

CANCER GENETICS & PREVENTION

CHEK2 Check-in

PATIENT INFORMATION

[Contact Dana Farber for an appointment](#) if you or a family member has a CHEK2 mutation.

What is CHEK2?

CHEK2 is the official abbreviation for the gene called checkpoint kinase 2. This gene codes for a protein called CHK2 – which is a serine threonine kinase. CHEK2 is one of many genes called tumor suppressor genes, which means that it helps the cells regulate their life cycle.

What does the CHEK2 gene specifically do?

CHEK2 produces the protein CHK2 that helps the dividing process of cells by making sure there are no mistakes in the division.

Sometimes when cells are dividing and copying the DNA over, mistakes can happen. Proteins like CHK2 help by recognizing there is a mistake and making sure the new cell either has the right information copied into it or by stopping the copying process to make sure a damaged cell arrests in development – this way only cells with all the correct information are born. CHEK2 is just one of many tumor suppressor genes, and works hand in hand with many other such genes.

What does it mean to have a mutation in CHEK2?

Having a mutation in CHEK2 means that somewhere in the code of the CHEK2 gene there is a change. Some changes lead to the gene not being able to produce the correct protein and some changes won't affect the protein. There are some changes that are not understood well, as it is not known whether the change can lead to a functioning protein or not.

If there is a change or mutation that interrupts the protein from being formed or from working well, there can be an increased risk of developing certain cancers. Since CHK2 “polices” the division process, a mistake in the instructions for it can mean that the cells will be able to divide with fewer controls in place and DNA copying errors can happen. Cells with copying errors can more easily become cancer cells.

Therefore, having a mutation in CHEK2 can make a person more likely to develop certain types of cancer. The cancers most frequently described in people with a CHEK2 mutation are breast cancer, colon cancer, and prostate cancer. There is also possibly a higher risk for kidney and thyroid cancer.

Does having a mutation in CHEK2 mean I will develop cancer?

No, having certain mutations puts you at higher risk of getting certain types of cancer, but some people with CHEK2 mutations do not develop cancer.

The risk of breast cancer in women with CHEK2 is believed to be about double that of a woman without a mutation in CHEK2 (20-25% lifetime risk). Because of this increase, women with a CHEK2 mutation should have regular breast screening.

The exact figures for colorectal or prostate cancers are not available, because CHEK2 has only been explored for a short period of time. We do not currently have enough data to give reliable risk estimates. However, people with CHEK2 mutations should talk to their primary care physicians and their genetics team regarding screening for colon and prostate cancer.

Since we cannot predict which people with the mutation will develop cancer, it is important to be up to date with screenings to detect any changes early. Some women with CHEK2 may also decide to talk to their medical team within the context of their personal and family history about possibly having breast surgery (bilateral mastectomy) to prevent cancer.

Will I pass this to my children?

Since we have 2 copies of every gene, most people with a CHEK2 mutation will have one healthy copy and one copy with the mutation. When we have a child, we pass down one copy of each of our genes – so a person with a mutation in CHEK2 could pass down either the healthy copy or the copy with the mutation. The risk of passing down a mutation to a child is 50%. However, which copy we pass is random.

It is also important to remember that having a CHEK2 mutation does not mean that either you or your children will develop cancer - just that you are at a higher risk for it.

If you have found out you carry a CHEK2 mutation, you may choose to let your family members know. Your brothers, sisters, and your parents can get testing to see if they carry this mutation too and need more frequent screening. Since screening does not start until adulthood, we will usually only test your children when they are 18 or older. This makes sure your child understands why they are getting tested, what they are getting tested for, and allows them to make an informed decision regarding testing.

My test result says VUS – do I have a mutation or not?

In order to make us all unique in ourselves, we all have small changes in our DNA – these are normal and just part of who we are and will not be reported in genetic tests. Sometimes when certain changes are found, scientists and doctors may not know if that is a change that causes a change in the protein and causes the condition, or whether that is just a normal change that does not interrupt the protein from working correctly. Those changes are called “variants of unknown significance” or VUS.

As more people have testing and more investigation goes into the VUS, they are better understood, a VUS may be “upgraded” to a pathogenic or disease-causing mutation if research shows that the change does interrupt the protein and puts people at higher risk. Or it can be “downgraded” to a benign or not disease-causing change – a normal deviation from the normal sequence that does not affect the person carrying it.

If you have a VUS, your clinical team will let you know when your change is better understood and whether this change is upgraded or downgraded and help you manage your health accordingly.

Insurance

Does my insurance cover testing?

Most insurance companies do cover genetic testing, but you need to check with your insurance as there may be co-pay and co-insurance costs. Due to advances in technology, there is also out-of-pocket direct-to-consumer testing available at a low cost.

Can I be discriminated by insurance companies for having a mutation in CHEK2?

In the US, the Genetic Information Nondiscrimination Act (GINA) was enacted in 2008 and it prohibits insurance companies and employers from using genetic information to make decisions. It forbids insurance companies to deny or increase premiums to people with a genetic condition and employers to make hiring or firing decisions based on a person's genetic information.

While this does currently protect people with a CHEK2 mutation, nobody can guarantee that this legislation will continue to be in place forever.

When did we begin testing for CHEK2?

Mutations in CHEK2 were first associated with breast cancer in 1999. However, few people were tested routinely for this mutation in the early 2000s or even the early 2010s. With testing methods changing due to improved and cheaper technology from single gene analysis to panel tests, CHEK2 mutation testing has been offered more and more in the last few years (after 2013). Most panels that look at breast cancer genes now include CHEK2 among their candidate genes.

Why isn't there more information about CHEK2 available?

CHEK2 has only been associated with cancer risks since 1999, and studies are still ongoing to better understand this gene and the effects of changes in this gene. It is difficult to give estimates of risk when we have not studied the people carrying a mutation in CHEK2 sufficiently.

Most people with a CHEK2 mutation have not been tested and do not know they have this mutation. Only in recent years have we started testing people for it.

Is there any way I could help doctors and scientists understand CHEK2 better?

Absolutely! There are many research studies looking at people with rare changes. Ask your primary care physician or your local cancer center if they can recommend a study you could participate in, or check out the studies below.

For even more information, visit the NIH website's summary of the CHEK2 gene:

<https://ghr.nlm.nih.gov/gene/CHEK2>

Current Research Studies and Clinical Trials

Biobanks and Registries

[PROMPT - Prospective Registry of MultiPlex Testing](#)

This online research registry for patients and their families helps researchers answer the question: "How do genetic variants affect your cancer risk?" It aims to better understand non-BRCA variants and mutations in

cancer predisposition genes. Adults with a personal or family history of a VUS or deleterious mutation in a cancer predisposition gene are eligible. Participation includes a one-time saliva donation, access to medical records, family history collection, and access to a pathology specimen, if applicable.

13-325 (SEARCH)

The purpose of this study is to better identify individuals and families with increased genetic susceptibility to cancer. Anyone with a personal or family history of cancer known or suggested to have been caused by gene mutation is eligible. Participation includes a one-time blood or saliva sample and access to medical records.

10-458 (ACT for Others)

The purpose of this study is to better understand breast cancer development in high-risk groups. Adult women with an increased risk of breast cancer who are planning to have a prophylactic mastectomy are eligible. Participation includes a one-time mastectomy tissue sample or a one-time skin biopsy.

[ICARE Inherited Cancer Registry](#)

ICARE is a registry-based research study and represents a clinical-research-community partnership among medical practitioners, researchers and members of the general population. The common goal of its efforts is to improve the lives of patients and families at risk for inherited cancer susceptibility.

[Creighton University Hereditary Cancer Center Available Studies](#)

Here you will be able to find a list of available Breast/Ovarian Cancer Family Studies currently underway at the Hereditary Cancer Center at Creighton University School of Medicine. Contact Carrie Snyder, MSN, APRN-CNS, APNG at csnyder@creighton.edu if you are interested in any studies listed.

[Mayo Clinic Inherited Breast Cancer Study](#)

A group of doctors and scientists led by Dr. Fergus Couch at the Mayo Clinic in Rochester, Minnesota, are conducting this study to advance understanding of how breast cancer is inherited through families. In this study they aim to establish the risks of cancer for deleterious mutations and VUS in each of the clinically tested breast cancer genes, so that families and their health care providers can better manage their risk of breast cancer. To answer these questions, they plan to use mutation results from genes currently included on genetic testing panels for breast cancer, along with information on the history of cancer in families and on breast cancer risk factors collected using a questionnaire.

[American BRCA Outcomes and Utilization of Testing Patient-Powered Research Network \(ABOUT Network\)](#)

The ABOUT Network is a national patient-powered research network focused on hereditary breast and ovarian cancer (HBOC) that will be expanded in significant ways through the proposed funding and is well positioned to participate in and contribute to the planned U.S. patient-centered network for comparative effectiveness research. Facing Our Risk of Cancer Empowered, Inc.(FORCE) and a team of HBOC

researchers based at the University of South Florida (USF) have combined their strengths in advocacy, research, and engaging community participation to pursue better information, services, and outcomes for the patient community to which they belong and conduct collaborative research that extends beyond academia to research powered by patients being cared for in communities across the country.

[Columbia University Interview Study: Constructions and Understandings of Cancer Genetic Risk](#)

This study seeks to shed light on how genetic risk for cancer is made visible, communicated, understood, and acted upon. Through 12 months of fieldwork combining document analysis, participant observation, and in-depth interviews with health professionals and mutation carriers, this study will investigate the following three key questions: 1. How is BOC genetic risk made visible in the era of multi-gene panel testing? 2. How is genetic risk information understood and acted upon by diverse carriers of BOC mutations? 3. Finally, how are relationships among and between laboratory researchers, medical experts, and patients being transformed by the utilization of multi-gene panel tests? To participate or find out more, contact Ronna Popkin at atrp2471@columbia.edu or 608-556-3823.

Publications Library – Journal Articles Relevant to CHEK2

General Population Studies

- [Increased Risk for Other Cancers in Addition to Breast Cancer for CHEK2*1100delC Heterozygotes Estimated From the Copenhagen General Population Study.](#) Näslund-Koch C, Nordestgaard BG, Bojesen SE. Journal of Clinical Oncology. 2016 34:1s1, 1208-1216

This is a very large population study done in Denmark. Almost 87,000 people were studied to try to establish some cancer risk figures for CHEK2 1100delC carriers.

The people who participated had their blood drawn and filled out a survey about lifestyle to correct for certain risk behaviors like smoking. It was found that 0.8% of this white Danish population carried a CHEK2 1100delC mutation (670 individuals in this study). This is similar to the results found in a large Dutch study that saw slightly over 1% of the population carrying a CHEK2 1100delC mutation.

Comparing those who did have the CHEK2 mutation and those who did not, it was seen that there was an increase in cancer, specifically breast cancer, and the breast cancers occurred somewhat earlier than in the group without a CHEK2 mutation.

Other cancers were also seen more frequently in those carrying CHEK2 mutations but the sample size was not large enough to give reliable evidence that this is due to the CHEK2 mutation. However, they do conclude that the risk of developing cancers other than breast are elevated in people carrying a CHEK2 mutation.

CHEK2 and Breast Cancer

- [Survival and contralateral breast cancer in CHEK2 1100delC breast cancer patients: impact of adjuvant chemotherapy.](#) M Krieger, A Hollestelle, A Jager, P E A Huijts, E M Berns, A M Sieuwerts, M E Meijer-van Gelder, J M Collée, P Devilee, M J Hooning, J W M Martens, and C Seynaeve. *Br J Cancer*. 2014 Aug 26; 111(5): 1004–1013.

In this Dutch study, women with breast cancer with and without CHEK2 mutations were followed to see if the risk of developing a breast cancer in the other breast was higher, whether there was a difference in long term survival, and whether people with CHEK2 reacted differently to chemotherapy.

193 women with CHEK2 1100delC mutations were identified from a pool of over a thousand women with hereditary breast cancer who were not BRCA1 or 2 positive, and over 3500 women with breast cancer without knowledge of their family history. The women were followed for 7 years and it was found that among the CHEK2 mutation carriers, the likelihood of developing a breast cancer in the other breast was higher.

However, the 6-year survival was the same between women with a CHEK2 mutation and women without. In relation to their chemotherapy reaction, the study did not find any difference between women with a CHEK2 1100delC and women without.

The study concludes that since the risk of developing cancer in the other breast is higher than in women without a mutation, additional screening like that received by women who have a BRCA1 or BRCA2 mutation might be in order for women with a CHEK2 1100delC mutation.

- [Identification of Women With an Increased Risk of Developing Radiation-Induced Breast Cancer: A Case Only Study.](#) Broeks A, Braaf LM, Huseinovic A, Nooijen A, Urbanus J, Hogervorst FB, Schmidt MK, Klijn JG, Russell NS, Van Leeuwen FE, Van 't Veer LJ. *Breast Cancer Res*. 2007;9(2)

In this study done by a Dutch group, the question whether radiation can increase a second breast cancer in the unaffected breast of women who have a mutation in *BRCA1*, *BRCA2*, *CHEK2* and *ATM* was explored. All 4 of these genes are DNA repair genes, meaning that they make sure the DNA gets copied correctly into new cells. This is particularly important in people who receive radiation, as the radiation can lead to copying errors.

51 women with a mutation in one of these four genes, as well as nearly 200 women without a mutation who all developed a second breast cancer, were followed and the researchers compared whether they had received radiotherapy or not.

The result was that women with a mutation seem to have an increased risk of developing a second breast cancer if they receive radiation. Therefore, it is important for women to know whether they have a mutation prior to receiving treatment, to help decide which treatment may be most beneficial for them.

CHEK2 and Colorectal Cancer

- [Beyond the usual suspects: features of hereditary colorectal cancer in a CHEK2 cohort.](#) Bucheit, L., Grzybowski, J., McFarland, R., LaDuca, H. Ambry Genetics, Aliso Viejo, CA. Scientific Poster Presented at CGA 2015 Annual Meeting.

This is a poster published by researchers at Ambry Genetics, a genetic testing company. They looked through a cohort of 534 CHEK2 mutation carriers, and did not limit it to the CHEK2 1100delC mutation. They were investigating how different mutations in CHEK2 could affect hereditary colon cancer and how 1100delC compared to other mutations.

The results were that some people with unexplained hereditary colon cancer did have CHEK2 mutations, and more than half had mutations that were not the better-understood 1100delC mutation. They concluded that a full analysis of CHEK2 should be done in cancer panel tests and not just a specific analysis looking for the 1100delC mutation.

However, more work needs to be done to fully understand how CHEK2 plays a role in these colon cancers and how it compares to other genes. In order to see how high the risk for developing colon cancer is in people with CHEK2 mutations, a larger population study would be necessary, as everyone in this group had a family history of colon cancer and most had a personal history of colon cancer.

Genotype-Phenotype Information on non-1100delC

- [PALB2, CHEK2 and ATM rare variants and cancer risk: data from COGS.](#) Southey, MC et al. J Med Genet 2016; 53:800–811.

This very large study, that comprised three consortia of people studied through population-based studies or hospital-based studies, looked at rare mutations in the CHEK2 gene, as well as PALB2 and ATM.

Six rare mutations in CHEK2 were chosen and looked at in relation to cancer development for three types of cancer: breast, ovarian, and prostate. These six mutations were chosen because in laboratory tests they were predicted to interrupt the protein in some way. Since they had extremely large numbers of people's results and history available, they were able to find enough mutation carriers to study these rare mutations.

The results were that in 2 of the 6 rare mutations (c.349A>G and c.1036C>T) there was a slight increase in breast cancer risk. However, this was not big enough to place women with these rare changes in a "high risk" category. One of the mutations (CHEK2 c.538C>T) needed additional investigation in order to be able to make a statement.

- [Patient survival and tumor characteristics associated with CHEK2:p.I157T - findings from the Breast Cancer Association Consortium.](#) Muranen, TA et al. Breast Cancer Res. 2016 Oct 3;18(1):98.

In this Finnish study, the rare mutation in CHEK2 p.I157T is compared to the well described 1100delC mutation to see if it has similar characteristics in terms of disease progression, metastasis, and survival.

On a molecular level the two mutations work very differently: 1100delC interrupts the protein and turns it into a non-functioning protein, while p.I157T changes its shape and interferes with it working well. Both affect how efficiently CHEK2 works in different ways but since both are associated with increased risk for breast cancer, this study wanted to explore other similarities and differences.

The tumor types found in carriers of the two mutations are different – while in 1100delC most tumors are in the breast ducts, in p.I157T most are in the lobules. CHEK2 1100delC carriers have a worse prognosis with a higher incidence of relapse and breast cancer mortality, which is not seen with CHEK2 p.I157T. There was no difference between p.I157T carriers and people without a mutation.

In conclusion, because of the way the two mutations act on the protein and change it, they have a different molecular and biological effect on breast tissue and this can also affect prognosis.

CHEK2 and Men

- [Male breast cancer in a multi-gene panel testing cohort: insights and unexpected results.](#) Pritzlaff M et al. Breast Cancer Res Treat. 2017 Feb;161(3):575-586.

This retrospective study looks at men diagnosed with breast cancer over a 4-year period and their genetic testing status. Of the 708 men with male breast cancer, 97 tested positive for a mutation and the second most reported gene was CHEK2 (after BRCA2). Men with CHEK2 1100delC mutations had an average earlier diagnosis than men without a mutation or those with other CHEK2 mutations.

Overall the paper concludes that all men with breast cancer should have a multi-gene panel to make sure no mutation is missed.

- [CHEK2 mutation and risk of prostate cancer: a systematic review and meta-analysis.](#) Wang Y et al. Int J Clin Exp Med. 2015 Sep 15;8(9):15708-15.

In this meta-analysis studies that explored CHEK2 mutations and prostate cancer were reviewed. While the study was limited by not having a large enough number of participants, it concludes that men with CHEK2 1100delC and CHEK2 I157T mutations have an increased risk of prostate cancer.

- [Inherited DNA-Repair Gene Mutations in Men with Metastatic Prostate Cancer.](#) Pritchard CC et al. N Engl J Med. 2016 Aug 4;375(5):443-53.

In this multicenter study, men with metastatic prostate cancer had gene analysis to see if mutations in DNA-repair genes were represented more frequently than in the general population.

Nearly 700 men had genes analyzed, and 11.8% were found to have a mutation in a DNA repair gene, with CHEK2 being the third most-frequent after BRCA2 and ATM. This is significantly higher than in the general population, and also much higher than in the population of localized prostate cancers, and so the study concludes that having a DNA repair gene mutation does increase chances of having metastatic disease.

Since there was no correlation with age of onset and having a mutation can be a sign for more aggressive types of cancer, this study concludes that men with prostate cancer at any age should be considered for gene testing of DNA repair genes.