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Case report

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Myelodysplastic syndrome diagnosed by genetic testing for hereditary cancer: a case report

Sarah Ridd[1], Larissa Peck[1], Aniket Bankar[1], George S. Charames[2,3], Jordan Lerner-Ellis[2,3], Radhika Mahajan[2], Peter J. B. Sabatini[1,3], Andrew Wong[2], Janet Malcolmson[1] & Raymond H. Kim[1,2,4,5]

Genetic testing for solid tumor syndromes typically uses peripheral blood leukocytes (PBL) as the source of germline DNA. This approach has shortcomings in certain situations, such as somatic mosaicism and hematologic malignancies. Here we describe a case where germline genetic testing on PBL revealed an unsuspected diagnosis of myelodysplastic syndrome (MDS). A 68-year-old male with a history of three solid tumors and a significant family history of cancer underwent germline genetic testing with a 76-gene hereditary cancer panel. Initial testing using PBL revealed deletions of the entire *APC* and *CTNNA1* genes, suggestive of a contiguous deletion of chromosome 5 (del(5q)). Subsequent testing on cultured fibroblasts was negative, indicating the deletions were somatic. Bone marrow analysis confirmed the presence of del(5q) and a diagnosis of MDS. This case demonstrates the potential to uncover hematologic disorders through hereditary cancer genetic testing, emphasizing the importance of careful results interpretation, multidisciplinary follow-up, and DNA source selection.

Germline genetic testing for hereditary forms of cancer commonly uses massively parallel next-generation sequencing (NGS) to identify single-nucleotide variants and small insertions/deletions[1]. The most common DNA source for NGS testing is peripheral blood leukocytes (PBLs) due to their overall dependability and minimal invasiveness[2]. However, in patients with hematologic disorders, leukocytic DNA can affect the accuracy of germline test results by detecting both somatic and germline variants. Examples of conditions affecting PBL genetic testing include clonal hematopoiesis of indeterminate potential (CHIP), hematologic malignancies, somatic reversion, somatic mosaicism, or chromosomal abnormalities[3]. In these patients, alternative tissue DNA sources such as cultured fibroblasts are often recommended[4]. Therefore, genetic testing results on PBL for patients with solid tumor hereditary cancer syndromes may be reflective of an undiagnosed hematologic condition, suggesting how these events may confound genetic testing results[5]. Repeat testing using alternative tissue types for low-level variant calls may help to clarify these differentials[6]. Examples of confounding results include the observation of low variant allele fractions (VAFs), multiple pathogenic variants, and other non-germline findings[7].

Hereditary cancer panel testing may offer further observations that are outside of the original reason for testing. Multiple gene deletions on germline panels, for example, could demonstrate larger cytogenetic abnormalities that are not fully captured by NGS panel testing. The genes *APC* and *CTNNA1* are often represented in multi-gene panels for common solid tumor syndromes and have also been known to play a role in the hematopoietic system and the pathogenesis of myelodysplastic syndromes (MDS)[8,9]. The *APC* and *CTNNA1* genes are located approximately 26 megabases apart on the long arm of chromosome 5, offering potential further implications in germline panel testing. Other examples include *BRCA2, RB1* (located on 13q), and *TP53* (located on 17p), commonly included in hereditary cancer testing. 13q and 17p deletions are typically associated with chronic lymphoid leukemia, offering broader implications for hematopoietic neoplasms to be inadvertently detected through cancer panel testing[10,11].

MDS is a group of clonal hematopoietic disorders characterized by an ineffective production of blood cells leading to cytopenia and dysplastic cell morphology, with a high risk of transformation to acute myeloid leukemia[12,13]. Clinically presenting as easy bleeding/bruising, infections, fever, or fatigue, MDS is diagnosed through an evaluation of both peripheral blood and bone marrow specimens[14]. Cytogenetic abnormalities are often observed in MDS patients, with the most common being a deletion of the long arm of chromosome 5 (del(5q)), observed in 15–26% of cases[15,16]. Isolated del(5q), however, is not always associated with MDS[17].

[1]Princess Margaret Cancer Centre, University Health Network, Toronto, ON, Canada. [2]Sinai Health System, Toronto, ON, Canada. [3]Department of Laboratory Medicine and Pathobiology, University of Toronto, Toronto, ON, Canada. [4]Division of Clinical and Metabolic Genetics, The Hospital for Sick Children, Toronto, ON, Canada. [5]Ontario Institute for Cancer Research, Toronto, ON, Canada. e-mail: Raymond.Kim@uhn.ca

To our knowledge, the diagnosis of MDS through hereditary cancer genetic testing has not been previously reported. Here we describe a case where genetic testing for hereditary forms of solid tumors on PBLs revealed an unsuspected diagnosis of MDS, underscoring the importance of considering hematologic conditions when interpreting genetic test results.

Results

Case report

A 68-year-old male with a personal history of Ewing's sarcoma at age 16, breast cancer at age 53, and papillary thyroid cancer at age 57 was referred for a genetics assessment. His family history included early-onset breast cancer in his daughter, oligodendroglioma in his brother, glioblastoma in his father, and various additional cancers in multiple relatives [Fig. 1].

Genetic testing in PBL

NGS hereditary cancer panel testing was completed using DNA isolated from PBLs from the patient, analyzing 76 solid tumor susceptibility genes. Testing was performed at the Pathology and Laboratory Medicine laboratory at Mount Sinai Hospital in Ontario, Canada. Initial results revealed pathogenic whole gene deletions of both *APC* and *CTNNA1* at low allele fractions (~20%), as well as three heterozygous variants of uncertain significance (VUS) in *POT1*, *MLH3,* and *ATM* [Table 1 and Fig. 2].

Genetic testing in cultured fibroblasts

Due to these unusual PBL genetic testing results, a skin punch biopsy was performed to repeat the same NGS multi-cancer panel on DNA isolated from cultured fibroblasts. This testing confirmed the VUS in *POT1* and *MLH3* as germline, but did not detect the *APC* or *CTNNA1* deletions, nor the VUS in *ATM* [Table 1 and Fig. 2].

Cascade testing in family members

At the time of the proband's breast cancer diagnosis (age 53), no prior genetic testing had been done in the family. The proband first received targeted testing for the common Ashkenazi Jewish variants in the *BRCA1* and *BRCA2* genes as an initial targeted approach. This returned negative, and given the lack of identified variants, a broad 76-gene comprehensive cancer panel was conducted. The daughter diagnosed with breast cancer at age 28 also received a 76-gene comprehensive panel, including *POT1* familial variant testing, which was negative. The unaffected daughter received a targeted panel for common Ashkenazi Jewish variants and *POT1* familial variant testing, also returning negative. Finally, the proband's

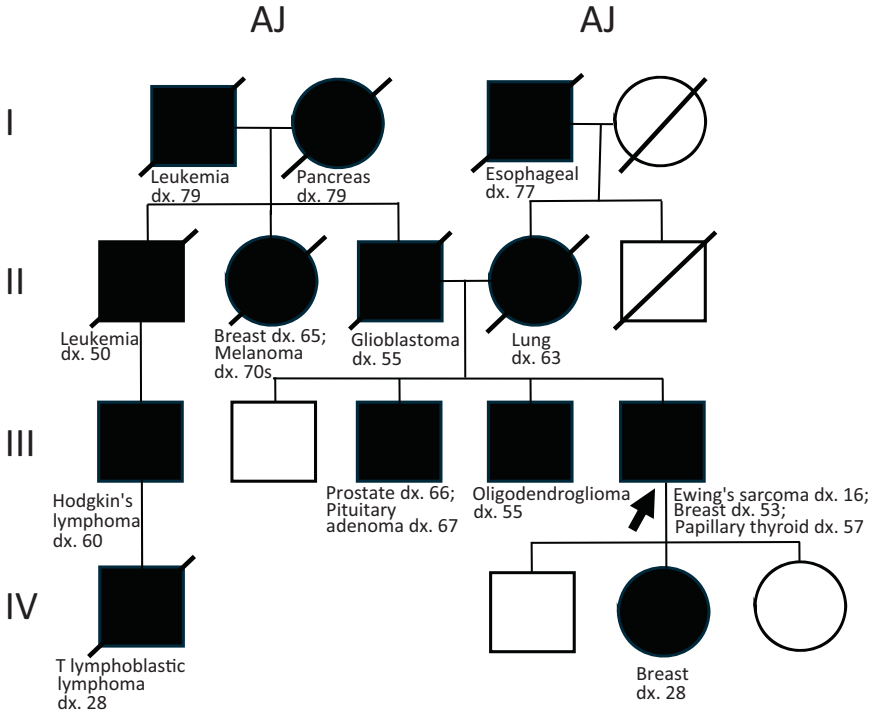

Fig. 1 | Four-generation pedigree. Arrow: case-specific proband; square: male family members; circle: female members; black-shaded symbols: members affected by cancer; white-fill: no relevant disease; strikethrough: deceased members; AJ: Ashkenazi Jewish decent; dx: diagnosis (age in years).

Table 1 | NGS on various tissue sources offers distinct results

Gene, transcript	Variant, prediction	Zygosity	Interpretation	PBL DNA	Fibroblast DNA
APC, NM_000038.6	c.1-?_8532 + ?del, p.?	Low allele fraction (~20%)	Pathogenic	X	
CTNNA1, NM_001903.5	c.1-?_2721 + ?del, p.?	Low allele fraction (~20%)	Pathogenic	X	
ATM, NM_000051.3	c.8667 T > A, p.Asp2889Glu	Heterozygous	Uncertain Significance	X	
MLH3, NM_001040108.1	c.2315 T > C, p.Val772Ala	Heterozygous	Uncertain Significance	X	X
POT1, NM_015450.3	c.(-38 + 1_-39-1)_(9 + 1_10-1) dup, p.?	Heterozygous	Uncertain Significance	X	X

Sequencing reveals two pathogenic variants and three variants of uncertain significance in PBL DNA. Only two variants of uncertain significance were identified in fibroblast DNA. "X" indicates the NGS detection of a variant.

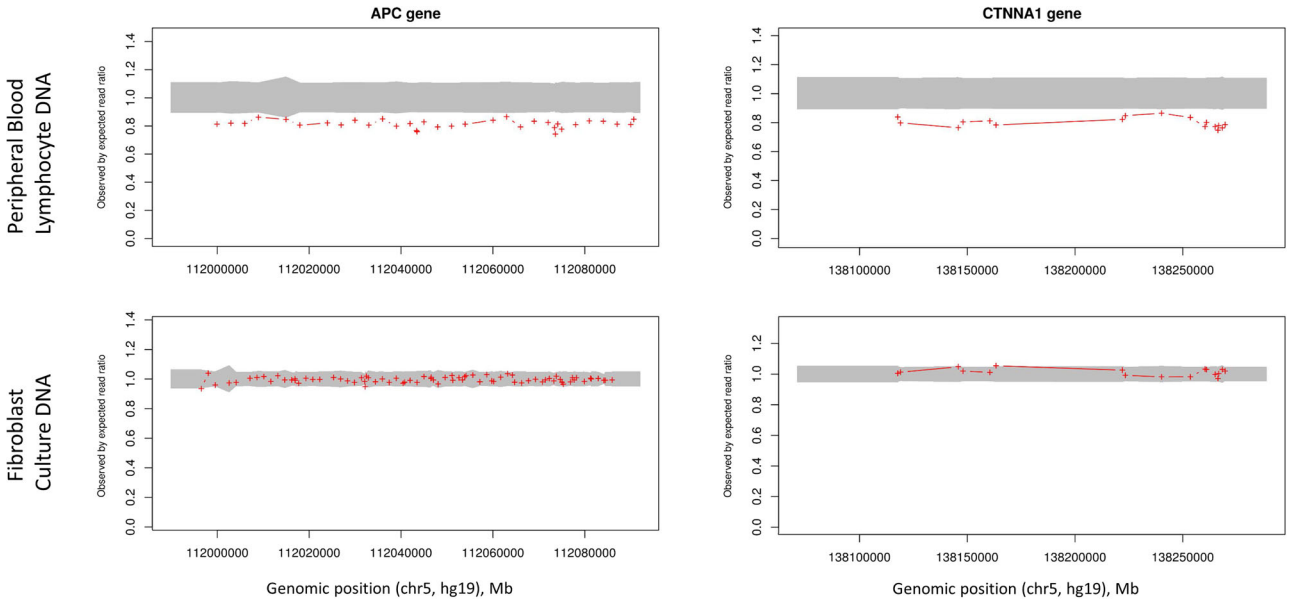

Fig. 2 | Copy number variant (CNV) plots of normalized probe coverage (gray) relative to variance of other samples within the sequencing run. Whole gene deletions in the sequencing data of both *APC* and *CTNNA1* genes in PBL DNA, but not in DNA from cultured fibroblasts of the same patient, following analysis by the ExomeDepth bioinformatics tool. The red crosses represent, for all sequencing probes spanning the gene of interest, the ratio of observed/expected number of reads for the patient sample as previously described[18]. The gray shaded region represents the estimated 99% confidence interval for the observed ratio of all probes in the absence of a CNV call. Two or more contiguous red crosses below the gray shaded area are indicative of a putative deletion, while red crosses above the shaded area are likely a duplication.

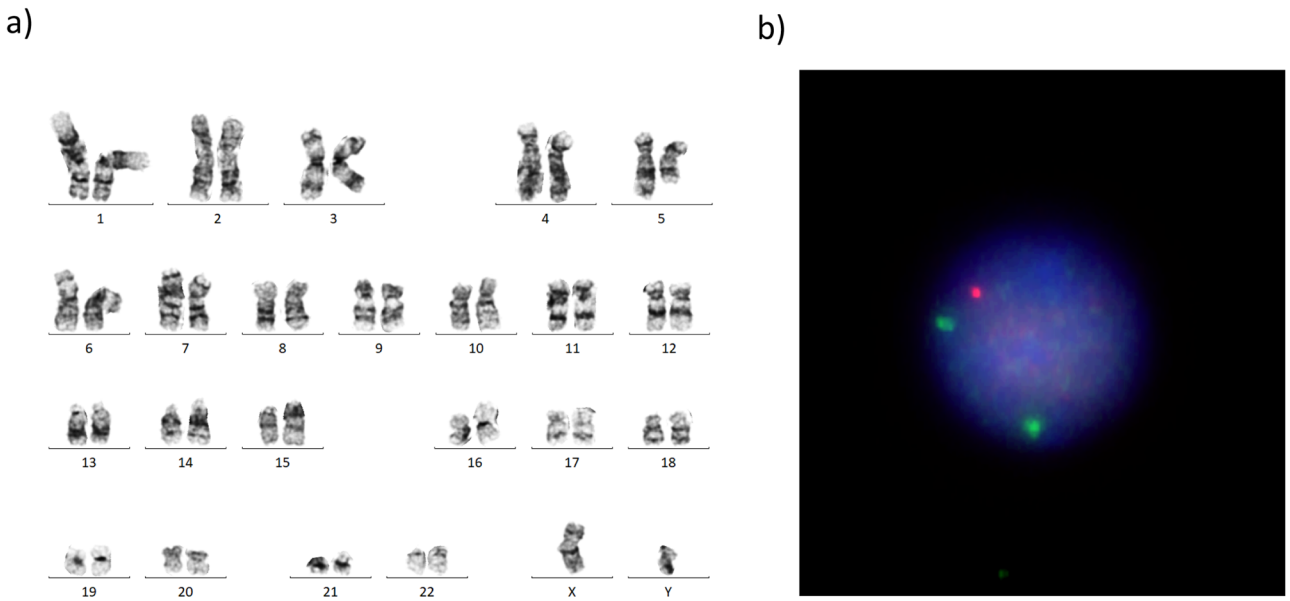

Fig. 3 | Cytogenetic MDS studies on bone marrow. a G-banded karyotype analysis of a single metaphases showing del(5q). **b** Interphase FISH image showing del(5q) with one 5q31.2 signal (red) and two 5p15.3 signals (green). Image capture and processing were done using Neon software (MetaSystems, Altlussheim, Germany).

unaffected brother tested negative for the 76-gene comprehensive panel. No other affected family members have been tested at this time.

Hematologic evaluation

Complete blood count (CBC) revealed a slightly low hemoglobin level of 119 g/L (normal 140–180 g/L), normal absolute neutrophil and platelet count. A bone marrow biopsy revealed normocellular bone marrow with trilineage hematopoiesis, megakaryopoiesis demonstrated a significant number of hypolobulated forms (>10%), CD34+ blasts up to 4% by immunohistochemistry, and peripheral blood demonstrated mild macrocytic anemia. The patient did not report any constitutional symptoms, frequent infections, or bleeding manifestations related to MDS. G-banded karyotyping failed to yield a sufficient number of metaphase cells for analysis; however, a single metaphase was karyotyped and did show a del(5q). Fluorescence in situ hybridization (FISH) analysis confirmed the del(5q) in 52.5% of nuclei [Fig. 3]. This MDS reflex panel did not identify any other lesions by FISH. NGS for a 49-gene MDS panel did not contain any clinically relevant variants. The patient was diagnosed with MDS, with an IPSS-M risk calculation scoring very low.

Telomere studies

The *POT1* germline finding raised concern given the personal and familial incidence of cancers associated with the *POT1* gene, which is associated with

long telomeres[19]. A 6-panel telomere length assay was completed, and the patient's telomere lengths were found to be in the low range for his age. This finding is likely related to his MDS and not suggestive of a telomere biology disorder.

Discussion

This case report illustrates a unique diagnostic pathway where germline genetic testing for a solid tumor hereditary cancer syndrome can reveal an occult diagnosis of a hematologic condition. The 68-year-old patient with multiple primary cancers and a significant family history of cancer underwent genetic testing on PBL for the purpose of investigating a potential hereditary cancer syndrome, ultimately uncovering a MDS that was newly diagnosed. We present this case to highlight the importance of accurate interpretation and to describe when follow-up investigations are needed to explain incidental findings that are revealed through genetic testing of PBLs.

In the reported patient, further investigations were prompted by the *APC* and *CTNNA1* pathogenic deletions. Independently, pathogenic variants in these genes may suggest germline cancer predisposition implications. Multi-locus Inherited Neoplasia Allele Syndrome (MINAS) was considered in the review of the two pathogenic deletions; however, it was considered unlikely in our patient given the lack of polyposis and gastric cancer in our patient and family[20].

Analysis by the ExomeDepth bioinformatics tool offered unique clinical insights to the case when the read ratio of PBL CNV was abnormal, but repeat testing on fibroblast DNA was not. The limit of detection for CNV analysis by NGS is typically ~20%–30%. The single-nucleotide variant limit of detection is ~5%. Reliably detecting somatic or mosaic copy number losses above the 20–30% limit of detection is therefore what may be expected for detecting germline heterozygous copy number losses and gains. The read ratio cutoff called by ExomeDepth for germline CNVs, and specifically deletions, is set to 0.75. For duplications, the read ratio is set to 1.25. The intention to increase sensitivity for calling germline CNVs and minimize the risk of false negatives means the samples can have suboptimal uniformity of coverage, affecting their read ratios. In the clinical germline testing, the NGS CNV call was confirmed by multiplex ligation-dependent probe amplification before final interpretation, lowering the potential for false-positive calls at the NGS CNV caller stage. No other losses with similar reads were noted in our case.

A growing practice for germline laboratories to report the VAF of pathogenic variants is becoming increasingly useful[21]. The NGS genetic testing report included the VAF of the whole gene deletions in *APC* and *CTNNA1*. Further communication with the laboratory was made to clarify the results. Consideration for clinical laboratories to report variants that fall below certain allele fraction thresholds for heterozygous calls should be noted, as this case demonstrates the importance of reporting low VAFs that otherwise may be at risk of being inadvertently filtered out. Peripheral blood acts as a unique DNA sample when considering the hematologic implications of germline testing. The presence of hematologic conditions complicates germline versus somatic variant calling, and VAF alone does not offer a diagnostic alternative. Further investigations and multidisciplinary input from genetics, laboratory scientists, and hematologists are necessary. With PBL NGS detecting low allele fraction reads of ~20% VAF in the *APC* and *CTNNA1* genes in the reported patient, testing on a secondary tissue source was initiated. Cultured fibroblast testing did not confirm the deletions, nor the *ATM* VUS, and thus these were considered somatically acquired. The further impression of a somatic contiguous deletion was indicated, given the proximity of the *APC* and *CTNNA1* genes on 5q.

The association of del(5q) and MDS prompted a hematologic evaluation in this patient. Workup demonstrated mild macrocytic anemia, indicating that something hematologic was occurring in the patient. Despite not meeting the defining threshold for cytopenia[22], dysplasia with FISH-confirmed del(5q) led to this patient's clinical diagnosis of MDS. Given the family history of hematologic malignancies, a 187-gene inherited bone marrow failure panel on germline fibroblast DNA was conducted. No clinically actionable variants were found. The FISH-confirmed del(5q) ultimately led to the demonstration and potential of hereditary cancer genetic testing panels to uncover hematologic disorders. Notably, a referral from the cancer genetics team to the hematology team included a detailed discussion to achieve a comprehensive clinical understanding, emphasizing the crucial role of close collaboration.

Cascade testing as a result of the proband's suspicious family history for *POT1* was initiated. All tested family members, including the daughter affected with breast cancer at 28, returned as *POT1* VUS negative. These findings, along with the telomere length assay results, supported the classification of the *POT1* c.(−38 + 1_-39-1)_(9 + 1_10-1)dup variant as a variant of uncertain significance.

Our case demonstrates the implications of unknown hematologic disorders when germline genetic testing is performed on blood. Although there is consensus that peripheral blood should not be used for germline genetic testing in individuals diagnosed with a hematologic condition such as MDS, there remains a challenge in the unknown presence of hematologic disorders[23]. In the reported patient, a contiguous gene deletion of 5q was observed in blood and was absent in cultured fibroblasts. Without further recommendations from a genetic counselor to obtain a secondary DNA sample, there is a hypothetical risk of misinterpreting the initial results[24]. Genetic testing on PBL is often not preceded by a CBC, and some hematologic conditions, such as CHIP, have normal blood counts. Therefore, we emphasize the value of close collaboration with genetic counselors, laboratory geneticists, oncologists, and pathologists when reviewing and interpreting genetic testing reports, as further investigations may be warranted[25,26].

Methods

Ethics

All procedures performed were conducted in accordance with the ethical principles of the Declaration of Helsinki. Written consent from the patient was obtained in compliance with all relevant ethical regulations with the University Health Network Research Ethics Board. The patient willingly agreed to share their anonymized data for this scientific publication. Measures to respect the privacy of the patient have been taken and are reflected throughout this report. The CARE guidelines: Consensus-based Clinical Case Reporting Guideline Development checklist[27] have been taken into consideration while writing this case report and can be found in the Supplementary Information.

Specimen selection

Despite our initial goal of testing blood as germline DNA, we uncovered a somatic contiguous gene deletion of 5q. Negative repeat germline genetic testing on cultured fibroblasts indicated that the deletions found in the blood were limited to the initial sample. Blood functioned as a source of somatic tumor DNA, allowing for the potential of the initial results to be misinterpreted in a germline context. We reinforce the importance of specimen selection in hereditary cancer testing and illustrate the importance of considering hematologic disorders when incidental findings are revealed.

Molecular genetic analysis

Comprehensive Hereditary Cancer Panel (76 genes): *AIP, APC, ATM, AXIN2, BAP1, BARD1, BMPR1A, BRCA1, BRCA2, BRIP1, CDC73, CDH1, CDK4, CDKN1B, CDKN2A, CHEK2, CTNNA1, DICER1, EGFR, EGLN1, EPCAM, EXT1, EXT2, FH, FLCN, GALNT12, GREM1, HOXB13, KIT, LZTR1, MAX, MEN1, MET, MITF, MLH1, MLH3, MSH2, MSH3, MSH6, MUTYH, NBN, NF1, NF2, NTHL1, PALB2, PDGFRA, PMS2, POLD1, POLE, POT1, PRKAR1A, PTCH1, PTEN, RAD51C, RAD51D, RB1, RECQL, RET, RNF43, RPS20, SDHA, SDHAF2, SDHB, SDHC, SDHD, SMAD4, SMARCA4, SMARCB1, SMARCE1, STK11, SUFU, TMEM127, TP53, TSC1, TSC2, VHL.*

Gene sequencing was performed by NGS on an Illumina NovaSeq 6000 instrument following library prep using the Illumina DNA Prep with Enrichment commercial kit and custom-designed Twist probes for the full coding regions and splice sites (±15 base pairs from the exon boundaries) as

well as targeted non-coding variants. Regions with coverage <20× are sequenced by Sanger sequencing.

The detection of single-nucleotide variations was performed following the Best Practices for Variant Calling with the Genome Analysis Toolkit (GATK 4.1.0) published by the Broad Institute. DNA sequence mapping is performed using the GRCh37/hg19 assembly as the genome reference build. Detection of exon-level copy number variations uses the published[18] and internally validated tool ExomeDepth 1.1.0.

Hematological Malignancies Panel (49 genes): *ASXL1, BCOR, BCORL1, BRAF, CALR, CBL, CEBPA, CSF3R, CTNNA1, CUX1, DDX41, DNMT3A, ETNK1, ETV6, EZH2, FBXW7, FLT3, GATA2, GNAS, IDH1, IDH2, IKZF1 IRF1, JAK1, JAK2, KIT, KMT2A, KRAS, MPL, MYD88, NOTCH1, NPM1, NRAS, PAX5, PHF6, PPM1D, PTPN11, RAD21, RUNX1, SETBP1, SF3B1, SH2B3, SRSF2, STAG2, TET2, TP53, U2AF1, WT1, ZRSR2.*

Extracted DNA was analyzed using the University Health Network Hematological Malignancies Panel v2.0, which examines exonic coding regions and 2 base pairs of flanking intronic sequences of 49 clinically relevant genes in hematological malignancies. This assay was designed using Oxford Gene Technologies (OGT) target enrichment hybrid capture followed by paired-end sequencing on the Illumina sequencing platform. Variant calls are generated using the UHN Clinical Laboratory Genetics custom bioinformatics pipeline with alignment to the human genome reference build GRCh37/hg19 and assessed using Alissa Interpret. Minimum acceptable coverage for all reported genomic regions is >100×.

Cytogenetic and molecular analysis of bone marrow

Bone marrow was cultured without mitogenic stimulation, and metaphase slides were fixed and prepared with Leishman's stain for G-banded analysis. FISH slides were hybridized for regions 5q31.2 (red) and 5p15.3 (green) using CytoCell Del(5q) Deletion probes. Genomic DNA was extracted from the bone marrow and sequenced using a custom panel from OGT as previously described[28].

Data availability

Genetic data that support the findings of this study are available in ClinVar [https://www.ncbi.nlm.nih.gov/clinvar/]. Accession codes for the data are as follows: SCV000590965.4; SCV005414514; SCV005414516; SCV005402445.1; SCV005414515. For further requests, qualified researchers may contact R.H.K. [raymond.kim@uhn.ca].

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Author contributions

L.P. idealized the manuscript. S.R. wrote the initial manuscript draft. R.H.K., S.R., L.P., J.M., P.J.B.S., A.B., A.W., G.S.C., and J.L.E. contributed to the editing of the manuscript. R.M. supported the genetic data deposition. All authors read and approved the final manuscript.

Competing interests

The authors declare no competing interests.

Additional information

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Correspondence and requests for materials should be addressed to Raymond H. Kim.