-Eidens, P. Andrew Futreal, Keith Harshman, Sean Tavtigian, Qingyun Liu, Charles Cochran, L. Michelle Bennett, Wei Ding, Russell Bell, Judith Rosenthal, Charles Hussey, Thanh Tran, Melody McClure, Cheryl Frye, Tom Hattier, Robert Phelps, Astrid Haugen-Strano, Harold Katcher, Kazuko Yakumo, Zahra Gholami, Daniel Shaffer, Steven Stone, Steven Bayer, Christian Wray, Robert Bogden, Priya Dayananth, John Ward, Patricia Tonin, Steven Narod, Pam K. Bristow, Frank H. Norris, Leah Helvering, Paul Morrison, Paul Rosteck, Mei Lai, J. Carl Barrett, Cathryn Lewis, Susan Neuhausen, Lisa Cannon-Albright, David Goldgar, Roger Wiseman, Alexander Kamb, Mark H. Skolnick*

A strong candidate for the 17q-linked *BRCA1* gene, which influences susceptibility to breast and ovarian cancer, has been identified by positional cloning methods. Probable predisposing mutations have been detected in five of eight kindreds presumed to segregate *BRCA1* susceptibility alleles. The mutations include an 11–base pair deletion, a 1–base pair insertion, a stop codon, a missense substitution, and an inferred regulatory mutation. The *BRCA1* gene is expressed in numerous tissues, including breast and ovary, and encodes a predicted protein of 1863 amino acids. This protein contains a zinc finger domain in its amino-terminal region, but is otherwise unrelated to previously described proteins. Identification of *BRCA1* should facilitate early diagnosis of breast and ovarian cancer susceptibility in some individuals as well as a better understanding of breast cancer biology.

cer is often familial in origin, although the risks in relatives are not as high as those for early-onset breast cancer (*10*, *11*). The percentage of such cases that are due to genetic susceptibility is unknown.

Like many other genes involved in familial cancer, *BRCA1* appears to encode a tumor suppressor, a protein that acts as a negative regulator of tumor growth. Cancer-predisposing alleles typically carry mutations that cause loss or reduction of gene function. Predisposition to cancer is inherited as a dominant genetic trait, whereas the predisposing allele generally behaves as a recessive allele in somatic cells. Thus, a single inherited copy of the mutant allele causes predisposition, and loss or inactivation of the wild-type allele completes one of the steps in progression toward malignancy. When chromosome loss is observed in breast and ovarian tumors from patients who carry *BRCA1* predisposing alleles, the wild-type copy of *BRCA1* is invariably lost while the presumptive mutant allele is retained (*12–14*). This finding supports the hypothesis that *BRCA1* is a tumor suppressor gene and suggests that the functional BRCA1 protein is present in normal breast and ovarian epithelium tissue and is altered, reduced, or absent in some breast and ovarian tumors.

Genetic analysis of recombinant chromo-

BRCA2

(GSK3-α), was the site of phosphorylation in each phosphopeptide, both *in vitro* (Fig. 4*b*) and *in vivo* (not shown). The ^{32}P-labelling of other (more acidic) tryptic phosphopeptides was not increased by insulin (Fig. 4*d*). These peptides have been noted previously in GSK3 from A431 cells and shown to contain phosphoserine and phosphotyrosine[11].

PKC-δ, ε and ζ are reported to be activated by mitogens, and PKC-ζ activity is stimulated *in vitro* by several inositol phospholipids, including PI(3,4,5)P_3, the product of the PI 3-kinase reaction[26]. However, purified PKC-ε[27], PKC-δ and PKC-ζ (data not shown) all failed to inhibit GSK3-α or GSK3-β *in vitro*. Moreover, although PKC-α, β1 and γ inhibit GSK3-β *in vitro*[27], GSK3-α is unaffected, while their downregulation in L6 myotubes by prolonged incubation with phorbol esters abolishes the activation of MAPKAP kinase-1 in response to subsequent challenge with phorbol esters, but has no effect on the inhibition of GSK3 by insulin (not shown).

Taken together, our results identify GSK3 as the first physiologically relevant substrate for PKB. The stimulation of glycogen synthesis by insulin in skeletal muscle involves the dephosphorylation of Ser residues in glycogen synthase that are phosphorylated by GSK3 *in vitro*[2]. Hence the 40–50% inhibition of GSK3 by insulin, coupled with a similar activation of the relevant glycogen synthase phosphatase[28], can account for the stimulation of glycogen synthase by insulin in skeletal muscle[2] or L6 myotubes[29]. The activation of glycogen synthase and the resulting stimulation of glycogen synthesis by insulin in L6 myotubes is blocked by wortmannin, but not by PD 98059 (ref. 29), just like the activation of PKB and inhibition of GSK3. However, GSK3 is unlikely to be the only substrate of PKB *in vivo*, and identifying other physiologically relevant substrates will be important because PKB-β is amplified and overexpressed in many ovarian neoplasms[23]. □

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1. Embi, N., Rylatt, D. B. & Cohen P. *Eur. J. Biochem.* **107,** 519–527 (1980).
2. Parker, P. J. J., Caudwell, F. B. & Cohen, P. *Eur. J. Biochem.* **130,** 227–234 (1983).
3. Welsh, G. I. & Proud, C. G. *Biochem. J.* **294,** 625–629 (1993).
4. Nikolakaki, E., Coffer, P., Hemelsoet, R., Woodgett, J. & Defize, L. *Oncogene* **8,** 833–840 (1993).
5. de Groot, R., Auwerx, J., Bourouis, M. & Sassone-Corsi, P. *Oncogene* **8,** 841–847 (1993).
6. Fiol, C. *et al. J. biol. Chem.* **269,** 32187–32193 (1994).
7. Siegfried, E., Chou, T.-B. & Perrimon, N. *Cell* **71,** 1167–1179 (1992).
8. He, X., Saint-Jeannet, J.-P., Woodgett, J. R., Varmus, H. E. & Dawid, I. B. *Nature* **374,** 617–622 (1995).
9. Hughes, K., Ramakrishna, S., Benjamin, W. B. & Woodgett, J. R. *Biochem. J.* **288,** 309–314 (1992).
10. Cross, D. A. E. *et al. Biochem. J.* **303,** 21–26 (1994).
11. Saito, Y., Vandenheede, J. R. & Cohen, P. *Biochem. J.* **303,** 27–31 (1994).
12. Sutherland, C., Leighton, I. A. & Cohen, P. *Biochem. J.* **296,** 15–19 (1993).
13. Sutherland, C. & Cohen, P. *FEBS Lett.* **338,** 37–42 (1994).
14. Welsh, G. I., Foulstone, E. J., Young, S. W., Tavare, J. M. & Proud, C. G. *Biochem. J.* **303,** 15–20 (1994).
15. Alessi, D. R., Cuenda, A., Cohen, P., Dudley, D. & Saltiel, A. L. *J. biol. Chem.* **270,** 27489–27494 (1995).
16. Kuo, C. J. *et al. Nature* **358,** 70–73 (1992).
17. Stambolic, V. & Woodgett, J. R. *Biochem. J.* **303,** 701–704 (1994).
18. Eldar-Finkelman, H., Seger, R., Vandenheede, J. R. & Krebs, E. G. *J. biol. Chem.* **270,** 987–990 (1995).
19. Vlahos, C. J., Matter, W. F., Hui, K. Y. & Brown, R. F. *J. biol. Chem.* **269,** 5241–5248 (1994).
20. Coffer, P. J. & Woodgett, J. R. *Eur. J. Biochem.* **201,** 475–481 (1991).

Identification of the breast cancer susceptibility gene *BRCA2*

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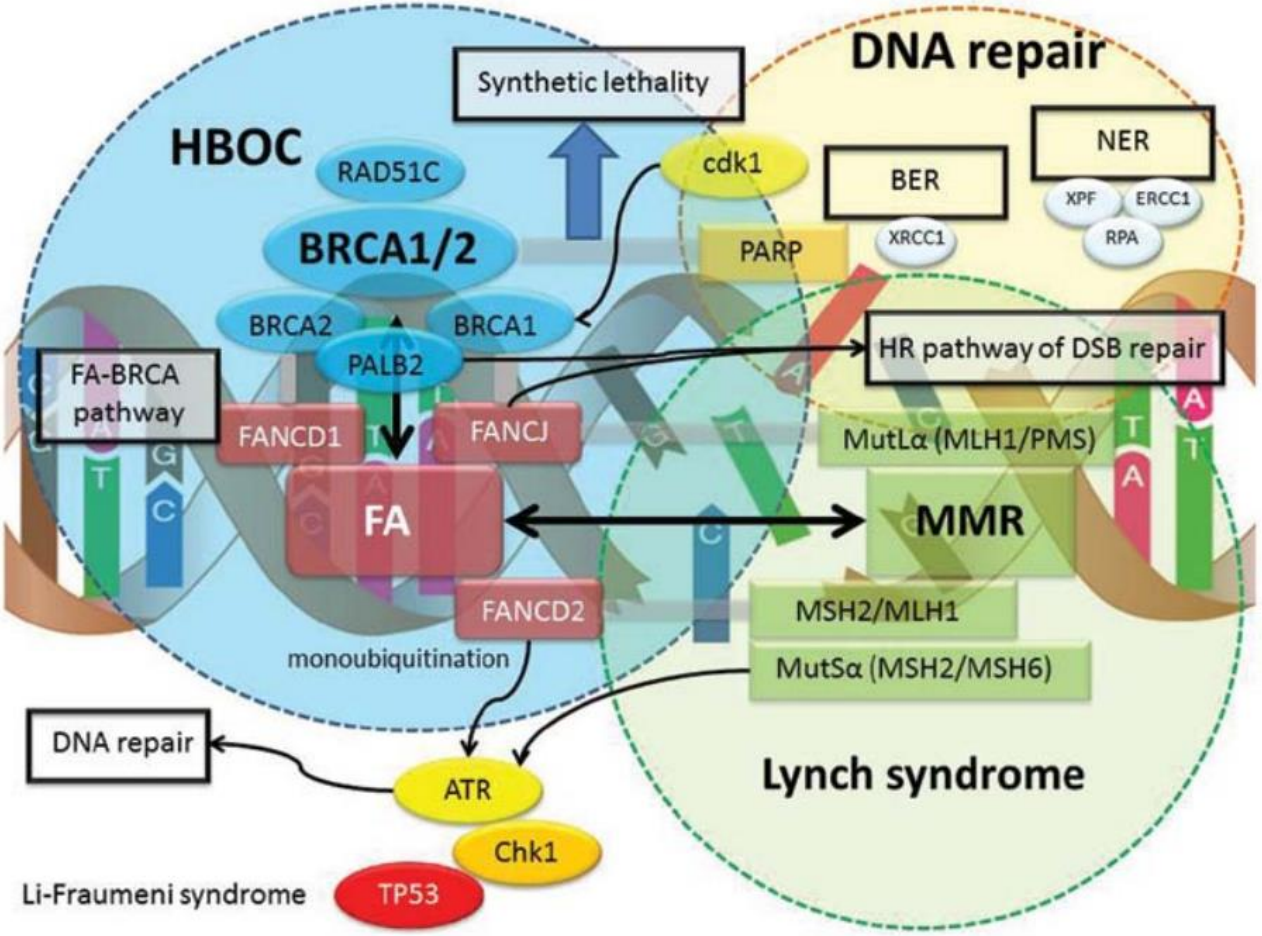
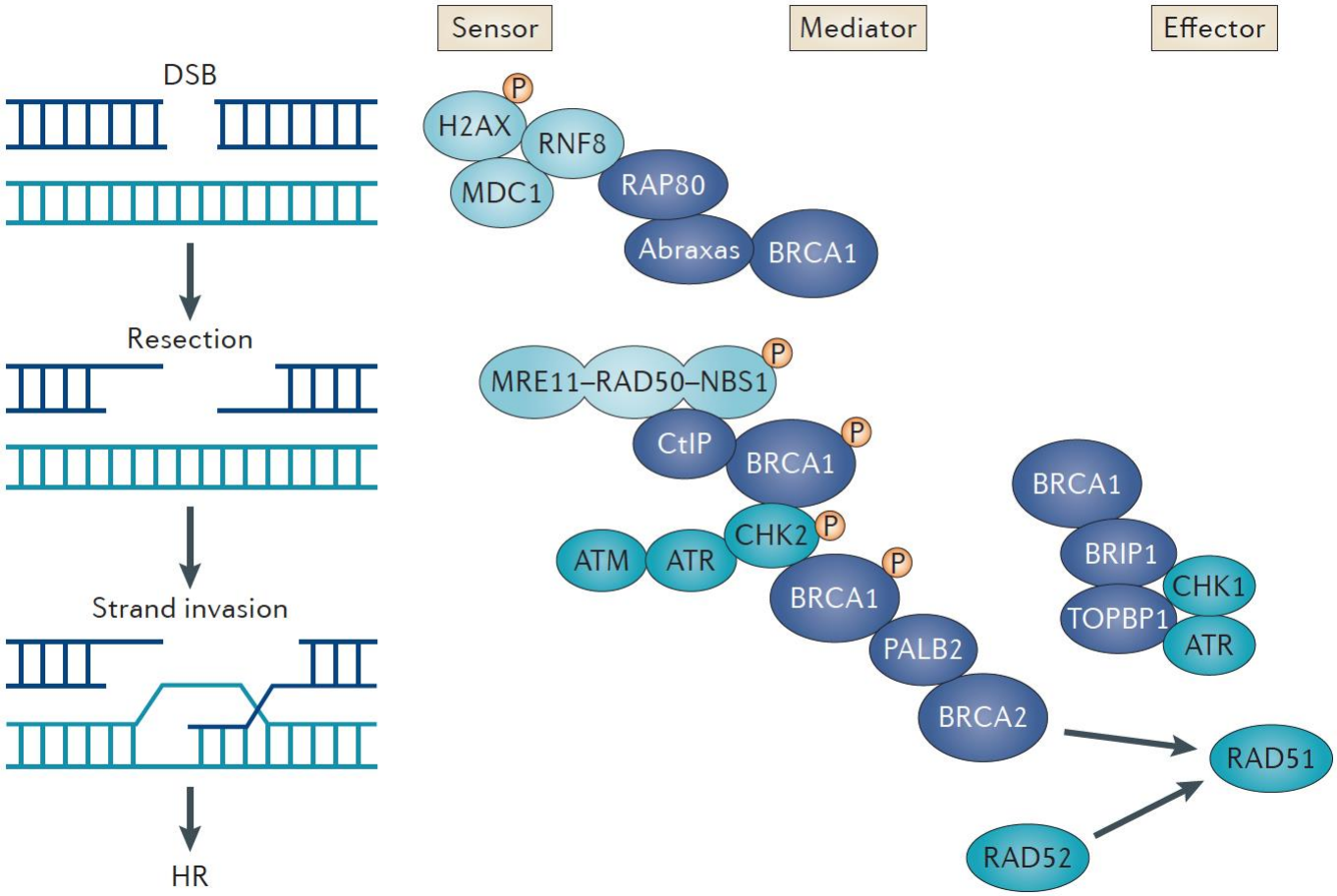
Ailesel Meme-Over Kanseri



Kobayashi H et al., Oncology Report , 2013

BRCA1-2



Roy R et al., Nat Rev Cancer, 2012

BRCA1-2

Function	Domain	Direct binding	Indirect binding
BRCA1			
Recruitment to DNA damage sites	BRCT	Abraxas	RAP80
DNA end resection	BRCT and RING?	CtIP	MRN complex
G2/M checkpoint	BRCT	Abraxas	RAP80
	BRCT	CtIP	MRN complex
	SCD (S1423 and S1524 phosphorylation)	ATM	MRN complex
S-phase checkpoint	SCD (S1387 phosphorylation)	ATM	MRN complex
	BRCT	BRIP1	TOPBP1
Repair during DNA replication	BRCT	BRIP1	TOPBP1
HR	Coiled-coil and S988 phosphorylation	PALB2	BRCA2
BRCA2			
HR	BRC	RAD51	
	DBD	DSS1	
	N terminus	PALB2	BRCA1
	C terminus	RAD51	CDK2

Roy R et al., Nat Rev Cancer, 2012

BRCA1-2 Klinik

	BRCA1 n (%)*	*BRCA2* n (%)*	OR†	95%CI	OR‡	95%CI
Morphology						
Invasive Ductal	2,387 (80)	1,515 (83)	1.00	-	-	-
Invasive Lobular	67 (2.2)	153 (8.4)	3.3	(2.4-4.4)	-	-
Medullary §	281 (9.4)	40 (2.2)	0.25	(0.18-0.35)	-	-
Other	258 (8.6)	116 (6.4)	0.81	(0.63-1.02)	-	-
ER, PR, HER2, TN						
ER-positive	625 (22)	1,475 (77)	11.4	9.8-13.2	10.0	8.2-12.1
PR-positive	539 (21)	1,084 (64)	6.8	5.8-7.9	5.5	4.5-6.6
HER2-positive	138 (10)	121 (13)	1.5	1.1-2.1	1.3	0.9-1.9
Non-TN (vs. TN)	411 (31)	700 (84)	11.0	8.8-13.8	9.0	6.8-11.8
Grade						
Grade 1	64 (3)	100 (7)	1.0	-	1.0	-
Grade 2	481 (20)	603 (43)	1.01	0.72-1.44	1.1	0.67-1.8
Grade 3	1,822 (77)	711 (50)	0.32	0.23-0.45	0.71	0.44-1.17

Mavaddat N et al. Cancer Epidemiol Biomarkers, 2012

Ailesel Meme-Over Kanseri (HBOC)

Kanser Tipi	*BRCA1 (+) %*	*BRCA2 (+) %*
Kadın Meme	50-80	40-70
Over	<40	<20
Prostat	<30	<39
Pankreas	1.3-3.2	2.3-7

Shannon MK et al.Breast Cancer Screening and Diagnosis, 2015

	BRCA1 Taşıyıcısı		BRCA2 Taşıyıcısı	
Yaş	Meme Kanseri %	Over Kanseri %	Meme Kanseri %	Over Kanseri %
25	0	0	0	0
30	2	1	1	0
35	7	2	4	0
40	16	4	7	0
45	30	8	14	0
50	41	15	20	1
55	50	20	26	3
60	55	27	31	5
65	59	33	36	7
70	64	38	49	9
75	69	43	60	11
80	74	48	69	12

Firth HV et al. ODR, Clinical Genetics, 2008

BRCA1-2

- **Rezidüel risk:**
  - BRCA1 mutasyonu taşıyan 50 yaşındaki hasta olmayan kadın, geriye kalan hayatındaki meme kanseri riskini öğrenmek istiyor:

$$1 - \frac{\text{100-80 yaşına kadar hastalık geliştirme riski}}{\text{100-X yaşına kadar hastalık geliştirme riski}}$$

1- (100-74)/(100-41)=1-26/59=0,56 **%56**

BRCA1-2

- Kontrolateral Meme Ca geliştirme riski

Yaş	BRCA1 Taşıyıcısı	BRCA2 Taşıyıcısı
40	33	18
50	50	37
60	60	48
70	65	52
80	70	57

Firth HV et al. ODR, Clinical Genetics, 2008

Erkek Meme Kanseri

- Meme Ca ve erkek kanserlerin %1'i
  - İsrail: 1,08/100bin/yıl
  - Tayland 0,14/100bin/yıl
- Postmenapozal kadın meme kanserine benzer
- En önemli risk faktörü aile öyküsü
  - 1. derece akraba 2-5 kat risk artışı
- %10 herediter

	High penetrance	Moderate penetrance	Low penetrance
Genes	*BRCA2*, *BRCA1*	*CHEK2*, *PALB2*	2q35, 6q25.1 (*ESR1*), 10q21.2, 11q13.3, 12p11.22, 14q24 (*RAD51L1*) and 16q12.1 (*TOX3*)
Population frequency	<0.1%	MAF 1%	MAF >10%
Cancer risk (odds ratio)	>10.0	>2.0	0.76–1.57

Rizzoli P et al. Annals of Oncology, 2013

ACMG

Breast cancer, female	• Breast cancer dx at age ≤50 • Triple-negative breast cancer dx at age ≤60 • ≥2 primary breast cancers in the same person • Ashkenazi Jewish ancestry and breast cancer at any age • ≥3 cases of breast, ovarian, pancreatic, and/or aggressive prostate cancer in close relatives, including the patient • Breast cancer and one additional LFS tumor (Table 5) in the same person or in two relatives, one dx at age ≤45 • Breast cancer and ≥1 PJ polyp in the same person • Lobular breast cancer and diffuse gastric cancer in the same person • Lobular breast cancer in one relative and diffuse gastric cancer in another, one dx at age <50 • Breast cancer and two additional Cowden syndrome criteria (Table 4) in the same person
Breast cancer, male	• Single case present
Ovarian/Fallopian tube/ primary peritoneal cancer	• Single case present in the patient or a FDR

Hampel H et al. Genetics in Medicine, 2014

NCCN

Box 1.1 NCCN Criteria for Referral to Genetics Provider: Hereditary Breast and/or Ovarian Cancer Syndrome Testing Criteria [a,b,c] (V4.2013)

Individual from a family with a known deleterious BRCA1/BRCA2 mutation

Personal history of breast cancer[d] + one or more of the following:

- Diagnosed at age ≤45 years
- Two breast primaries[e] when first breast cancer diagnosis occurred ≤ age 50 years
- Diagnosed at age ≤50 years with ≥1 close blood relative with breast cancer at any age or with a limited family history
- Diagnosed at age ≤60 years with a triple-negative breast cancer
- Diagnosed at any age with ≥1 close blood relative[f] with breast cancer diagnosed ≤50 years
- Diagnosed at any age with ≥2 close blood relatives[f] with breast cancer at any age
- Diagnosed at any age with ≥1 close blood relative with epithelial ovarian cancer
- Diagnosed at any age with ≥2 close blood relatives[f] with pancreatic cancer or aggressive prostate cancer (Gleason score ≥7) at any age
- Close male blood relative[f] with breast cancer
- For an individual of ethnicity associated with higher mutation frequency (e.g., Ashkenazi Jewish), no additional family history may be required.[g]

Personal history of epithelial ovarian[h] cancer

Personal history of male breast cancer

Personal history of pancreatic cancer or aggressive prostate cancer (Gleason score ≥7) at any age with ≥2 close blood relatives[f] with breast and/or ovarian[h] and/or pancreatic or aggressive prostate cancer (Gleason score ≥7) at any age

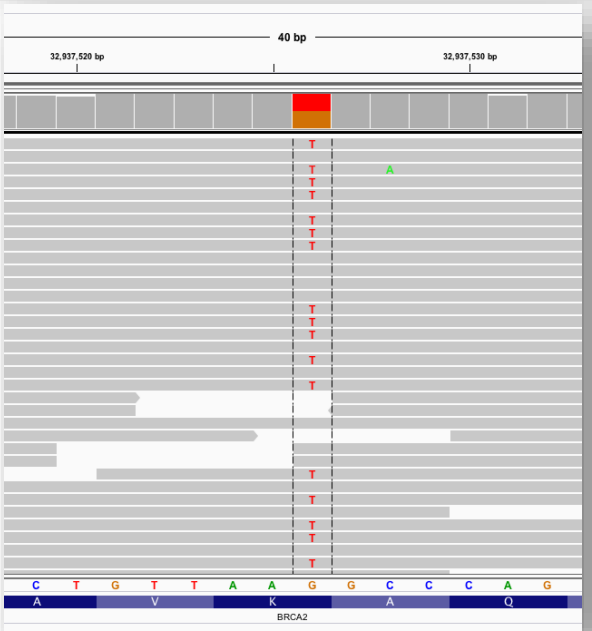
Family history only (significant limitations of interpreting test results for an unaffected individual should be discussed):

- First- or second-degree blood relative meeting any of the above criteria
- Third-degree blood relative with breast cancer[d] and/or ovarian[h] cancer with ≥2 close blood relatives[f] with breast cancer (as least one with breast cancer ≤50 years) and/or ovarian[h] cancer
- Clinical judgment should be used to determine if the patient has reasonable likelihood of a mutation, considering the unaffected patient's current age and the age of the female unaffected relatives who link the patient with the affected relatives
- Testing of unaffected individuals should only be considered when an appropriate affected family member is unavailable for testing

BRCA1-BRCA2

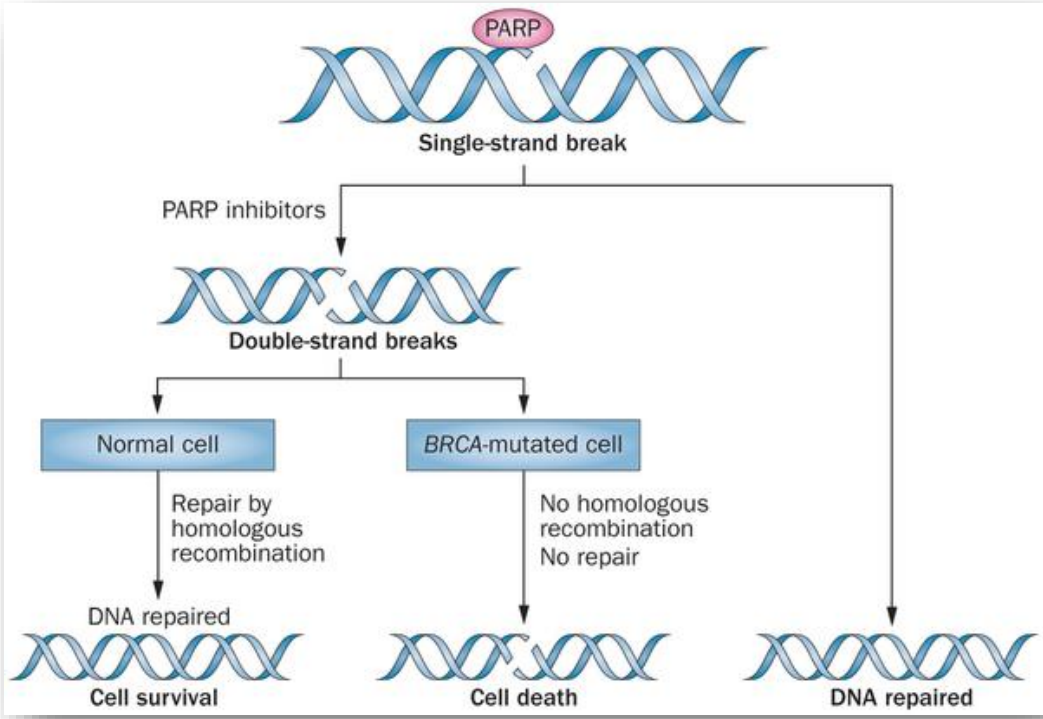
- 737 olgu
  - 90 bağımsız olguda mutasyon
    - Dünyada ilk defa tanımlanan 12 mutasyon
  - %12,2

- **BRCA1**
  - 44 olguda
    - 37 farklı mutasyon
    - 5 over kanseri
    - 1 ailede over kanseri
    - Ortalama tanı yaşı:46
- **BRCA2**
  - 46 olguda
    - 39 farklı mutasyon
    - 3 over kanseri
    - 1 ailede over kanseri
    - Ortalama tanı yaşı:51,5



PARP İnhibitörleri

- poly-(ADP-ribose) polymerase (PARP)
  - DNA kırık tamiri
- PARP+BRCA1/BRCA2
  - Sentetik letal
- ATM
- PTEN



Sonneblick A et al. *Nature Reviews Clinical Oncology*, 2015

Ailesel Meme-Over Kanseri Sendromları

- *BRCA ilişkili HBOC*
- *Li-Fraumeni*
  - TP53
  - Hayat boyu kanser riski %100
  - Meme CA riski 60 yaşına kadar %50

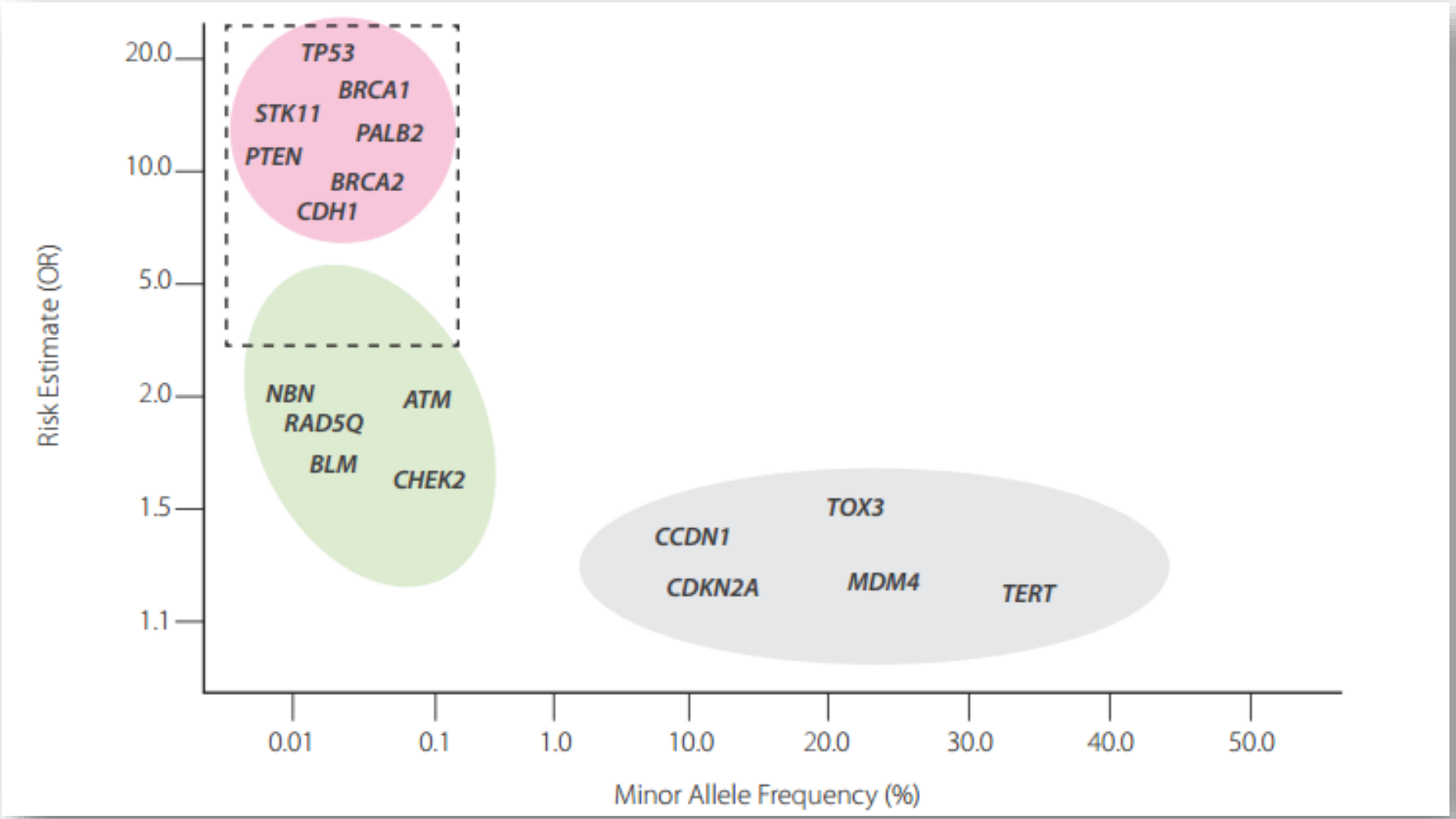
- Soft-tissue sarcoma
- Osteosarcoma
- Brain tumor
- Breast cancer (often early onset)
- Adrenocortical tumor
- Leukemia
- Bronchoalveolar cancer
- Colorectal cancer

- *Peutz Jeghers*
  - STK11
  - Mukokutanöz lezyonlar (%95)
  - Meme Ca
    - %55
  - Over Ca
    - %21

Ailesel Meme-Over Kanseri Sendromları

- *PTEN Hamartom Tümör Sendromu*
  - PTEN
  - Hayat boyu Meme Ca riski
    - %85
  - Endometriyal kanser
- *Kalıtsal Diffüz Gastrik Kanser Sendromu*
  - CDH1
  - Invaziv Lobuler Meme Ca
    - %60
- *Lynch Sendromu*
  - HNPCC (**MSH2, MLH1**, MSH6, PMS2, EPCAM)
  - Kolon, EM, Over ve mide Ca
  - Meme Ca ilişkisi tartışmalı
    - Ortaya çıkma yaşı 44-65
  - Multigen paneller sayesinde
    - 112/21 olguda HBOC kriterleri

Ailesel Meme-Over Kanseri



Bogdanova et al. Herediatry Cancer in Clinical Practice, 2013

MiSeq TruSight Cancer

AIP	CEBPA	FANCA	KIT	PRF1	SLX4
ALK	CEP57	FANCB	MAX	PRKAR1A	SMAD4
APC	**CHEK2**	FANCC	MEN1	PTCH1	SMARCB1
ATM	CYLD	FANCD2	MET	**PTEN**	**STK11**
BAP1	DDB2	FANCE	MLH1	**RAD51C**	SUFU
BLM	DICER1	FANCF	MSH2	**RAD51D**	TMEM127
BMPR1A	DIS3L2	FANCG	MSH6	RB1	**TP53**
BRCA1	EGFR	FANCI	MUTYH	**RECQL4**	TSC1
BRCA2	EPCAM	FANCL	NBN	RET	TSC2
BRIP1	ERCC2	FANCM	NF1	RHBDF2	VHL
BUB1B	ERCC3	FH	NF2	RUNX1	WRN
CDC73	ERCC4	FLCN	NSD1	SBDS	WT1
CDH1	ERCC5	GATA2	**PALB2**	SDHAF2	XPA
CDK4	EXT1	GPC3	PHOX2B	SDHB	XPC
CDKN1C	EXT2	HNF1A	PMS1	SDHC	
CDKN2A	EZH2	HRAS	PMS2	SDHD	

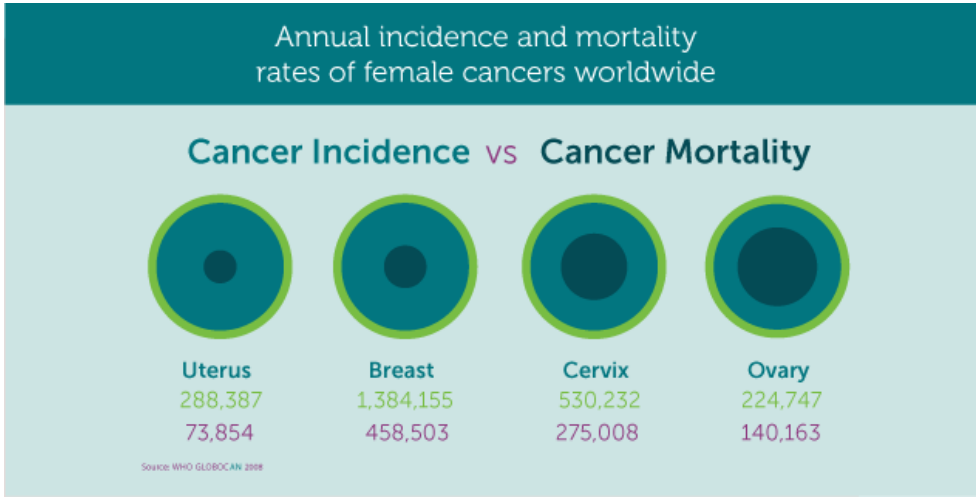
Cumulative target region size	255 Kb
Number of target genes	94
Number of target exons	> 1,700
Probe size	80-mer
Number of probes	~4,000
Recommended mean coverage	100×
Target minimum coverage	20×
Percent exons covered based on coverage metrics	≥ 95%

Meme Over Kanser Paneli

- BRCA1 BRCA2 (-)
- Aile öyküsü (+)
  - 36 olgunun 12'sinde
    - PALB2 geninde 1'i daha önceden tanımlı 1'i yeni
    - CHEK2 geninde 1'i daha önceden tanımlı 1'i yeni
    - ATM geninde tanımlı 2
    - RAD51 geninde 1 yeni
    - FANCI geninde 1 tanımlı
    - SLX4 geninde 1 tanımlı
    - TP53 geninde 1 tanımlı
    - CDH1 geninde 1 tanımlı
    - BRIP1 geninde 1 yeni

Jinekolojik Kanser

- Kadınlarda
  - Tüm kanserlerin
    - %16,3
  - Kanserden ölümlerin
    - %13,9
- Serviks>Uterus>Over
- Uterus Ca
  - %5
- Over Ca
  - %20



Constantinouet P et al., Best Practice & Research Clinical Obstetrics and Gynaecology, 2017

Over Kanseri

- Kadınların en sık 7. kanseri
  - Yaşam boyu risk
    - %2
  - %90 EOC
    - %30-70 seröz adenokarsinom
- Aile öyküsü en önemli risk faktörü
  - 1. derece akraba
    - 1 tane 3 kat
    - 2 tane 6 kat

Constantinouet P et al., Best Practice & Research Clinical Obstetrics and Gynaecology, 2017

Over Kanseri

- Kalıtsal over kanseri
  - Daha erken başlangıçlı
  - Aile öyküsü daha fazla pozitif
  - Eşlik eden kanserler mevcut
    - ***HBOC***
      - Meme
    - ***Lynch Sendromu***
      - Kolon
      - Endometrium

Constantinouet P et al., Best Practice & Research Clinical Obstetrics and Gynaecology, 2017

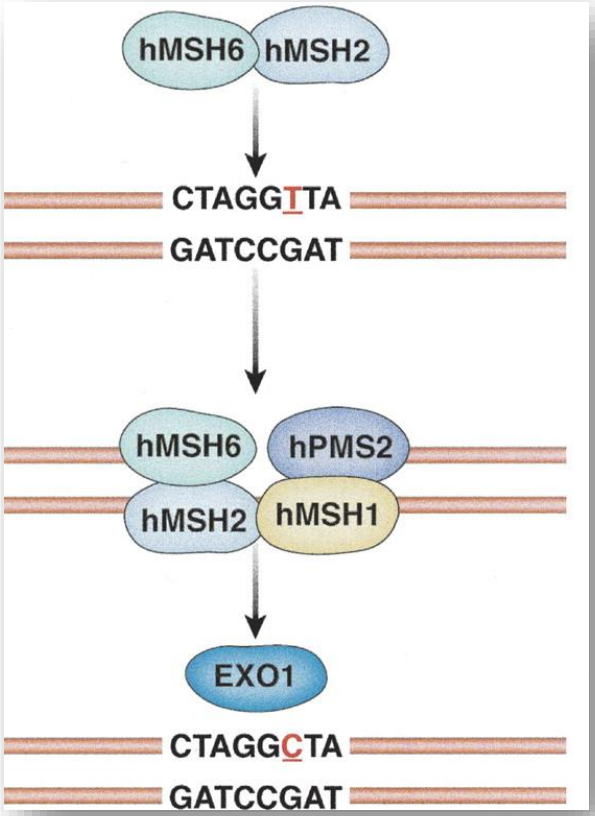
Over Kanseri

- BRCA1-2 pozitif olgularda
  - %60-100 seröz adenokarsinom
  - High Grade seröz EOC
  - Prekürsör lezyon
    - Fallopian tüpler

Constantinouet P et al., Best Practice & Research Clinical Obstetrics and Gynaecology, 2017

Over Kanseri-Lynch Sendromu

- Hayat boyu over ca riski
  - %10
- Tüm kalıtsal over kanseri olgularının
  - %10-15'i
- Mutasyon
  - MLH1 ve MSH2
- Başlangıç yaşı
  - Hem sporadik hem de HBOC'den erken
- Düşük grade
- Histopatolojik tip karışık
- BSO+histerektomi



Constantinouet P et al., Best Practice & Research Clinical Obstetrics and Gynaecology, 2017

Over Kanseri

- Profilaktik BSO
  - Over CA riskini
    - %80-96 azaltır
  - Mortaliteyi
    - %60-70
  - Küçük bir oranda primer peritoneal Ca riski kalır
  - Önerilen yaş
    - BRCA1
      - 35-40
    - BRCA2
      - 40-45

Constantinouet P et al., Best Practice & Research Clinical Obstetrics and Gynaecology, 2017

Endometriyal Kanser

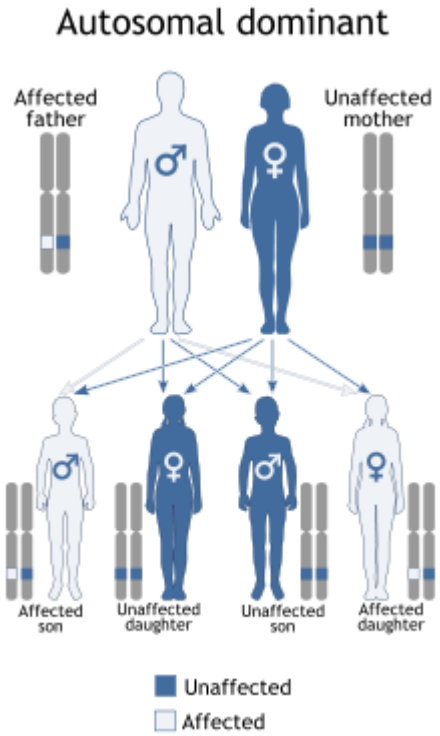
- Yaşam boyu risk %2,4
  - 65-70 yaş grubunda %6

- Uterus kanserlerinin
  - %95 endometriyal kanser
    - %85 endometrioid
- Riskler
  - Obezite
  - Tamoxifen
  - HRT

Constantinouet P et al., Best Practice & Research Clinical Obstetrics and Gynaecology, 2017

Endometriyal Kanser

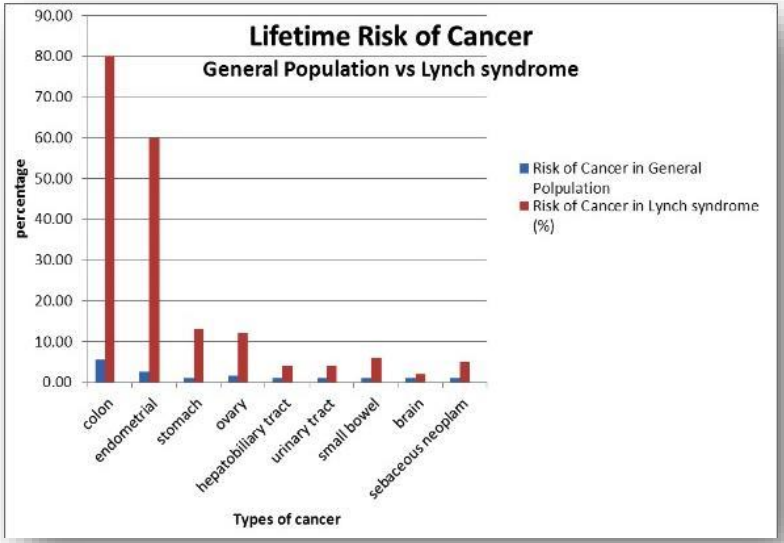
- Aile öyküsü
  - %5
  - 20-54 yaşları arasında risk fazla
- Lynch Sendromu
  - Kolorektal+endometriyal kanser
  - %2
  - OD kalıtım



Constantinouet P et al., Best Practice & Research Clinical Obstetrics and Gynaecology, 2017

Endometriyal Kanser

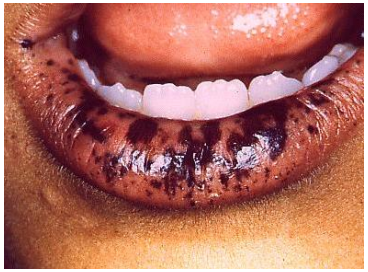
- 70 yaşına kadar EK riski
  - %39
  - Median yaş 47,5
  - MSH6 en yüksek risk
    - %26-71
  - PMS2 en düşük risk
    - %15



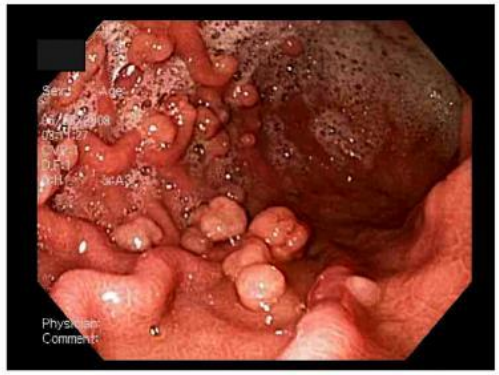
- 40 yaşından sonra
  - Histerektomi +BSO

Constantinouet P et al., Best Practice & Research Clinical Obstetrics and Gynaecology, 2017

Herediter Servikal Kanser



- **Peutz Jeghers S.**
  - STK11
  - OD
  - GIS hamartomatöz polipozis
  - Kansere yatkınlık
    - Adenoma malignum
      - Yaşam boyu risk %10
    - Overyan seks kord tümör
    - Meme
    - İnce bağırsak
  - Profilaktik histerektomi düşünülebilir



Constantinouet P et al., Best Practice & Research Clinical Obstetrics and Gynaecology, 2017

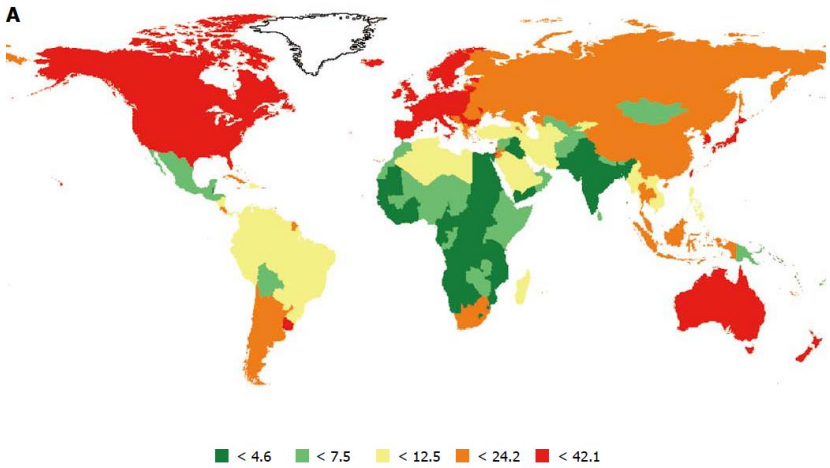
Vulva Kanseri

- Fankoni Anemisi
  - OR
  - Klinik bulgular
    - Boy kısalığı
    - Radial ray anomalileri
    - Mikrosefali
    - KI disfonksiyonu
    - Vulva kanseri
      - 2411 kat risk artışı

Alter BP et al., Br J Haematol, 2010

Kolorektal Kanser

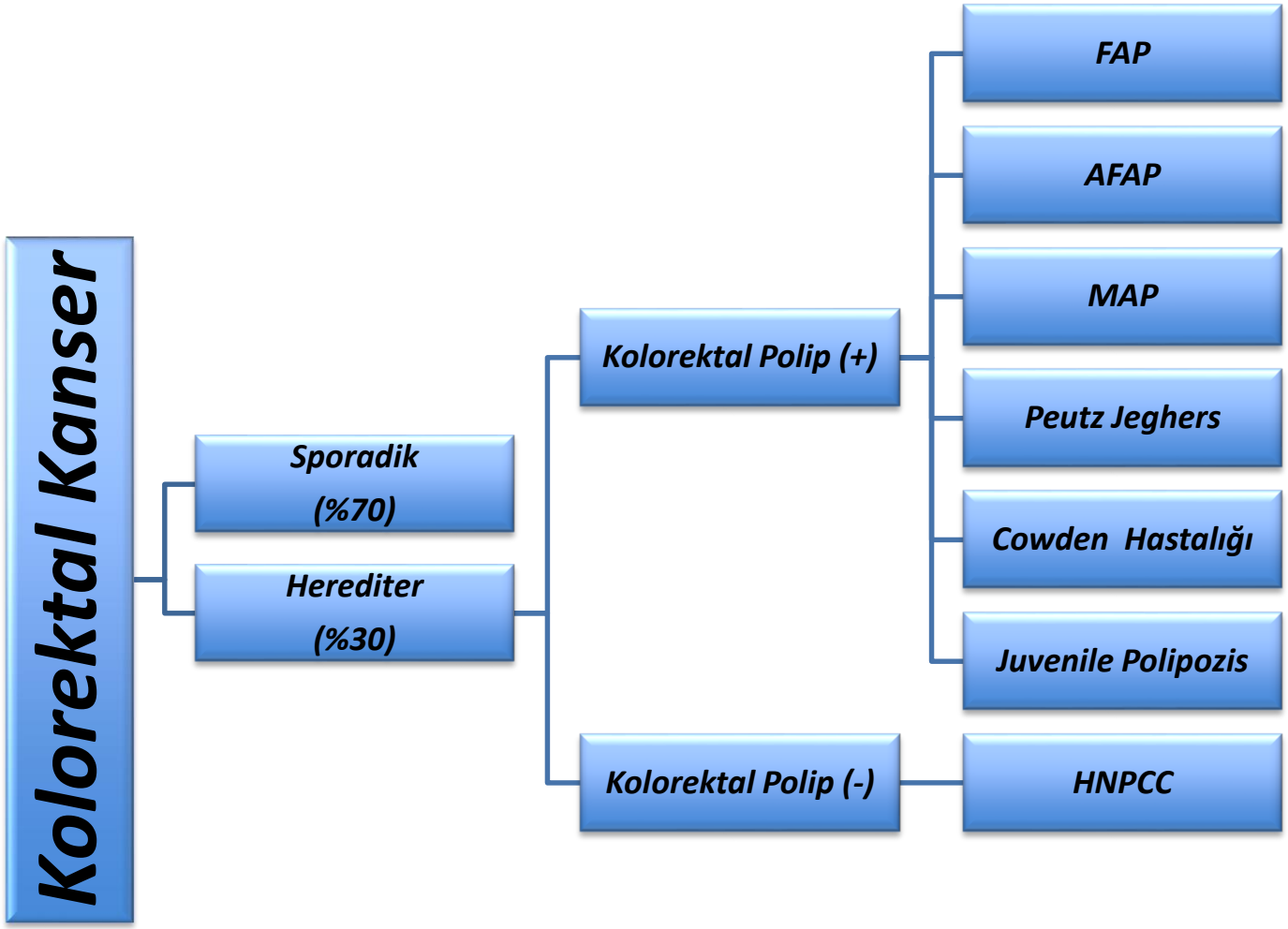
- Görülme sıklığında
  - 3. (1 milyon yeni tanı/yıl)
- Kanserden ölümlerde
  - 4. (600.000 ex/yıl)
- %30-35 genetik faktörler (ailesel)
  - %5’ i iyi tanımlanmış Mendeliyan kalıtım



Patel SG et al. Curr Gastroenterol Rep. 2012

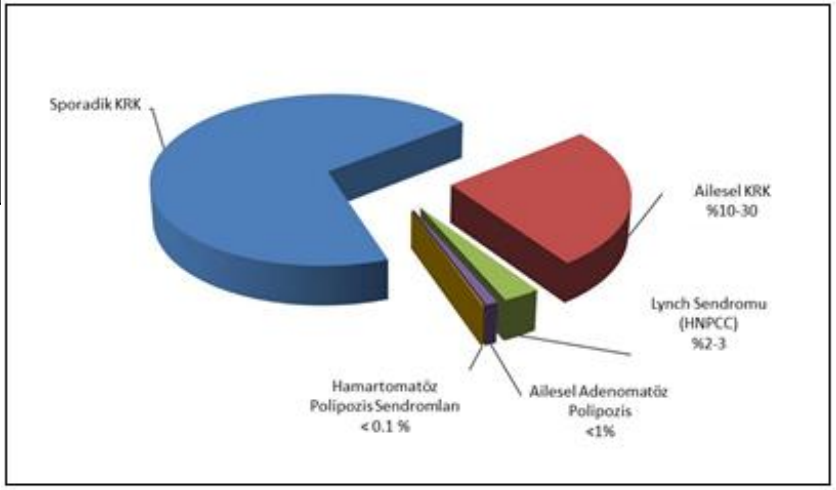
Esteban Jurado C et al. World J Gastroenterology, 2014

Kolorektal Kanser

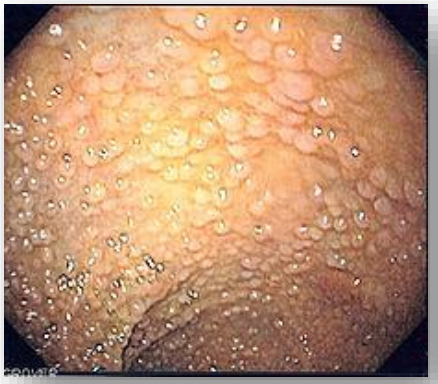


Kolorektal Kanser

Sendrom	Gen
Non polipozis ile giden kolon kanserleri	
Lynch Sendromu (LS)	MMR
Polipozis ile giden kolon kanserleri	
Adenomatöz polipozis	
Familyal adenomatöz polipozis (FAP)	APC
Attenuated familyal adenomatöz polipozis (AFAP)	APC
MUTYH ile ilişkili polipozis (MAP)	MUTYH
Hamartomatöz polipozis	
Peutz-Jeghers sendromu (PJS)	STK11 (LKB1)
Juvenile polipozis sendromu (JPS)	SMAD4, BMPR1A
Cowden sendromu (CS)	PTEN



FAP



- 1/8324 canlı doğum
- APC geni
- Kolon ve rektum da 100-1000 polip
- Cerrahi yapılmazsa 40-50 yaşında
  - %100 kolorektal kanser
- Olguların %30’ unda mutasyon saptanamaz

Lee GH et al. World J Gastroenterology, 2014

FAP- Ekstrakolonik

- ***Malign***
  - Duedonal kanser en sık 2. kanser
    - %4-12 yaşam boyu risk
  - Pankreatik, tioid, hepatoblastom ve medullablastom kümülatif riski %1-2 arasında

- ***Benign***
  - CHRPE
  - Osteom
  - Epidsermoid kist
  - Fibrom
  - Desmoid tümörler
    - APC geni 1444. kodon sonrası mutasyonlar

Attenuated Familyal Adenomatöz Polipozis (AFAP)

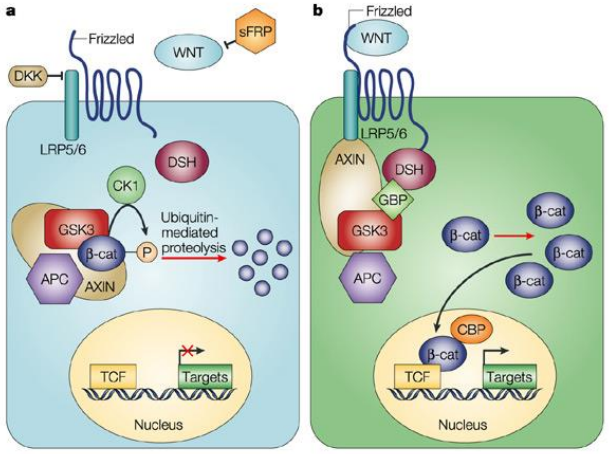
- FAP' ın daha hafif formu
  - 100 altında polip
  - Geç başlangıç
  - FAP' ın %8' i
  - CRC gelişme riski %70

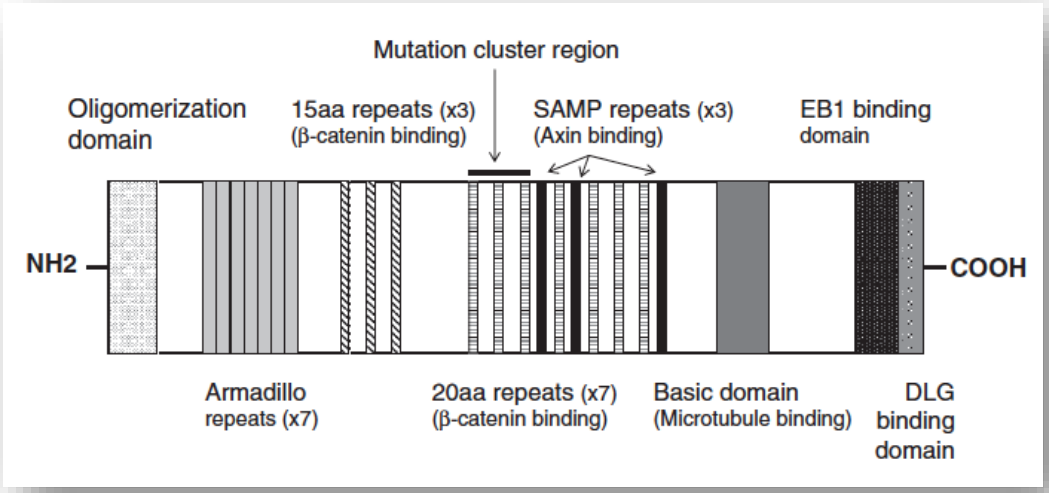
- APC ya da MUTYH geninde
  - %72

- ***APC genindeki mutasyonlar***
  - Kodon 157' den önce
  - Kodon 1595' ten sonra
  - Ekzon 9 alternatif splicing' e uğrayan fragmanında

APC

- APC geni
  - 5q21-q22
  - 16 ekzon,2843 aa
  - 1683 mutasyon
    - Non sense ve frameshift mutasyonlar
  - %15-20 de novo





Genetics of Colorectal Cancer, Springer, 2009

APC Genotip Fenotip Korelasyonu

Groups	Genotype	Gene and codons
Unclassified mutation	0	—
Mild FAP (5′ mutations)	1	*APC* 0–178, alternatively spliced region of exon 9 (312–412)
Mild FAP (3′ mutations)	2	*APC* >1550
Classical FAP	3	*APC* 179–1249 (excluding 312–412 of exon 9)
Severe FAP	4	*APC* 1250–1549
MAP	5	Chromosome 1 position 34.3-32.1

	Genotype 0: unknown mutation	Genotype 1: *APC* 0–178, alternatively spliced region of exon 9 (312–412)	Genotype 2: *APC* >1550	Genotype 3: *APC* 179–1249 (excluding 312–412 of exon 9)	Genotype 4: *APC* 1250–1549
Total number of samples ($n = 175$)	19 (10.9%)	26 (14.9%)	26 (14.9%)	73 (41.71%)	31 (17.7%)
Median age of onset of polyps (years)	20.3 (12.4–28.2)	35.6 (34.6–36.6)	32.2 (19.0–45.4)	15.9 (13.8–18.0)	14.8 (11.11–18.6)
Mean age of onset of polyps (years)	19.6 (16.3–22.8)	37.4 (31.6–43.2)	29.1 (23.6–34.6)	21.5 (18.6–24.5)	19.40 (16.2–22.6)

Newton KF et al. Clin Genet, 2012

APC Genotip Fenotip Korelasyonu

	Genotype 0: unknown mutations	Genotype 1: *APC* 0–178, alternatively spliced region of exon 9 (312–412)	Genotype 2: *APC* >1550	Genotype 3: *APC* 179–1249 (excluding 312–412 of exon 9)	Genotype 4: *APC* 1250–1549	Genotype 5: *MutYH* (chromosome 1)
Total number of samples (%), $n = 428$	80 (18.7)	49 (11.5)	52 (12.2)	175 (40.9)	60 (14.0)	12 (2.8)
Number of dead patients (%)	31 (38.8)	12 (24.5)	21 (40.4)	54 (30.9)	22 (36.7)	4 (33.3)
Censored data (%)	49 (61.3)	37 (75.5)	31 (59.6)	121 (69.1)	38 (45.0)	8 (66.7)
Cause of death CRC (%)	20 (64.5)	6 (50.0)	9 (42.9)	34 (63.0)	12 (54.5)	3 (75.0)
Cause of death, other FAP-related tumour (%)	2 (6.5) 1 duodenal cancer 1 pancreatic cancer	3 (25.0) 2 duodenal cancer 1 thyroid cancer	5 (23.8) 1 hepatoblastoma 4 desmoids (19.05)	5 (9.23) 1 duodenal cancer 1 oesophageal cancer 1 gastric cancer 2 desmoids	5 (22.7) 1 duodenal cancer 1 pancreatic cancer 1 bony tumour 1 desmoid 1 hepatoblastoma	1 (25) 1 gastric cancer
Cause of death, unrelated (%)	3 (9.7)	3 (25.0)	5 (23.8)	9 (16.7)	3 (13.7)	0
Cause of death unknown (%)	5 (16.1)	0	2 (9.5)	6 (11.1)	2 (9.1)	0
Median survival (years) and 95% CI	56.6 (44.3–69.0)	74.9 (59.0–90.8)	61.0 (50.0–72.0)	63.0 (56.3–69.8)	48.1 (40.6–55.6)	69.7 (no CI as high proportion censored data)

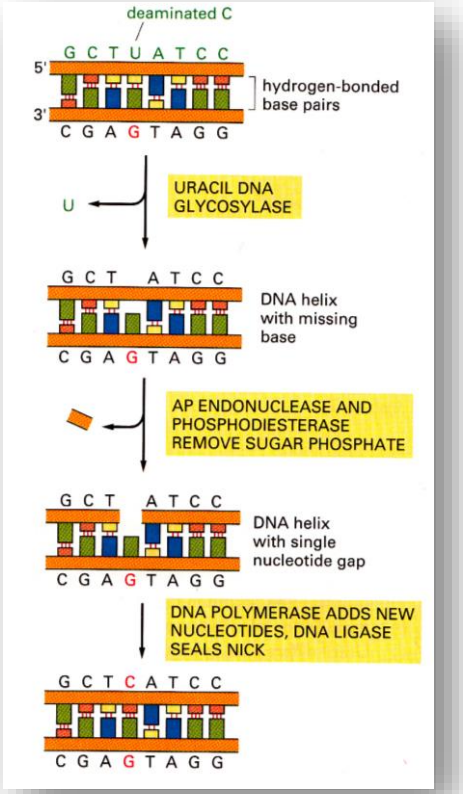
Newton KF et al. Clin Genet, 2012

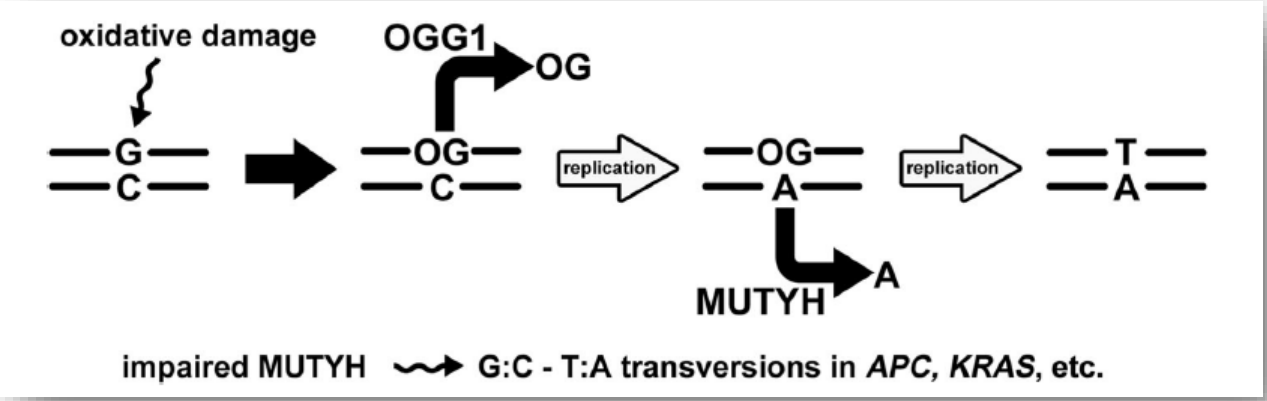
MUTYH ile İlişkili Polipozis (MAP)

- KRK→%0.3-1
- 10-100 adenom
- Ortalama tanı yaşı 45
- Klinik olarak AFAP'a benzer
  - FAP/AFAP'ta görülen ekstrakolonik ve ekstraintestinal bulgular + ama daha nadir
- ***KRK gelişme riski %35-63***
- ***APC (-) polipozisli olguların %20-30'unda MUTYH +***

MAP

- ***MUTYH geni***
  - Otozomal resesif kalıtım
  - Base excision repair
  - APC, KRAS geninde
    - G:C –T:A transversiyonu





Yamaguchi S et al. Surg Today, 2014

Diğer Kolonik Polipozis Sendromları

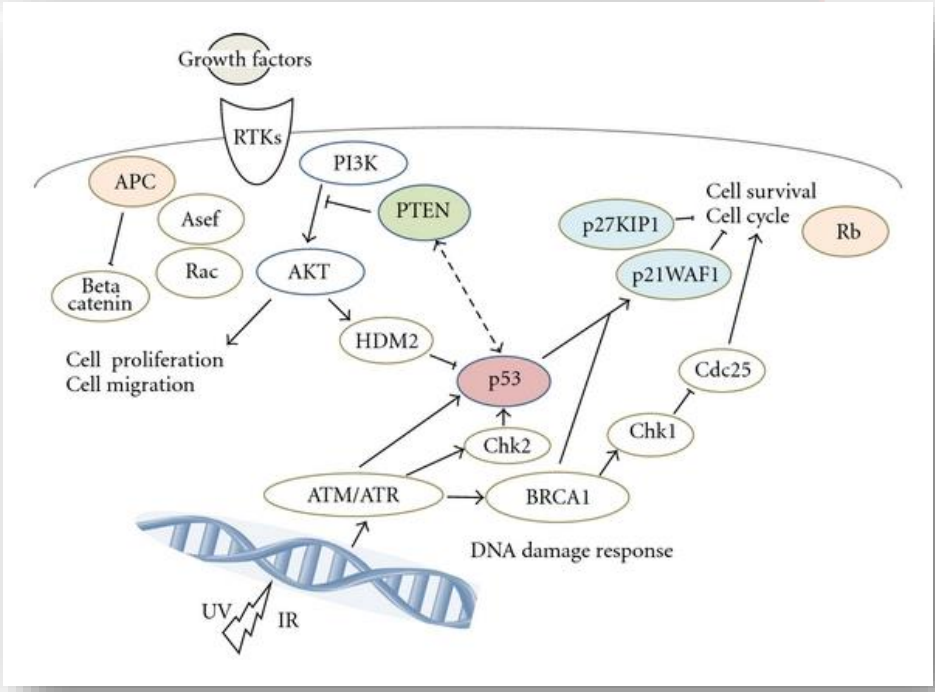
Syndrome	Phenotype	Genetics	Cancer risk	Screening
Hyperplaplastic polyposis	Multiple hyperplastic polyps	Unknown	Colorectal 7–70%	Colonoscopy 2-yearly
MAP	10–100 adenomatous polyps	MYH gene Autosomal recessive	Colorectal 80%	Colonoscopy 2-yearly Gastroscopy 2-yearly
Peutz–Jeghers	Hamartomatous polyposis and mucocutaneous pigmentation	LKB1/STK11 Autosomal dominant	Colorectal 39% Stomach 29% Breast 54% Ovarian 21%	Colonoscopy 2-yearly Gastroscopy 2-yearly Small bowel Breast and ovarian
Juvenile polyposis	Multiple gastrointestinal hamartomas	SMAD4 BMPR1A PTEN Autosomal dominant	Colorectal 68% Gastric 15–21%	Colonoscopy 2-yearly Gastroscopy 2-yearly Small bowel
Cowden's	Hamartomatous polyposis and benign cutaneous tumours	PTEN Autosomal dominant	Breast 30–50% Thyroid 10%	Breast Thyroid Baseline endoscopy

Omundsen M et al. ANZ J Surg, 2012

PHTS

PTEN Hamartom Tümör Sendromu

- Cowden Hastalığı
- Bannayan-Riley-Ruvalcaba S.
- Lermitte-Duclos Hastalığı
- Makrosefali-OSB



Cowden Hastalığı

- OD
- 1/200 bin
- Olguların %35-60' ında polip
- Melanoma, meme, tiroid, EM, kolorektal ve böbrek kanserlerine yatkınlık

	Number of cancers		
Cancer	**Observed**	**Expected**	**SIR**
Breast[a]	67	2.64	25.4
Thyroid	48	0.94	51.1
Endometrium[a]	24	0.56	42.9
Colorectal	12	1.17	10.3
Kidney	15	0.49	30.6
Melanoma	9	1.06	8.5

[a]Female subjects only.

Tan MH et al. Clin Cancer Res, 2012

Cowden Hastalığı

- PTEN mutasyonu
  - Penetrans %80
  - %80 olguda mutasyon saptanır
  - Genotip fenotip korelasyonu yok

Tan MH et al. Clin Cancer Res, 2012

Herediter Nonpolipozis Kolorektal Kanser (Lynch Sendromu)

Mutant olan gene bağlı

- KRK;
  - MLH1 → %80
  - MSH2 → %77
  - MSH6 → %50
  - EPCAM → %75
  - PMS2 → %15-20
- Endometriyum kanseri;
  - MLH1 → %54
  - MSH2 → %21
  - MSH6 → %16
  - EPCAM → %12
  - PMS2 → %15

Herediter Nonpolipozis Kolorektal Kanser (Lynch Sendromu)

Kanser	Lynch Sendrom (%)	Genel Populasyon
KRK - erkek	54-74	5
KRK - kadın	30-52	
Endometriyum	28-60	2
Over	6-7	1
Mide	6-9	<1
İnce barsak	3-4	<1
Pankreas	< 1-4	1
Hepatobilier trakt	1	Nadir
Üriner trakt	3-8	Nadir
Beyin	2-3	<1
Sebasöz deri tümörü/keratoakantom	1-9	nadir

Herediter Nonpolipozis Kolorektal Kanser (Lynch Sendromu)

- Mikrosatellit sekanslarının uzunluklarındaki değişiklikler→ mikrosatellit instabilte (MSI)
  - MSI, malign hücrelerde bozulmuş DNA tamirinin bir göstergesi
  - MMR eksikliğinin moleküler belirteci

- 5 tane mikrosatellit belirteç;
  - 2-↑ yeni allel MSI-High (MSI-H)
  - 1 yeni allel MSI-Low (MSI-L)
  - Değişiklik Ø mikrosatellit stable (MSS)

- MSI-H olan tümörlere→ MMR germline analizi +

Herediter Nonpolipozis Kolorektal Kanser (Lynch Sendromu)

- 1991 yılında Amsterdam Kriterleri
- 1999 yılında Amsterdam 2 kriterleri

Amsterdam II Kriterleri

En az 3 akrabada Lynch ile ilişkili kanser olmalı

2 ya da daha fazla jenerasyon etkilenmeli

50 yaşından önce 1 ya da daha fazla akrabada tanı almalı

Olgulardan biri diğer ikisinin birinci derece akrabası olmalı

FAP dışlanmalı

Tümör dokusu patolojik değerlendirmeden geçmeli

Herediter Nonpolipozis Kolorektal Kanser (Lynch Sendromu)

- 1997 yılında Bethesda kriterleri
- 2004 yılında Revize Bethesda kriterleri
  - %90 sensitivite ve %80 spesifite
  - Germline mutasyon taşıyıcıların %70- 80'ini +

Revize Bethesda Kılavuzu
50 yaş veya öncesi kolorektal kanser tanısı almış olmak
Yaştan bağımsız olarak senkron ya da metokron kolorektal kanser veya Lynch ile ilişkli diğer tümörlerin bulunması
60 yaş altında kolorektal kanserli olguda Lynch benzeri histoloji olması
Bir veya daha fazla birinci derece akrabasında KRK veya HNPCC ilişkili tümör bulunan olgular, olguların birinde kanser 50 yaştan önce saptanmış olmalı
KRK'li bir olguda, yaşa bakılmaksızın 1 veya 2. derecede akrabalarında iki veya daha fazla HNPCC ilişkili tümör bulunanlar

Kolorektal Kanser-Trusight Cancer

AIP	CEBPA	FANCA	KIT	PRF1	SLX4
ALK	CEP57	FANCB	MAX	PRKAR1A	SMAD4
APC	CHEK2	FANCC	MEN1	PTCH1	SMARCB1
ATM	CYLD	FANCD2	MET	PTEN	STK11
BAP1	DDB2	FANCE	MLH1	RAD51C	SUFU
BLM	DICER1	FANCF	MSH2	RAD51D	TMEM127
BMPR1A	DIS3L2	FANCG	MSH6	RB1	TP53
BRCA1	EGFR	FANCI	MUTYH	RECQL4	TSC1
BRCA2	EPCAM	FANCL	NBN	RET	TSC2
BRIP1	ERCC2	FANCM	NF1	RHBDF2	VHL
BUB1B	ERCC3	FH	NF2	RUNX1	WRN
CDC73	ERCC4	FLCN	NSD1	SBDS	WT1
CDH1	ERCC5	GATA2	PALB2	SDHAF2	XPA
CDK4	EXT1	GPC3	PHOX2B	SDHB	XPC
CDKN1C	EXT2	HNF1A	PMS1	SDHC	
CDKN2A	EZH2	HRAS	PMS2	SDHD	

Trusight Cancer

Cumulative target region size	255 Kb
Number of target genes	94
Number of target exons	> 1,700
Probe size	80-mer
Number of probes	~4,000
Recommended mean coverage	100x
Target minimum coverage	20x
Percent exons covered based on coverage metrics	≥ 95%

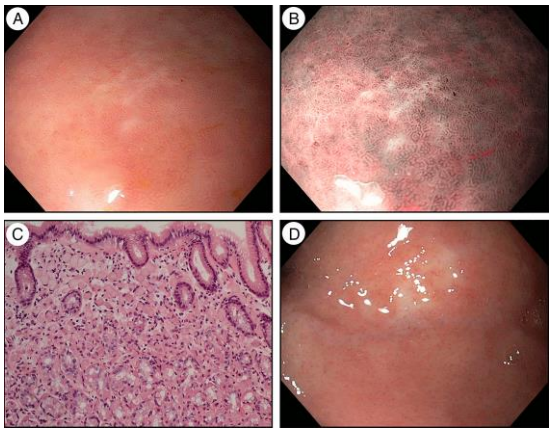
Kolorektal Kanser-Trusight Cancer

Gen	Mutasyon	Mutasyonun tanımlandığı yayın
APC	Heterozigot p.R805X (c.2413C>T)	Zuzana D 1996
	Heterozigot p.Q1447X (c.4339C>T)	Ensembl ve COSMIC
	Heterozigot p.I1307K (3920T>A)	Laken SJ 1996
	Heterozigot p.N1122KfsX3 (c.3364_3367delAATC)	Wallis YL 1999
	Heterozigot p.Q1328X (c.3982C>T)	Paul P 1993
	Heterozigot p.Y1262X (c.3786T>G)	**Çalışmamızda**
	Heterozigot p.E1309DfsX4(c.3927_3931delAAAGA)	Yasuo M 1992
MUTYH	Homozigot p.P295L (c.884C>T)	Sophie L 2006
MLH1	Heterozigot p.D450GfsX29 (c.1343_1344insG)	**Çalışmamızda**
	Heterozigot p.C39W (c.117T>G)	**Çalışmamızda**
	Heterozigot p.S595WfsX14 (c.1783_1784delAG)	Juul W 1996
	Heterozigot p.G67R (c.199G>A)	Pia T 1995
	Heterozigot p.S595WfsX14 (c.1783_1784delAG)	Juul W 1996
MSH6	Heterozigot p.F1103V (c.3307T>G)	**Çalışmamızda**

Mide Kanseri

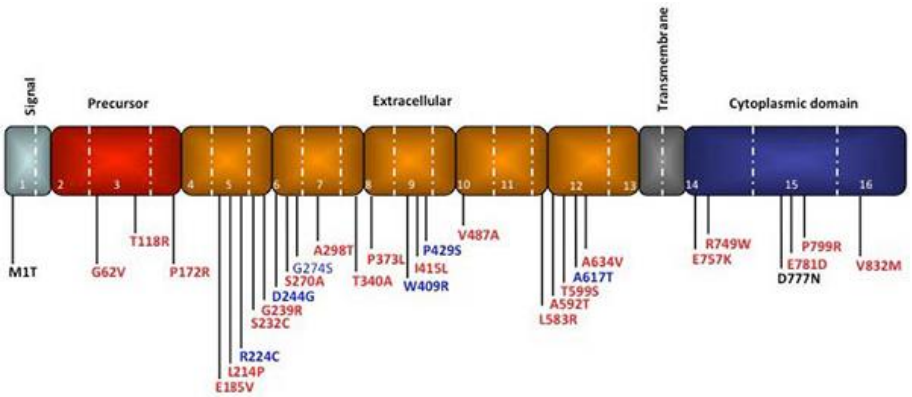
- Gastrik kanser
  - %10 aile öyküsü+
  - %1-3 bilinen kansere yatkınlık sendromu+

- İlgili kansere yatkınlık sendromları
  - Herediter diffüz gastrik kanser (CDH1)
  - HNPCC (Lynch)
  - Li-Fraumeni



Herediter Diffüz Gastrik Kanser

- Herediter diffüz gastrik kanser
  - CDH1 geni
    - E-cadherin



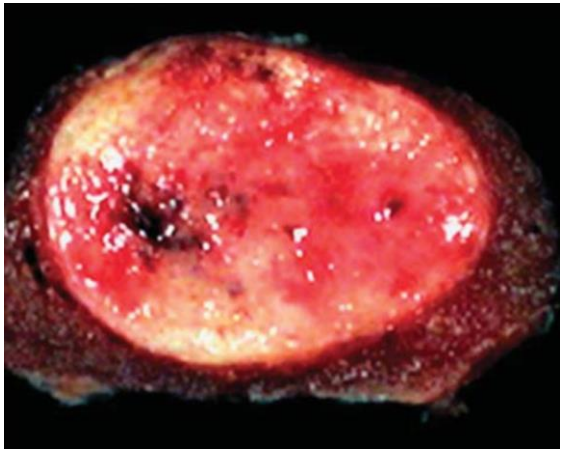
  - Kriterler
    - En az biri 50 yaş altı, 2 ya da daha fazla gastrik kanser tanılı 1./2. derece akraba
    - Yaştan bağımsız 3 ya da daha fazla gastrik kanser tanılı 1./2. derece akraba
    - Ailede 40 yaş altı diffüz gastrik kanser tanısı
    - Biri 50 yaş altı, gastrik kanser ve lobüler meme kanseri tanısı

van der Post RS, et al. J Med Genet 2015

Tiroid Kanseri

- Medüller tiroid Ca
  - Nöral krestten köken alan C tiroid hücreleri
  - Tiroid kanserlerinin %5'i
  - Ölümlerin %15'i
  - ~%25 herediter

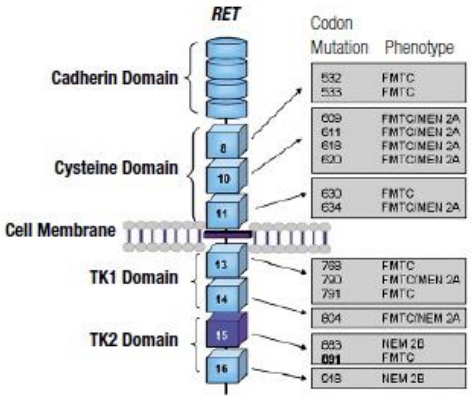
- Non-medüller tiroid Ca
  - %5-15 herediter



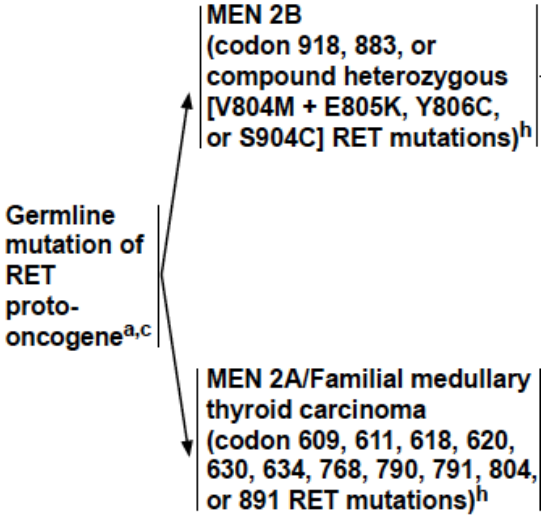
RET

- Medüller tiroid kanseri
  - FTMC
  - MEN2A
  - MEN2B

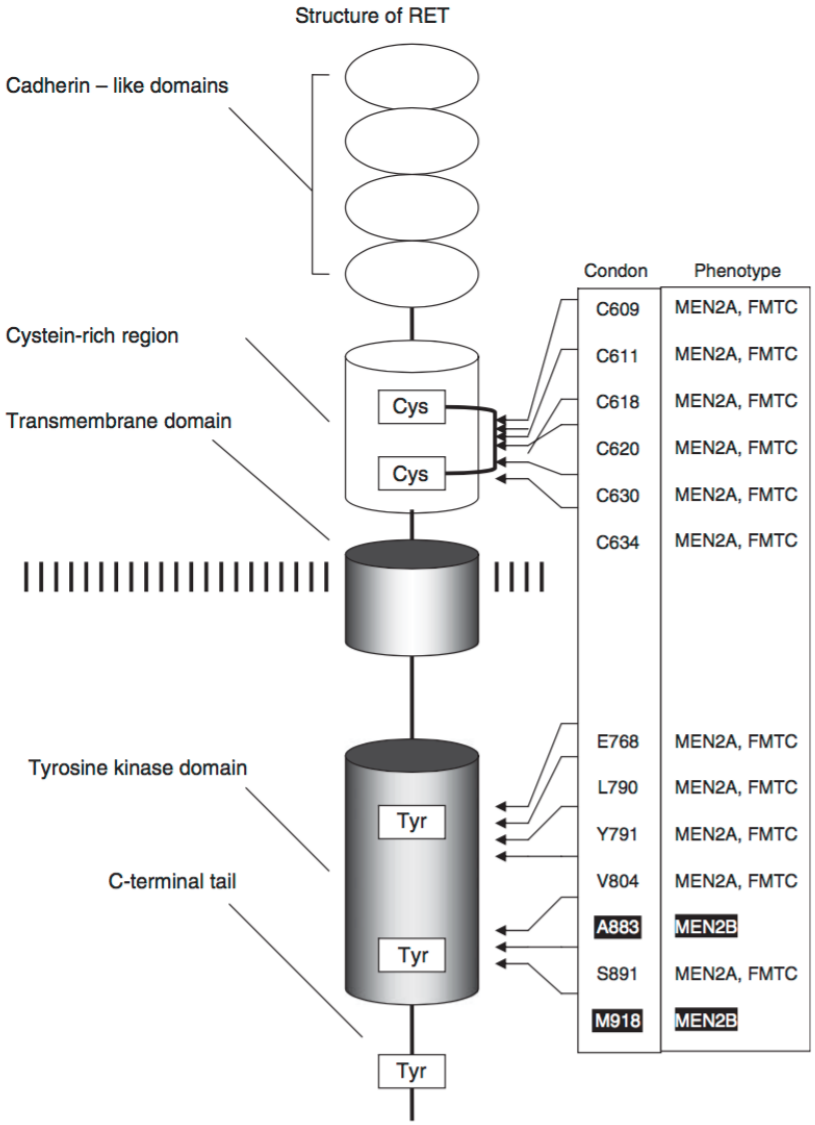
RET



Subtype	Medullary Thyroid Carcinoma	Pheochromocytoma	Parathyroid Disease
MEN 2A	95%	50%	20%-30%
FMTC	100%	0%	0%
MEN 2B	100%	50%	Uncommon



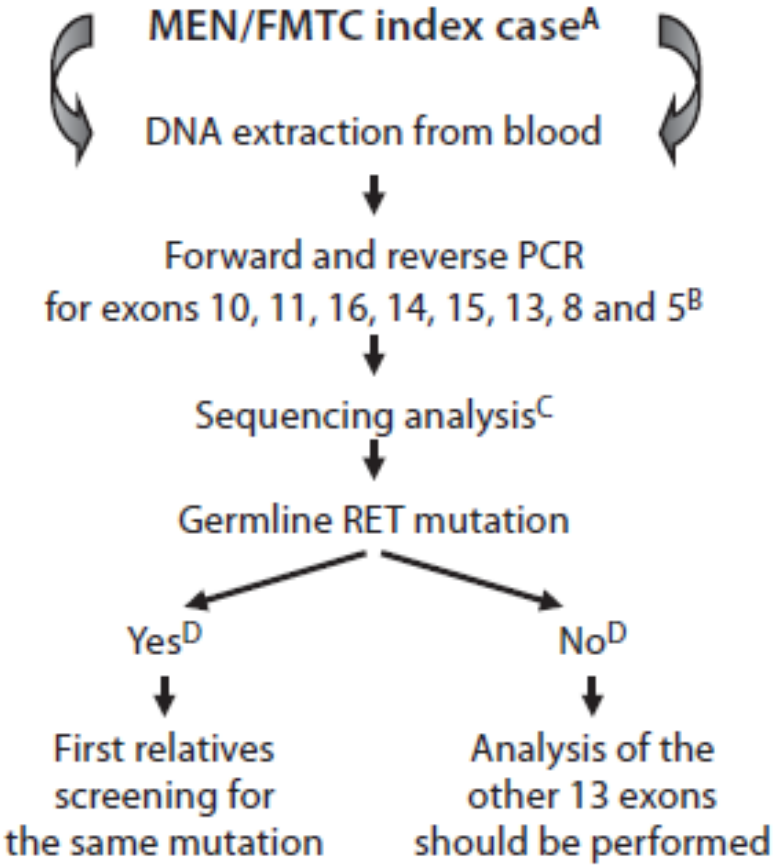
Tiroid Kanseri



RET mutation codons	*Prophylactic thyroidectomy*
838, 918	<1 year; within first 6 months
609, 611, 618, 620, 630, 634, 912	Before 5 years of age
533, 649, 666, 768, 790, 791, 804, 891	Before 5–10 years of age

Nose V. Modern Path, 2011

Tiroid Kanseri



Elisei R, et al. Eur Thyroid J 2012

Tiroid Kanseri

Syndrome	*Inheritance*	*Gene mutation*	*Location*	*Incidence of thyroid cancer*	*Type of thyroid cancer*
Familial adenomatous polyposis	Autosomal dominant	APC tumor suppressor gene	5q21	2–12%	PTC cribriform–morular variant or classical variant
Cowden's syndrome	Autosomal dominant	*PTEN*-tumor suppressor gene	10q23.2	>10%	Follicular and occasional PTC
Carney's complex	Autosomal dominant	PRKAR1-x	2p16 17q22–24	4 and 60%	Follicular and PTC
Werner's syndrome	Autosomal recessive	WRN gene	8p11–p12	18%	Follicular anaplastic PTC

Hampel H, et al. Genetics in Medicin, 2015