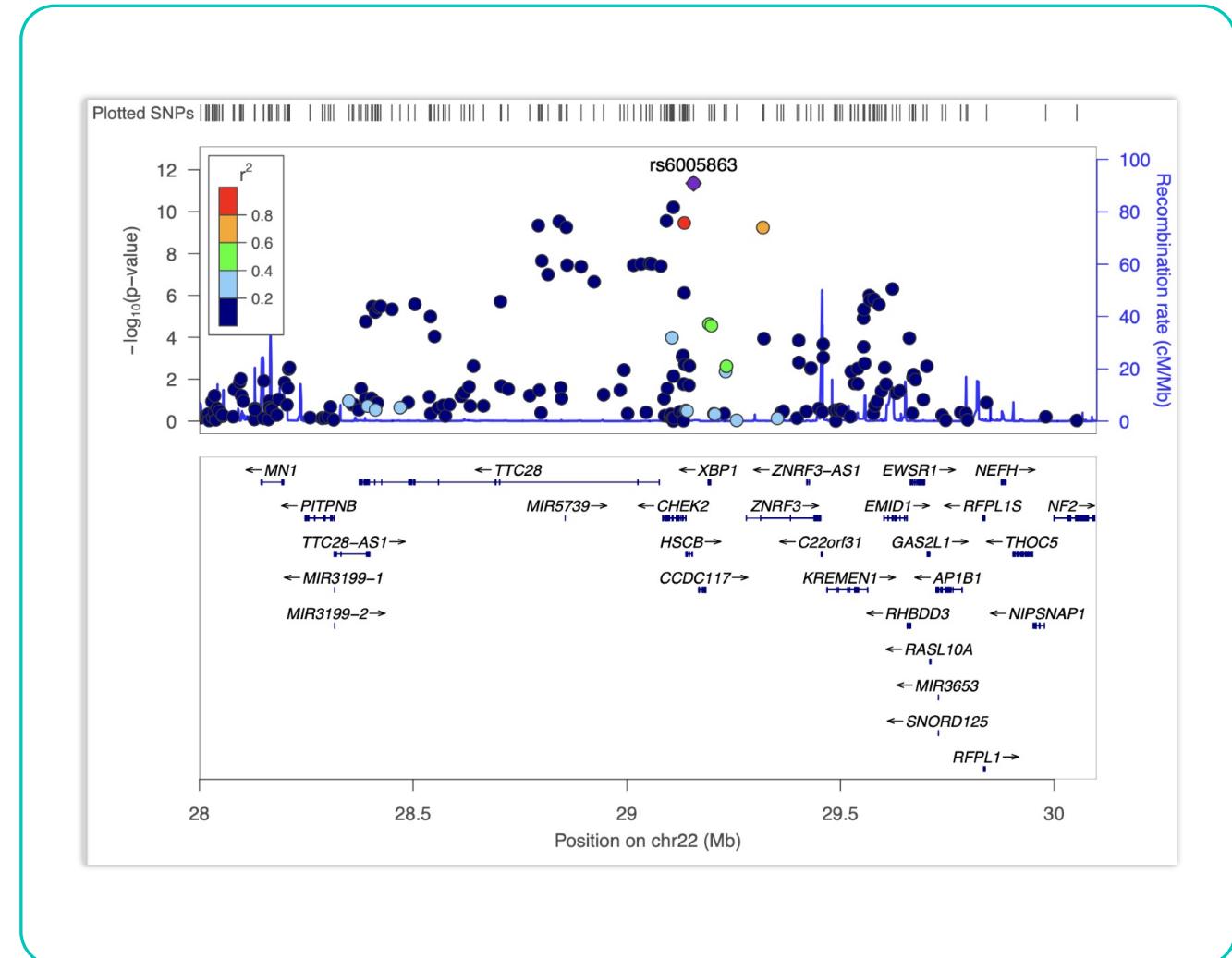


# How does mutation rs186430430 cause breast cancer?

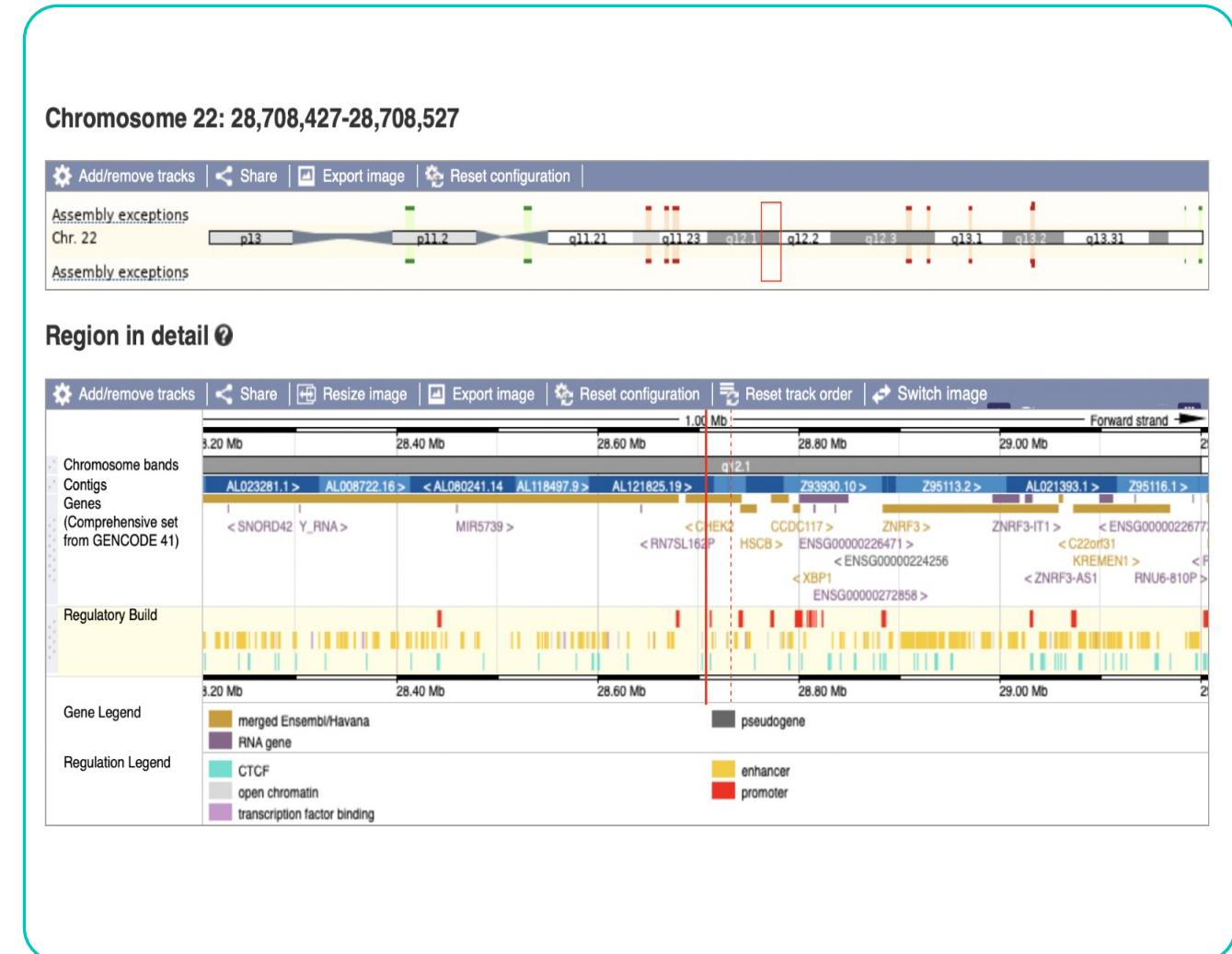
BY Xinyao Zhong

# Association with breast cancer



# Exact region of this mutation

Mapped Gene=CHEK2



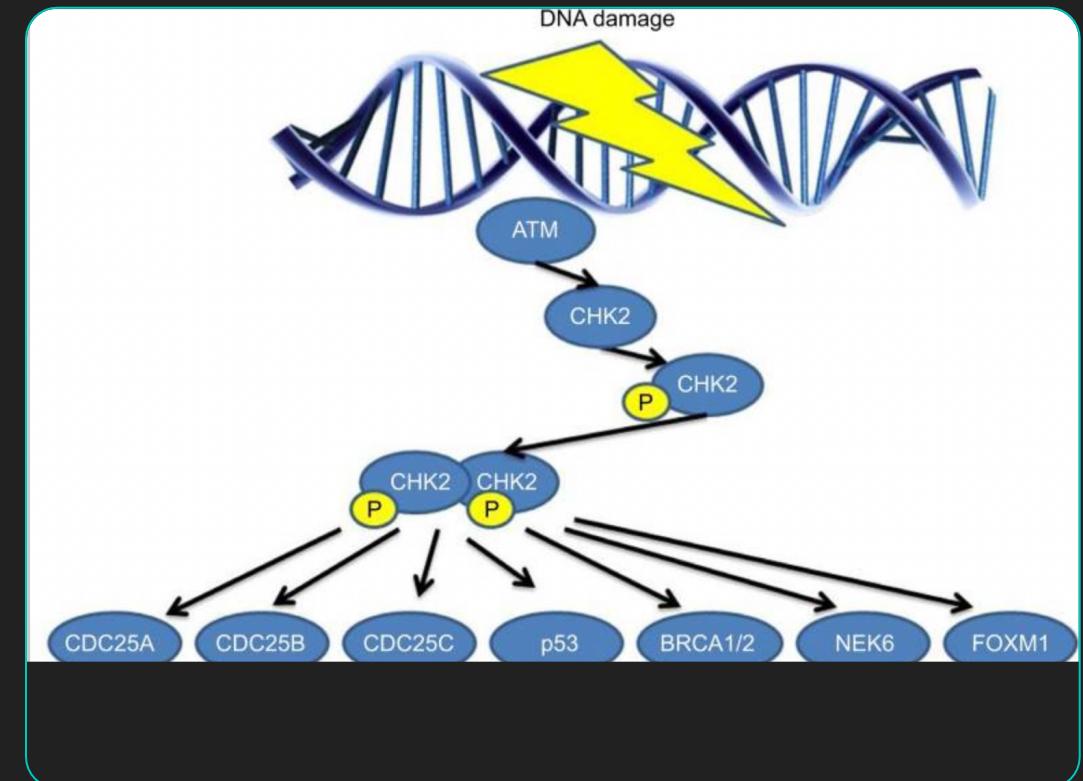
[https://asia.ensembl.org/Homo\\_sapiens/Variation/Explore?db=core;r=22:28707110-28708110;v=rs186430430;vdb=variation;vf=189165789](https://asia.ensembl.org/Homo_sapiens/Variation/Explore?db=core;r=22:28707110-28708110;v=rs186430430;vdb=variation;vf=189165789)

# CHEK2 gene (Checkpoint Kinase 2)

- CHEK2 gene encodes a protein called CHK2
- CHK2 protein is a cell cycle checkpoint regulator and putative tumor suppressor.
- It is involved in DNA repair, cell cycle arrest or apoptosis in response to DNA damage.

# How does CHK2 protein work?

- When DNA undergoes a double-strand break, CHK2 is activated.
- Specifically, *CHEK2* gene is activated by phosphorylation of Thr68 by ATM, which causes the dimerization of the gene enabling it to acquire kinase activity.
- Once activated, CHK2 phosphorylates downstream targets including CDC25 phosphatases, responsible for dephosphorylating and activating the cyclin-dependent kinases (CDKs).
- The Cdc25 phosphatases function as key regulators of the cell cycle during normal eukaryotic cell division and as mediators of the checkpoint response in cells with DNA damage.
- Thus, CHK2's inhibition of the CDC25 phosphatases prevents entry of the cell into mitosis



Chromatin state	Chromatin state window	Biosample	Organ	Dataset	File
Enhancers	chr22:29103000..29103600	GM12878	blood, bodily fluid	ENCSR538BFF	ENCFF178HVK
Enhancers	chr22:29103200..29103600	HeLa-S3	uterus, epithelium	ENCSR497SKR	
Enhancers	chr22:29103200..29103600	B cell	blood, bodily fluid	ENCSR702LRW	
Enhancers	chr22:29101600..29103800	B cell	blood, bodily fluid	ENCSR695EDP	

ENCSR695EDP

Chromatin state

Search for a biosample name, chromatin state, or organ  X

Strong transcription 85

Enhancers 4

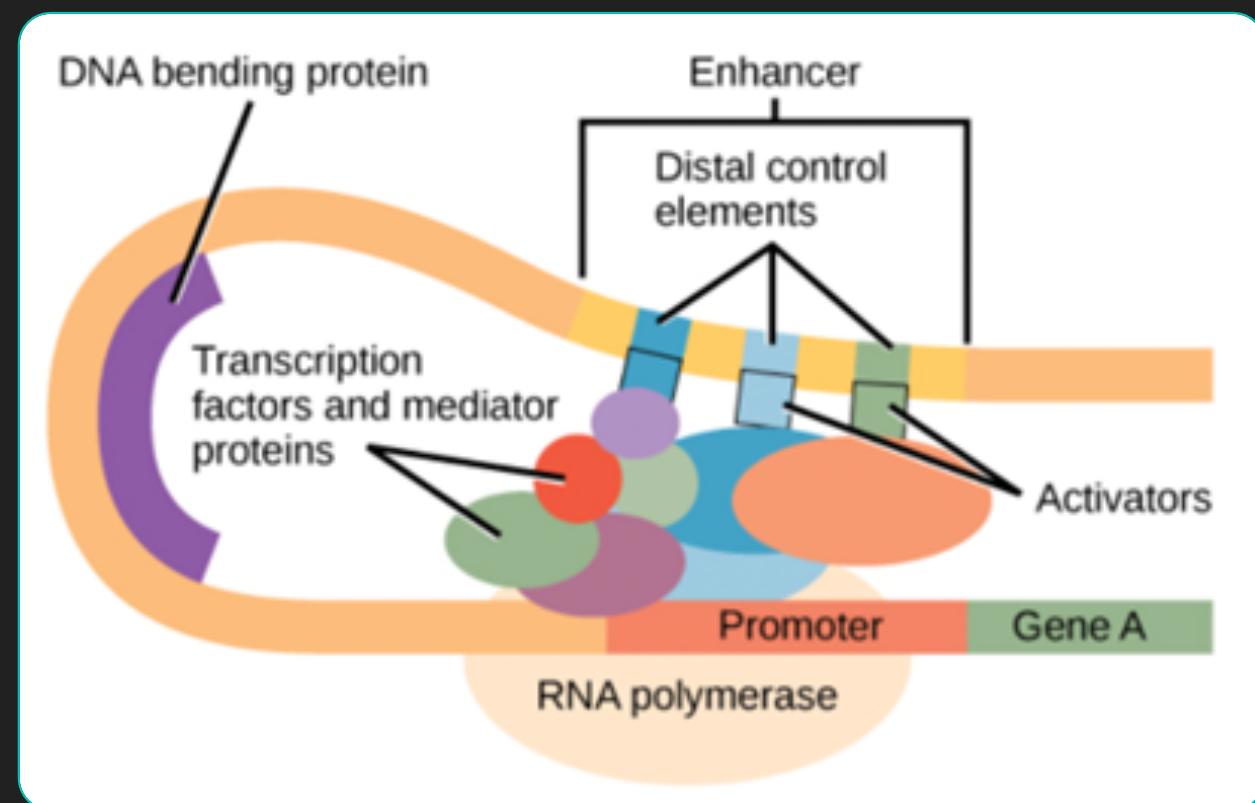
Quiescent/Low 38

# Mutation information on Regulomedb

- The mutation is in the enhancer region of the CHEK2 gene

# Enhancer and Transcription

- **Enhancer** is a short (50-100bp) region of DNA that can be bound by proteins (activators) to increase the likelihood that transcription of a particular gene will occur.
- Enhancer regions are binding sequences, or sites, for transcription factors.
- When a DNA-bending protein binds to an enhancer, the shape of the DNA changes. This shape change allows the interaction between the activators bound to the enhancers and the transcription factors bound to the promoter region and the RNA polymerase to occur.



# Mutation information on GWAS

- Intron Variant (non-coding region on the DNA)

## Variant: rs186430430

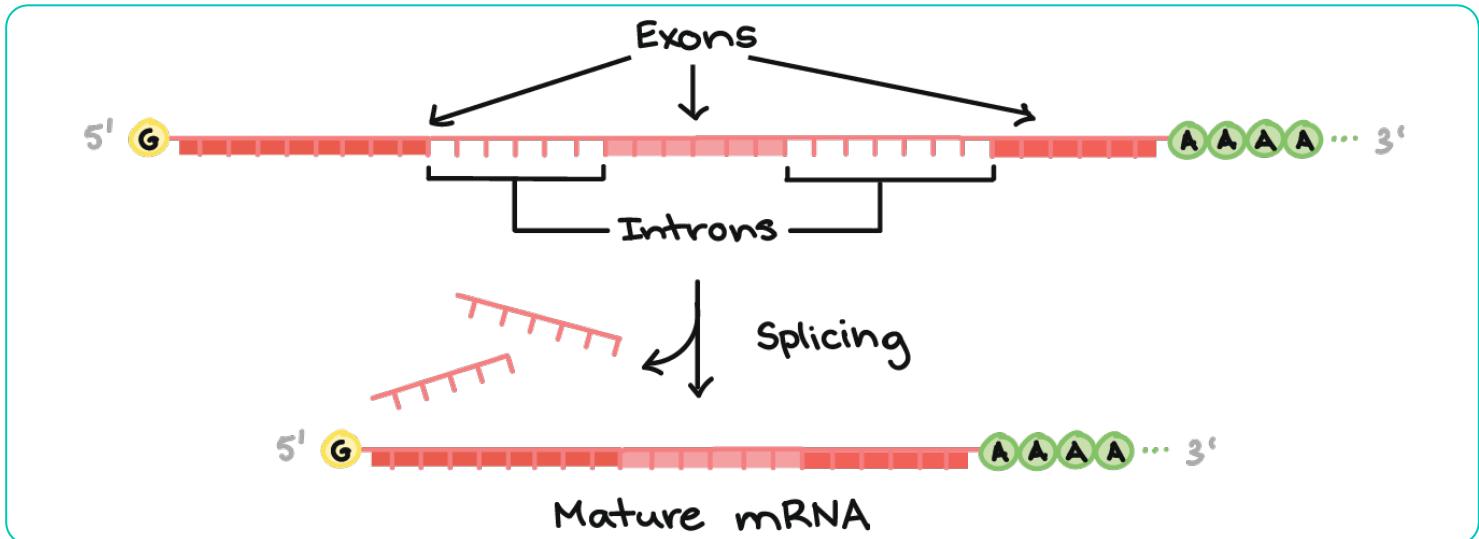
GWAS / Variants / rs186430430

### Variant information

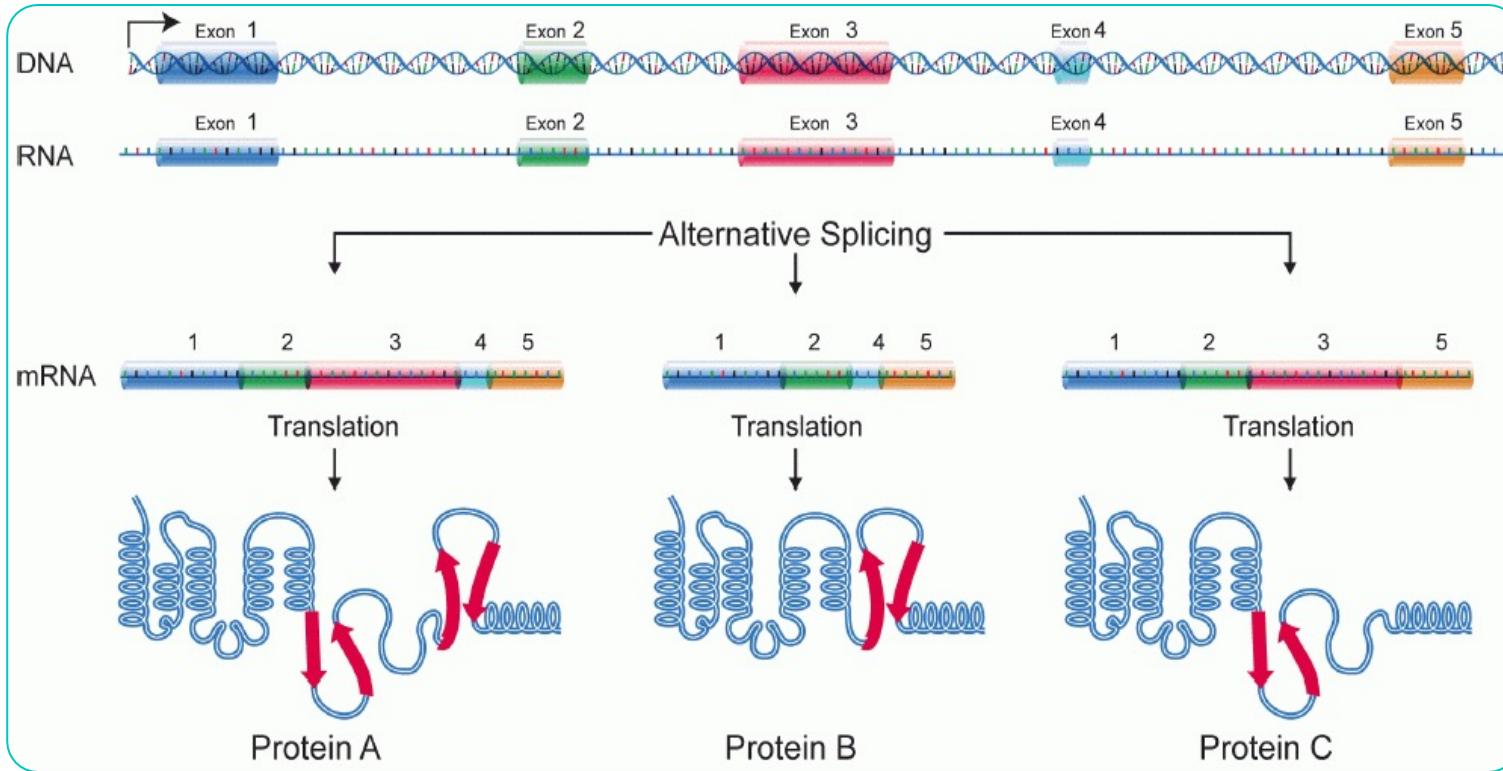
Location ⓘ	22:28707610	Alleles ⓘ	T/C (forward strand)
Cytogenetic region ⓘ	22q12.1	Minor allele ⓘ	C
Most severe consequence ⓘ	Intron variant	MAF ⓘ	0.000998
Mapped gene(s) ⓘ	CHEK2		

# Intron and mRNA splicing

- **Intron** is the sequence of DNA in between exons (coding regions) that is initially copied into RNA but is cut out of the final RNA transcript and therefore does not change the amino acid code.
- This happens in **RNA splicing** (the step when pre-mRNA is processed to form mature mRNA during transcription).
- In **splicing**, some sections of the RNA transcript (**introns**) are removed, and the remaining sections (**exons**) are stuck back together, to form the mature mRNA.



# Alternative splicing



- In alternative splicing, one pre-mRNA may be spliced in either of two or more different ways.
- In the diagram, the same pre-mRNA can be spliced in three different ways, depending on which exons are kept. This results in three different mature mRNAs, each of which translates into a protein with a different structure.

# To sum up

- Intronic variants can impact alternative splicing by interfering with splice site recognition.
- In this case, the mutation rs186430430 (an intron variant) is likely to interfere with splice site recognition and this may lead to retention of large segments of intronic DNA by the mRNA, or to entire exons being spliced out of the mRNA, so a different mRNA will be produced.
- Then, an abnormal protein, different from the original CHK2 protein is produced after translation.
- As a result, the protein will not perform its function of regulating cell cycle, so cancerous cells will undergo mitosis and proliferate.

Thank you for  
watching!