

SHORT REPORT

Homozygosity for CHEK2 p.Gly167Arg leads to a unique cancer syndrome with multiple complex chromosomal translocations in peripheral blood karyotype

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ABSTRACT

Background Chromosomal instability, as reflected by structural or copy-number changes, is a known cancer characteristic but are rarely observed in healthy tissue. Mutations in DNA repair genes disrupt the maintenance of DNA integrity and predispose to hereditary cancer syndromes.

Objective To clinically characterise and genetically diagnose two reportedly unrelated patients with unique cancer syndromes, including multiorgan tumorigenesis (patient 1) and early-onset acute myeloid leukaemia (patient 2), both displaying unique peripheral blood karyotypes.

Methods Genetic analysis in patient 1 included TruSight One panel and whole-exome sequencing, while patient 2 was diagnosed by FoundationOne Heme genomic analysis; Sanger sequencing was used for mutation confirmation in both patients. Karyotype analysis was performed on peripheral blood, bone marrow and other available tissues.

Results Both patients were found homozygous for *CHEK2* c.499G>A; p.Gly167Arg and exhibited multiple different chromosomal translocations in 30%–60% peripheral blood lymphocytes. This karyotype phenotype was not observed in other tested tissues or in an ovarian cancer patient with a different homozygous missense mutation in *CHEK2* (c.1283C>T; p.Ser428Phe).

Conclusions The multiple chromosomal translocations in patient lymphocytes highlight the role of CHK2 in DNA repair. We suggest that homozygosity for p.Gly167Arg increases patients' susceptibility to non-accurate correction of DNA breaks and possibly explains their increased susceptibility to either multiple primary tumours during their lifetime or early-onset tumorigenesis.

INTRODUCTION

Hereditary cancer syndromes are caused by germline mutations in cancer-predisposing genes. They are often characterised by multiple primary tumours, such as Li-Fraumeni syndrome caused by *TP53* mutations, or an early age of disease onset, for example, *BRCA1/2* mutations predisposing to breast and ovarian cancer.¹ Cancer-predisposing

genes can be divided to different functional groups. One such group includes DNA repair genes (DRGs), such as *ATM*, *BRCA1* and *CHEK2*, which encode for tumour suppressor proteins with a crucial role in maintaining DNA integrity and genomic stability. Accordingly, abnormal DRG activity significantly increases cancer risk.² While the link between some recurrent DRG variants with cancer and genomic instability is well established, identification of new variants requires demonstration of causality in genomic instability and cancer to allow informed genetic and clinical counselling of the patient and his family. Moreover, the study and characterisation of variants can lead to better understanding of the tumorigenesis process and suggest potential interventions for cancer treatment.^{3,4}

We describe two patients, one with multi primary tumours and the other with early-onset leukaemia, both exhibiting lymphocyte karyotype with multiple chromosomal translocations. Both patients were found to share a germline homozygous *CHEK2* variant, c.499G>A; p.Gly167Arg.

MATERIALS AND METHODS

Participants and ethical standards

All participants signed informed consent as customary. Participants were evaluated by medical geneticists, as well as by their referring physicians, that is, gastroenterologist and haemato-oncologist. Additional clinical data were obtained from medical records.

Molecular genetics analysis

DNA was extracted from peripheral blood samples of patients and their participating family members. Initially, a sequencing library from patient 1's DNA was prepared with the TruSight One (TSO) targeted sequencing panel, consisting of ~4800 disease-related genes, according to the manufacturer's protocol (Illumina, San Diego, California, USA) and sequenced on a NextSeq500 sequencer (Illumina). Whole exome sequencing (WES) of patient 1's DNA sample was performed in collaboration with the Regeneron Genetics Center (RGC). Fastq files were analysed using the Genoox Ltd. data analysis



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platform (Tel Aviv, Israel), including read mapping and alignment to the human reference genome (GRCh37/hg19), variant calling, annotation and variant classification.

Sequencing data were filtered as follows: (1) rare variation with minor allele frequency (MAF) <0.05 in public general population databases and our in-house database of over 1000 Israeli exomes; (2) protein-altering variants (non-synonymous, nonsense, frameshift and splice site); and (3) variants observed in cancer-related genes. Missense variants were assessed in silico for pathogenicity using software implemented in Alamut Visual (<https://www.interactive-biosoftware.com/alamut-visual/>); ConSurf was used for conservation analysis.⁵

Karyotype analysis

Karyotype analysis of patient 1's peripheral blood lymphocytes was performed based on standard protocols and repeated independently in the Cytogenetics laboratories at Rambam Health Care Campus (RHCC) and Beilinson Hospital on samples taken at different time points. In addition, bone marrow, fibroblasts and renal tumour tissue samples were karyotyped at RHCC. For patient 2, karyotyping was performed on lymphocytes and bone marrow (RHCC), and for patient 3, karyotype analysis included lymphocytes only (Beilinson Hospital).

Briefly, for lymphocyte analysis, heparinised whole blood was incubated for 72 hours in culture medium containing phytohemagglutinin (PHA); heparinised bone marrow was incubated in medium without PHA for 24 hours; skin biopsy and tumour tissue samples were cut and grown using a standard tissue culture protocols for fibroblast growth. Thereafter, colcemid solution was added, and cells were resuspended in hypotonic solution,

fixed and Giemsa-stained. Cells were visualised with Axioskop 40 microscope (Zeiss, Oberkochen, Germany) and analysed using the GenASIs software (Applied Spectral Imaging, Migdal HaEmek, Israel).

Chromosomal microarray analysis (CMA)

CMA analysis for detection of copy-number variations was performed on DNA derived from patient 1's blood and fibroblasts using the Cytoscan 750K array (Affymetrix, Santa Clara, California, USA). Results were analysed using the Chromosome Analysis Suite.

RESULTS

Case presentation and genetic analysis

Patients 1 and 2 were followed and diagnosed at RHCC. On the observation of their unique genotype and karyotype findings, we reached out to the Israeli Oncogenetics community in order to find similar cancer patients, that is, either with a similar karyotype or biallelic *CHEK2* mutations. This led to collaboration with the Genetics Institute at Rabin Medical Center (Beilinson Hospital) regarding patient 3.

Patient 1

A 68-year-old male patient of Christian Arab descent presented with multiorgan tumourigenesis. His cancer history includes dozens of intestinal polyps since age 35 years, thymoma at age 49 years, breast cancer (BC) at 65 years, prostate cancer at 66 years, left renal cell carcinoma, angiomyolipoma of the right kidney and sigmoid gastrointestinal stromal tumour at age 67 years. The

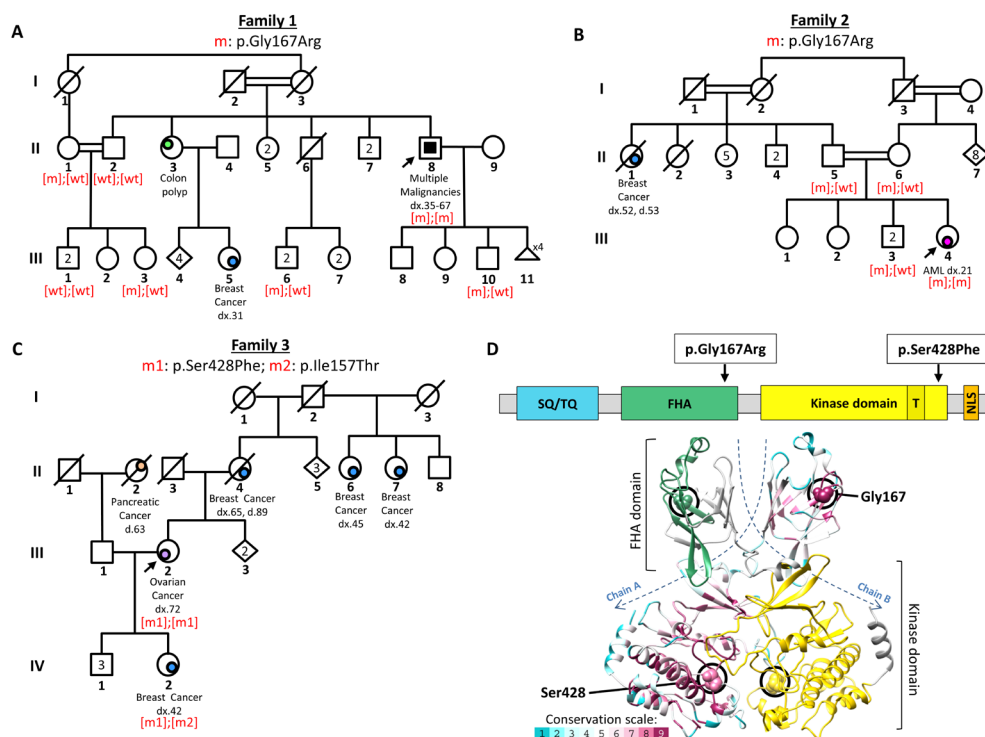


Figure 1 *CHEK2* homozygous mutations and cancer susceptibility. (A–C) Pedigrees of families 1–3 with homozygous *CHEK2* mutations and their personal and family cancer histories; (D) Top: schematic representation of the CHK2 protein denoting its functional domains: SQ/TQ motif, forkhead-associated (FHA) domain, kinase domain containing the activation T-loop and the nuclear localisation signal, as well as the location of homozygous mutations in families 1–3. Bottom: the three-dimensional crystal structure of the CHK2 homodimer (based on PDB #316U). Chain A represents the conservation of amino acids (based on ConSurf analysis), while chain B is coloured by domains (green: FHA domain, yellow: kinase domain). The location of Gly167 and Ser428 is highlighted.

patient is an offspring of healthy first cousins (figure 1A); family history was positive for a sister with a tubulo-villous adenoma at age 60 years, a niece with BC at age 31 years and a paternal first cousin once removed who died of BC at age 46 years.

Initial clinical genetic analysis included *BRCA1/2* sequencing and multiplex ligation-dependent probe amplification analysis, which were unremarkable. TSO panel analysis identified a homozygous missense mutation: c.499G>A; p.Gly167Arg in *CHEK2* (NM_007194.3). This variant was observed in a heterozygous state with MAF of 0.006% in gnomAD, 0.007% in the RGC database and in two families of Druze and Iraqi Jewish origins in the Rambam Genetics Institute database. The ClinVar entry for this variant (ID: 142524) has conflicting classifications; however, most classify it as 'likely pathogenic'. Segregation analysis in consenting relatives yielded only heterozygotes and non-carriers (figure 1A); two family

members (individuals II-3, III-5) refused testing. No other cancer-related variants were observed in the TSO panel or WES analyses.

Karyotype analysis of the patient's lymphocytes was performed due to a previous report of familial thymoma with a constitutional translocation.⁶ Karyotyping revealed multiple different chromosomal translocations involving various chromosomes and mostly unbalanced in 40%–60% of cells (figure 2). The translocations were observed independently in three separate tests by two cytogenetics laboratories, performed at different time points (total n=90 analysed cells). The patient's bone marrow (n=20) and fibroblasts (n=20) were normal and did not display the translocation phenotype; a chromosomal aberration, 46,X,-Y,+16,add(1)(p36), was detected in all renal tumour biopsy cells (n=5). Other tested family members had normal karyotypes. CMA analyses of the patient's DNA, derived from

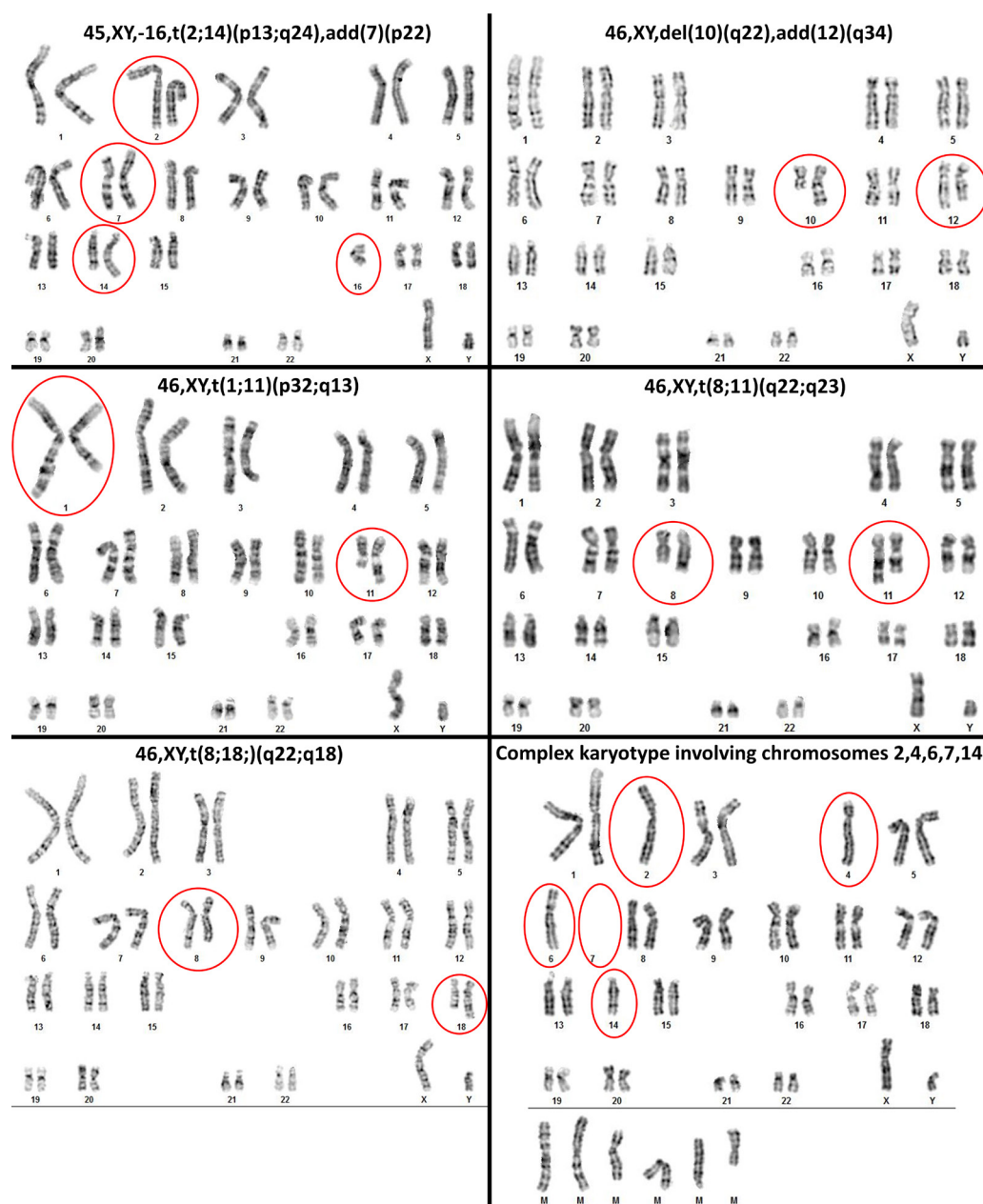


Figure 2 Multiple chromosomal translocations in a p.Gly167Arg homozygous patient. Multiple different chromosomal translocations were observed in 30%–60% of patient 1's lymphocytes. This figure presents karyotypes of six cells, each exhibiting different chromosomal aberrations (simple and complex) involving different chromosomes.

both blood and fibroblasts, did not reveal any pathogenic copy-number aberrations.

Patient 2

A 21-year-old woman of Christian Arab descent was diagnosed with acute myeloid leukaemia (AML) and hypocellular bone marrow. She is an offspring of first cousins (figure 1B) and resides in a village adjacent to patient 1's; there is no known family relation between the families. Family history includes a paternal aunt with BC at 52 years.

FoundationOne Heme genomic analysis (Roche, Basel, Switzerland) of patient's bone marrow demonstrated normal sequence of genes known to have recurrent mutations in AML but revealed *CHEK2* p.Gly167Arg with 90.6% mutation allele frequency. Sanger sequencing of DNA extracted from both blood (drawn after AML remission) and buccal swab, confirmed the homozygosity for the *CHEK2* variant is germline. The patient's parents and siblings were tested and were found with either heterozygous or wild-type genotype (figure 1B).

Karyotype analysis of the patient's bone marrow for AML diagnosis revealed 46,XX,t(3;8)(q26,q24),-7,-17,+2mar[3]/46,XX[14]. Lymphocyte analysis on AML remission revealed a multiple-translocation pattern similar to patient 1, that is, patient 2's lymphocytes exhibited different complex chromosomal translocations involving various chromosomes in ~30% of 30 analysed cells.

The patient underwent bone marrow transplantation from a fully matched unrelated donor; however, the disease relapsed 3 months post-transplantation.

Patient 3

A 72-year-old woman of Ashkenazi Jewish (AJ) descent was diagnosed with serous ovarian carcinoma. She tested negative for the AJ founder mutations in *BRCA1/2*. Family history consisted of her mother with BC at 65 years, two maternal aunts with BC at ages 42 and 45 years and a brother with several precancerous skin lesions. Her daughter was diagnosed with unilateral BC at 42 years and was found to be compound heterozygous for *CHEK2* c.470T>C; p.Ile157Thr and c.1283C>T; p.Ser428Phe by commercial next-generation sequencing testing. Following her daughter's diagnosis, patient 3 was tested for both *CHEK2* variants (G.G.A. Ltd, Katzin, Israel) and was found homozygous for p.Ser428Phe (figure 1C). No segregation data are available for other family members.

Karyotype analysis of patient 3 lymphocytes was normal, with only one cell exhibiting a balanced translocation between the short arms of chromosomes 7 and 14 (46,XX,t(7;14)(p11.1,11.2)[1]/46,XX[29]).

DISCUSSION

In this study, we report two patients with cancer exhibiting a unique karyotype of different multiple chromosomal translocations in lymphocytes, which was not observed in other tissues including bone marrow. While these patients differ in their oncological history, both were found homozygous for the *CHEK2* (NM_007194.3): c.499G>A; p.Gly167Arg variant, highlighting the protective role of *CHEK2* against genome instability.

The *CHEK2* gene encodes for a major double-strand breaks (DSB) and homologous recombination (HR) repair pathway serine/threonine kinase, CHK2.⁷ DSBs trigger DRG activity, leading to cell cycle arrest, apoptosis or correction via the highly regulated and accurate HR repair pathway, which employs a template-based correction mechanism. DSBs can also be repaired

by alternative pathways, such as the error-prone non-homologous end-joining (NHEJ) repair.^{2,8} Thus, NHEJ DSB repair can lead to translocations, as well as insertions or deletions of nucleotides in the repair process, causing genomic instability.^{2,8} Some *CHEK2* variants are known to increase risk for BC, leukaemia and other cancers, mostly in patients with heterozygous variants.⁹⁻¹² The portion of cancer patients with pathogenic variants in *CHEK2* was reported among the highest in a panel of cancer genes.¹³ Homozygous pathogenic variants in *CHEK2* have rarely been reported and include c.1100del, a loss-of-function variant relatively common among Europeans, known to increase the risk for breast and other cancer types in both homozygotes and heterozygotes,¹⁴ p.Arg474Cys, which was reported in a family with multiorgan tumours,¹⁵ and p.Ile157Thr, observed in patients with papillary thyroid carcinoma,¹⁶ which was also described in heterozygosity in a family with Li-Fraumeni syndrome.¹¹ While p.Gly167Arg has been previously reported in a heterozygous or compound heterozygous states, linked mostly to BC susceptibility,^{9,13} to our knowledge, ours is the first report of its homozygosity. The multiple different translocations observed in patients' peripheral blood karyotypes have not been described previously and were not observed in a patient homozygous for a different *CHEK2* missense variant (p.Ser428Phe, a moderate-penetrance AJ founder allele). Hence, they likely result from the susceptibility conferred by p.Gly167Arg towards aberrant DSB correction.

The CHK2 protein comprises 543 amino acids, distributed between several domains: SQ/TQ motif, forkhead-associated (FHA) domain, kinase domain containing the activation T-loop and the nuclear localisation signal (figure 1D).¹⁷ Pathogenic variants affecting CHK2 function can be found across the protein but are mostly concentrated in the kinase and FHA domains. The FHA domain is required for CHK2 dimerisation and its subsequent activation and autophosphorylation, as well as for interactions with phosphoproteins, including other DRGs such as *BRCA1*.^{9,17-19} The glycine-to-arginine substitution at position 167 affects a highly conserved residue in the FHA domain (figure 1D); since glycine and arginine differ in polarity, charge and size, the substitution is predicted to be pathogenic. Pathogenicity is supported by previously published functional data demonstrating that cells with CHK2 p.Gly167Arg have deficient DNA damage-response in a yeast system.⁹ Interestingly, the p.Ser428Phe variant found in patient 3 received a similar pathogenicity score in the same DNA damage test.⁹ The finding that homozygosity for p.Ser428Phe, situated in the kinase domain (figure 1D), does not lead to the severe cancer-susceptibility and DNA-breakage phenotype as p.Gly167Arg, implies that FHA domain function is critical for DNA repair and cannot be compensated, as opposed to the protein kinase activity alone.

A mouse model harbouring the c.1100del variant had increased rates of DSBs and tumourigenesis in both heterozygous and homozygous states, demonstrating the importance of this gene in DNA repair and cancer.²⁰ The DNA-breakage phenotype, manifesting as multiple chromosomal translocations in patient lymphocytes, corroborates the essential role of CHK2 in DSB repair. The observation of different unbalanced translocations only in blood karyotypes may be secondary to the use of the mitogen PHA for proliferation of mature lymphocytes, as a standard karyotyping method. We suggest that homozygosity for p.Gly167Arg in *CHEK2* increases patients' susceptibility to DSBs and shifts the balance to non-accurate DSB correction. This possibly explains the increased susceptibility of homozygotes to either multiple primary tumours during their lifetime or early-onset tumourigenesis. Taking into account the oncological

history of patient 1, similar patients with homozygosity for p.Gly167Arg require early detection and strict oncological follow-ups.

Although *CHEK2* is usually considered a moderate-penetrance gene, biallelic variants should be considered in patients with multiorgan tumourigenesis or early-disease onset. This is especially true for populations in which consanguinity and endogamy are prevalent, conferring higher risk for homozygosity. Moreover, we suggest that the multitranslocation karyotype can serve as a marker for clinicians to suspect biallelic *CHEK2* mutations.

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Contributors The first three authors (TP, NS-S and AK) contributed equally to this work. TP, NS-S and AK collected patient data and summarized clinical and genetic findings. TP, AK, CG-J, AM and ARS participated in genetic analyses, bioinformatics and data interpretation. NS-S, YG, YC, MF, GR-L, YO and EEH followed and treated the patients. NM and LB-S performed the karyotype analyses and interpreted karyotyping results. LB-S performed the chromosomal microarray analysis. TP, NS-S, AK and HBF drafted the manuscript. All coauthors critically reviewed the manuscript and approved the final submitted version.

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Data sharing statement All data regarding this study is available upon request.

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