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Title:

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Date:

2020-09-07

Citation:

De Silva, D. L. & Winship, I. (2020). Is CHEK2 a moderate-risk breast cancer gene or the younger sister of Li-Fraumeni?. BMJ Case Reports, 13 (9), <https://doi.org/10.1136/bcr-2020-236435>.

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Case report

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Accepted 22 July 2020

SUMMARY

The *CHEK2* gene is mostly considered as a moderate breast cancer gene with the result that many clinicians have a narrow focus. We present the 10-year journey of a man who had five different cancers and had iterative genetic testing including for Li-Fraumeni syndrome, eventually to discover a pathogenic variant in the *CHEK2* gene, possibly explaining his numerous cancers. This diagnosis offered him closure which he had desperately sought for well over a decade. A pathogenic variant in the *CHEK2* gene can potentially explain these cancers because of its function as a tumour suppressor gene. Consideration is warranted of what this means for individuals with *CHEK2* variants who may develop multiple cancers, their prognosis and whether different treatment modalities such as chemotherapy, radiotherapy or target agents would need modification. We encourage more research into the many faces of the *CHEK2* gene and the potential for predisposition to multiple cancers.

BACKGROUND

The *CHEK2* gene is well researched and published as a moderate breast cancer risk gene.¹ The frequency of the *CHEK2**1100delC allele is 0.3% in North America and lower than the respective frequency observed in European populations.²

Clarity about the importance of *CHEK2*, in the predisposition towards other cancers, has been gained slowly. *CHEK2* is a cell cycle checkpoint regulator and a tumour suppressor. The *CHEK2* gene is activated by phosphorylation of Thr68 by *ATM*, which causes the dimerisation of the gene enabling it to acquire kinase activity. *CHEK2* then reacts with downstream phosphatase *CDC25*, serine/threonine protein kinase *NEK6*, transcription factor *FOXO1*, *p53* protein and *BRCA1* or *BRCA2*.³ *CHEK2* regulates cell division by preventing cells from entering mitosis or arresting cell cycle in gap 1 phase (G1), in response to DNA damage.⁴ Furthermore, *CHEK2* protein interacts with several other proteins including *p53* and stabilisation of *p53* by *CHEK2* leads to cell cycle arrest in G1.⁵ There are multiple variants recognised within *CHEK2* such as 1100delC, I157T, R117G, I160M, G167R and G167A.⁶ The 1100delC variant is the most studied and implicated with breast and other cancers.⁷

CHEK2 mutation and breast cancer risk are well studied. According to Cybulski *et al*, the OR was higher for women with a first-degree or second-degree relative with breast cancer (OR 5.0; 95% CI 3.3–7.6) than for women with no family history

(OR 3.3; 95% CI 2.3–4.7).⁸ *CHEK2* is linked with multiple cancers including prostate cancer: 1100delC mutation (OR 3.29; 95% CI 1.85–5.85; *p*=0.00) and I157T missense mutation (OR 1.80; 95% CI 1.51–2.14; *p*=0.00).⁹ The age-adjusted and sex-adjusted HRs were 5.76 (95% CI 2.12–15.6) for stomach cancer, 3.61 (95% CI 1.33–9.79) for kidney cancer and 3.45 (95% CI 1.09–10.9) for sarcoma,¹⁰ and in a meta-analysis of a total of six studies including 4194 cases and 10,010 controls, a significant association of the *CHEK2* 1100delC variant with unselected colorectal cancer was found (OR 2.11; 95% CI 1.41–3.16; *p*=0.0003).¹¹

A decade ago, *CHEK2* was considered as predisposing to a possible ‘Li-Fraumeni-like’ phenotype¹² because of its role as a Tumour suppressor gene.^{13 14} When considered together with the family history of young-onset breast cancer and multiple tumours including glioma, this case is clinically suggestive of a Li-Fraumeni-like syndrome.

CASE PRESENTATION

A 52-year-old man was diagnosed with five cancers; germline DNA testing detected the heterozygous pathogenic variant, *CHEK2* 1100delC.

Clear cell renal cancer

In 2007, the patient, aged 40 years, was found to have 2 cm renal cell cancer in the right kidney, following an ultrasound scan for urinary tract symptoms. Laparoscopic right nephrectomy was done, and pathology was consistent with clear cell carcinoma of Furman grade 2. There was no perinephric or adrenal gland involvement.

The immunohistochemistry (IHC) examination of the tumour for succinate dehydrogenase B (SDHB) showed a normal pattern of staining, indicating that it was unlikely to harbour SDHx gene mutation.

His maternal aunt was concurrently diagnosed with pheochromocytoma at the age of 56 years, and the c.74C>T(p.pro25Leu) variant in the *VHL* gene was detected in her DNA, regarded at that time as pathogenic.

Glioma

In 2010, as part of the investigation of a possible diagnosis of von Hippel-Lindau syndrome, a brain MRI was done and demonstrated a possible low-grade glioma/astrocytoma in the right temporal lobe and diffuse signal abnormality in the left cerebellum and left temporal lobe. Brain MRI and the clinical



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To cite: De Silva DL, Winship I. *BMJ Case Rep* 2020;**13**:e236435. doi:10.1136/bcr-2020-236435



Figure 1 MRI.

picture was suggestive of the possibility of multifocal astrocytoma or a low-grade glioma. Figure 1 shows these features on the MRI scan. Figure 2 shows spectroscopy finding of increase choline that is compatible with a low-grade glial tumour. No biopsy was done as it was deemed too much of a risk at the time. The tumour was observed over time and treatment with radiotherapy was initiated in 2013 (50.4G/28#) as there were progressive symptoms with diplopia and dysarthria. Radiotherapy and a trial of steroid did not alleviate his symptoms, although his 6 monthly MRIs have remained unchanged.

Low-grade urothelial tumour

In 2011, a low-grade urothelial tumour was detected in his post-nephrectomy follow-up. He had persistent lower urinary tract symptoms; cystoscopy detected a tumour adjacent to the left ureteric outlet, consistent with low amplitude papillary urothelial cancer. This was surgically managed, and there is no evidence of recurrence to date.

Cutaneous basal cell cancer

In 2016, he had a non-healing ulcer in his forehead, which was a basal cell carcinoma. This was surgically resected with no post-operative complications.

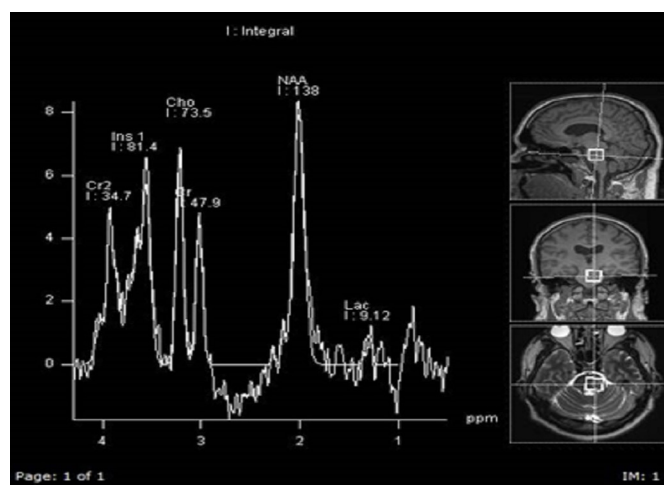


Figure 2 MR spectroscopy.

Multifocal bilateral papillary thyroid cancer

In 2019, he was diagnosed with bilateral multifocal papillary thyroid cancer that was breaching the capsule on the left side, but with no infiltration of overlying muscle. He had a completion thyroidectomy on the contralateral side, which detected an additional 5 mm papillary thyroid cancer. He had radioiodine therapy and is currently on thyroxine replacement with no evidence of metastasis.

Family history

His mother died of non-Hodgkin's lymphoma, positive for B-cell markers at the age of 47 years, in 1993. Her maternal aunt had pheochromocytoma at the age of 56 years and breast cancer at 66 years. IHC for SDHB was preserved in her pheochromocytoma specimen. The proband's sister was diagnosed with grade 3 estrogen positive (ER+) breast cancer at the age of 26 years and died at the age of 27 years, in 1999. Neither his sister nor mother had genetic testing.

Genetic testing

The proband's maternal aunt, who lived a significant distance away had genetic testing; no pathogenic mutation was detected in either BRCA 1 or BRCA2 genes. A variant identified in the VHL gene c.74C>T(p.Pro25Leu) was thought to be pathogenic at the time, and the extended family was advised that family testing was available. On this basis, our proband was offered testing for the family-specific variant. The DNA sample obtained from the patient was independently amplified and sequenced in opposite directions from exon 1 of the VHL gene. Analysis of this exon has not detected the c.74C>T variant. Soon thereafter, this variant was revised as unlikely to be pathogenic.

Subsequently, his aunt had next-generation sequencing (NGS) for MAX, RET, SDHAF2, SDHB, SDHC, SDHD, TMEM127 and multiplex ligation-dependent probe amplification (MLPA) for VHL, SDHA, MAX, SDHB, SDHC and SDHD. No pathogenic mutation was detected.

Our proband was offered MLPA and NGS for VHL and TP53. Complete sequence screening of all coding exons and intron-exon boundaries of the TP53 gene did not reveal the presence of a pathogenic variant. In MLPA, none of the tested exons showed a significant deviation from the normal range of the tested population, and duplicate tests were concordantly indicating a normal copy number.

Following his disease progression and with the recent diagnosis of papillary thyroid cancer as well as papillary urothelial cancer and the availability of broader panel testing, testing of 72 cancer predisposition genes was offered for him. The heterozygous pathogenic variant, CHEK21100delC was found.

OUTCOME AND FOLLOW-UP

Confirmation of a pathogenic mutation in the CHEK2 gene provided an answer for his propensity to cancers, affording him closure. The most recent CT scan done on the 13 May 2020 did not detect any disease recurrence of the thyroid and urothelial cancers. His MRI scans of the brain remain radiologically stable despite having subtle clinical progression occurring over a few years. We have offered predictive testing to his relatives; this is an autosomal dominant gene and therefore, his siblings and offspring would have a 50% chance of having the same variant. We were not able to test his aunt for the CHEK2 variant to date and verify the presence and variant segregation with the phenotypes. Genetic counselling will be provided to his extended family.

DISCUSSION

This man meets the modified Chompret criteria¹⁵ with multiple tumours including glioma, clear cell renal cell cancer, urothelial cancer, basal cell cancer as well as multifocal bilateral papillary thyroid cancers in combination with the family history. However, only cancer this man suffered from which is described in the Li-Fraumeni syndrome spectrum of cancers is a glioma. In the absence of a pathogenic variant in the *TP53* gene, we posit that his cancers are driven by the *CHEK2* mutation, potentially behaving like *TP53*.

Inherited RCC comprises 5% of all renal cell cancers,¹⁶ based on germline mutations in the *VHL*, *FH*, *BAP1*, *SDHB*, *SDHC*, *SDHS*, *TSC1*, *TSC2* and *MITF*¹⁷ genes. *CHEK2* has been implicated in RCC, especially the missense variant I157T.¹⁸ However, literature around *CHEK2* 1100delC is less clear. According to Näslund-Koch *et al*,¹⁰ *CHEK2**1100delC HR for kidney cancer is 3.45 (95% CI 1.09–10.9) that supports the theory of driving renal cell cancer, but *CHEK2**1100delC was not observed in any of the patients with renal cell cancer in Huzano and Kolosza,¹⁹ therefore, the data supporting the role of *CHEK2**1100delC are conflicting.^{10 17 19}

The link between *CHEK2* mutation and gliomas is plausible because of its role as a tumour suppressor gene; case reports published suggest *CHEK2* mutation as the possible cause of medulloblastomas,²⁰ as well as primary gliomas and astrocytomas.²¹ Germline mutations in *CHEK2* do not seem to cause either high-grade or low-grade gliomas, in contrast to the *TP53* gene.²² No biopsy was undertaken, so no tissue was available to seek somatic mutations.

Genotyping may be useful for the radiation oncologist when determining treatment options. The primary concerns include increased radiation toxicity, secondary cancers or lack of efficacy in certain tumours.

Truncating mutations in *ATM* causing breast cancer and radiation toxicity is one such instance.²³ There are concerns about *TP53* mutations and an increased risk of secondary cancer²⁴ or lack of radiation sensitivity with germline mutations.²⁵ There is insufficient information about *CHEK2* mutation and radiation. Still, it is possible that the tumour had a degree of radioresistance as evident by the lack of response to treatment.

In terms of his development of basal cell cancer, we believe radiotherapy might have played a role as his basal cell cancer developed on his forehead. Indeed few publications are confirming such existence, but the majority of patients do not survive after radiotherapy to develop secondary cancers such as basal cell carcinoma.²⁶ However, the role of *CHEK2* mutation in itself driving this or increasing radiosensitisation as a result of the underlying mutation cannot be discounted as well. We hypothesise the development of his basal cell carcinoma in this male to be most likely multifactorial.

The link between thyroid cancer and *CHEK2* is well published (OR 4.9; *p*=0.0006).¹⁸ In published data, *CHEK2* accounted for more than 15% of mutations found in an unselected population. If women are selected who had thyroid cancer with a family history of breast cancer, it becomes even more significant (OR 10; *p*=0.0004).²⁷

We hypothesise that the pathogenic variant in the *CHEK2* gene has rendered him more susceptible to the multiple cancers he has developed. It is reasonable to consider *CHEK2* as a gene with the potential to drive multiple cancers, comparable with *TP53*, rather than merely a moderate breast cancer risk gene.

Another important new paradigm in genetics is the concept of polygenic risk scores. This is the concept of several low

penetrant variants, further enhancing the lifetime risk of cancers and this well-described concerning *CHEK2* pathogenic variant in breast cancer.²⁸ Unfortunately, these models are still not incorporated at a clinical level, and we expect this to change in the future.

On the basis of this resurgence of support for a Li-Fraumeni-like phenotype and the importance of incorporating this into polygenic risk scores for risk management, we suggest more investigation of this gene.

Patient perspective

More than a decade ago my health journey started when I started going to the toilet at least five times a night, so the next day I made an appointment to see my doctor. He sent me for an MRI of my urinary tract which revealed a tumour on my right kidney which I had to get it removed. Then I had further scans of my urinary tract which revealed a tumour in my bladder. They took a biopsy, the result stated that it was cancer. I had an operation to remove it. My cousin told me that I should have genetic testing done because my mum passed away in her 40s due to non-Hodgkin lymphoma and my sister in her 20s due to breast cancer with a toddler.

A couple of months later I had a transurethral resection of the prostate (TURP). The MRI that I have every 6 months showed that I have glioma in my brainstem. I had undergone radiotherapy to my brain, which did not work. My symptoms did not change, my balance, vision and coordination have not improved. At my age, it will get worse. It is very frustrating. Unfortunately, the doctors cannot operate on the glioma because it is too dangerous. The MRI that I have every 6 months revealed that I have a growth within my thyroid, which I had half removed and 3 months later, had the other half removed. My ordeal carries on but I have not felt sorry for myself. I think positively and live my life to the best of my ability. Then my treating doctors found a gene connected to me after many years of research which is a big relief to me. Not knowing why I was getting so many cancers was very frustrating. Getting the news from my doctor brought a big relief to me and my family. I have a big road ahead of me which I will overcome.

Positive thoughts to one and all.

P.S. I would also like to thank Professor and all of the staff who cared for me at the tertiary hospital, also the professors, doctors, nurses and reception staff at my local cancer centre. My cancer centre treats patients with the utmost respect.

Learning points

- ▶ *CHEK2* mutations should be thought of as a gene mutation that can drive multiple cancers.
- ▶ More studies are required to ascertain the treatment effects of chemotherapy and radiotherapy for patients who have lesser-known germline mutations.
- ▶ Since the field of genomics is evolving rapidly, we need to keep searching for answers until we are satisfied all the questions have been answered.
- ▶ Genomics can be an important tool in the armoury that can provide closure to cancer patients and restore confidence in health professionals.

Acknowledgements University Of Melbourne Parkville Familial cancer Centre Victoria Australia.

Contributors DLDS contributed towards the planning, conception, design of the work, analysis and interpretation of data and the final production of the manuscript. DLDS have drafted the work and revisited it critically for important intellectual content. DLDS is accountable for the final approval of the version published. DLDS is also accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. IW contributed towards the planning and conception, design of the work, analysis, interpretation of data and supervision of DLDS.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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