CANCER GENOMICS & PROTEOMICS *22*: 354-362 (2025)
doi: 10.21873/cgp.20506

Clinical Characteristics and Chemosensitivity in Germline TP53 Pathogenic Variant Cases Identified by Cancer Genomic Testing

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Abstract

Background/Aim: The widespread implementation of cancer genomic profiling (CGP) has led to an increase in the detection of germline TP53 pathogenic variants (gTP53v) in patients who do not meet the classical Li-Fraumeni syndrome (LFS) criteria. The present study aimed to characterize the clinical features and treatment outcomes of gTP53v cases identified through routine CGP testing.

Patients and Methods: We conducted a retrospective analysis of 43 patients with gTP53v identified through CGP testing between June 2019 and August 2024. Clinical characteristics, molecular features, and treatment outcomes were analyzed and compared with TP53 wild-type cases from the same database (n=6,515).

Results: The median age at diagnosis was 38 years (range=1-83 years), with 58.1% of cases presenting with non-core LFS tumors. A genomic analysis revealed diverse variant types (missense: 32, frameshift: 8, and nonsense: 3) with variant allele frequencies ranging between 0.10 and 0.696. Among 37 patients who received first-line chemotherapy, the objective response rate was 62%, which was significantly higher than in TP53 wild-type cases (32%, p=0.02). Complete responses were observed in six patients and partial responses in 14.

Conclusion: The present results suggest that gTP53v carriers identified through CGP represent a broader clinical spectrum than classical LFS, while demonstrating potentially favorable treatment outcomes. These results challenge traditional paradigms and emphasize the need for individualized approaches to patient care, particularly in cases with atypical presentations requiring the careful interpretation of mosaicism, de novo mutations, and clonal hematopoiesis.

Keywords: Germline TP53, chemotherapy, Li-Fraumeni syndrome, cancer genome test.

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Received November 18, 2024 | Revised December 12, 2024 | Accepted January 8, 2025

Introduction

Li-Fraumeni syndrome (LFS) (1) is a rare hereditary cancer predisposition syndrome characterized by germline pathogenic variants in the TP53 tumor suppressor gene (2-4). The *TP53* gene, often referred to as "the guardian of the genome", plays crucial roles in cell cycle regulation, DNA repair, and apoptosis, and its dysfunction leads to various malignant phenotypes (5, 6). Classical LFS typically presents with early-onset cancers, particularly soft tissue sarcomas, osteosarcomas, brain tumors, adrenocortical carcinomas, and early-onset breast cancers (2, 7, 8). The clinical diagnostic criteria for LFS, including the classic LFS criteria and Chompret criteria, have been well established based on these characteristic features and have evolved over time to incorporate our growing understanding of the syndrome (9).

The recent widespread implementation of cancer genomic profiling (CGP) in clinical practice has markedly changed our perspective on hereditary cancer syndromes, including LFS (10, 11). Through a comprehensive genomic analysis, CGP has led to an increase in the incidental identification of germline *TP53* pathogenic variants (gTP53v) in patients who do not meet the traditional LFS criteria (12, 13). The interpretation of gTP53v in these cases poses significant clinical challenges because several possibilities need to be considered in the diagnostic process. Moreover, these findings indicate mosaicism, where the *TP53* variant is present in only a subset of tissues (14). Another important consideration is clonal hematopoiesis of indeterminate potential (CHIP), particularly in cases where variants are detected in tumor tissue with low variant allele frequencies (VAF) (13, 14). The distinction between these conditions carries crucial implications for cancer risk assessments, surveillance strategies, and genetic counseling approaches.

Although the prognostic implications of somatic *TP53* mutations have been extensively examined in various cancer types (15), the impact of germline *TP53* variants on treatment outcomes remains unclear. Recent studies suggested relationships between the germline findings and treatment responses or prognosis (16, 17). However, systematic analyses of treatment outcomes in gTP53v cases are notably lacking in the current literature. A more detailed understanding of the relationship between gTP53v and treatment outcomes may have important implications for therapeutic decision-making in these patients.

In the present study, we conducted a comprehensive analysis of the clinical characteristics and treatment outcomes of gTP53v cases identified through CGP testing at our institution. We specifically focused on two critical aspects: the interpretation and clinical significance of gTP53v in cases with atypical presentations and treatment outcomes. The results obtained herein provide valuable insights into the appropriate clinical management of incidentally identified gTP53v cases through CGP testing and may contribute to the optimization of treatment strategies for these patients.

Patients and Methods

Study design and data source. This retrospective study analyzed data from the Center for Cancer Genomics and Advanced Therapeutics (C-CAT) Database, which collects comprehensive genomic and clinical information from patients who underwent CGP in Japan. We included patients who underwent testing using the NCC Oncopanel® System (NOP) or GenMine™ TOP Cancer Panel (TOP) between June 1, 2019 and August 15, 2024 (NOP) and between August 1, 2023 and August 16, 2024 (TOP). The study protocol was approved by the Institutional Ethics Committee of Yamagata University (approval number: 2023-105) and the C-CAT Utilization Review Committee (approval number: CDU2023-032N).

Patient selection and classification. We systematically reviewed all cases with identified germline *TP53* variants in the database. Germline *TP53* variants were classified as pathogenic, based on stringent criteria requiring either an evidence level of F (Drugs that are at the research stage or have limited evidence of efficacy based

on preclinical studies (*e.g.*, *in vitro* studies and animal experiments) or case reports/case series. This level includes biomarkers that demonstrate stronger and more established evidence levels (equivalent to likely oncogenic or above in OncoKB) or with higher classification in the C-CAT Database, even if these biomarkers previously showed negative results in clinical trials. The C-CAT evidence level system integrates multiple lines of evidence, including population databases, computational predictions, functional studies, and clinical observations, to assess the pathogenicity of genetic variants. In comparative analyses of treatment outcomes, we identified control cases from the same database that underwent CGP testing during the same period and did not harbor germline *TP53* variants.

Clinical data collection and analysis. We extracted comprehensive clinical data from the C-CAT Database, encompassing patient demographics, clinical characteristics, and treatment outcomes. Demographic data included age at diagnosis, age at genomic testing, sex, the Eastern Cooperative Oncology Group (ECOG) performance status, smoking history, and alcohol consumption patterns. A thorough review of family history included the documentation of malignancies across three generations. A previous history of malignancies was carefully documented for each patient.

Tumor characteristics were extensively documented, including the primary tumor site, histological classification, disease stage at the initial diagnosis, and patterns of metastatic spread. A complete treatment history was compiled, including all lines of therapy and their respective outcomes.

Genomic analysis. The genomic analysis encompassed the detailed characterization of *TP53* variants, including variant type classification (missense, nonsense, frameshift, or splice site alterations), VAF, and the assessment of affected protein domains. Functional impact assessment was performed using multiple databases including OncoKB and ClinVar. We systematically analyzed co-occurring somatic alterations, namely, the tumor mutational burden (TMB). The analysis accounted for panel-specific considerations, with NOP examining 124 genes and TOP covering 747 genes, and both including a comprehensive analysis of copy number alterations.

Treatment outcome assessment. Treatment responses were primarily evaluated according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1, although assessment criteria may vary across participating institutions due to the registry-based nature of the database. We documented the best overall response achieved during treatment, categorizing responses as a complete response, partial response, stable disease, or progressive disease. The duration of a response was calculated from the date of the first documented response until disease progression or death. The safety assessment followed the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 guidelines. Severe adverse events were defined as Grade 3 or higher non-hematological toxicities.

Statistical analysis. Statistical analyses were performed using Microsoft Excel 2021 (Microsoft Corporation, Redmond, WA, USA) and Statcel Ver.5 (OMS Publishing, Saitama, Japan). The significance of differences was set at $p<0.05$ for all analyses. We implemented rigorous quality control measures throughout the data collection and analysis process. Regular data quality checks were performed to ensure accuracy, with the independent verification of key variables by multiple investigators. Cases with missing data were excluded from the corresponding statistical analyses.

Results

Patient demographics and clinical characteristics. Among patients who underwent CGP during the study period, we identified 43 cases harboring gTP53v (Table I). The median age at diagnosis was 38 years (range=1-83 years), with a female predominance (28 females, 15 males). The cohort

Table I. *Baseline characteristics of patients harboring germline TP53 alterations.*

Cases Harboring Germline *TP53* Alterations (n=43)	
Age group (years; median 38)	
0-9	8
30-39	8
10-19	6
70-79	6
60-69	5
50-59	4
40-49	3
20-29	1
80-89	1
Smoking history	
No	24
Yes	15
Unknown	4
History of heavy alcohol consumption	
No	35
Yes	2
Unknown	6
Family history (Cancer)	
Yes	37
No	3
Unknown	3
Germline *TP53* alteration types	
Missense mutations	32
Frameshift variants	8
Nonsense mutations	3
Double missense mutations	1
Cancer Genomics Panel	
NCC Oncopanel System	36
GenMine™ TOP Cancer Panel	7
ECOG PS	
0	27
1	13
2	1
Metastatic sites	
Lung	8
Bone	6
Liver	6
Other sites	19
None	6
Primary site	
Soft tissue/Bone	10
Central Nervous System	7
Pancreas	5
Colorectal	3
Esophageal/Gastric	3
Ovary	3
Breast	2
Lung	2
Uterus	2
Others	4

ECOG PS: Eastern Cooperative Oncology Group Performance Status.

had a generally favorable performance status, with 27 patients (62.8%) exhibiting ECOG PS 0 and 13 (30.2%) exhibiting PS 1. A family history of cancer was documented in 37 patients (86.0%). Twenty-four patients were non-smokers, while 15 were current or ex-smokers. Significant alcohol consumption was documented in only two patients.

The spectrum of malignancies demonstrated notable heterogeneity, with 18 patients (41.9%) presenting with core LFS-associated tumors and 25 (58.1%) exhibiting non-core tumors. Soft tissue sarcomas represented the most frequent tumor type (n=8), followed by central nervous system tumors (n=7), pancreatic cancer (n=5), and colorectal, esophageal, and ovarian cancers (n=3 each). Metastatic disease was observed in 28 patients at initial presentation, with the lung (n=8), bone (n=6), and liver (n=6) being common sites of metastasis.

Genomic landscape and molecular characteristics. A comprehensive genomic analysis revealed diverse *TP53* variant types, encompassing 32 missense mutations, eight frameshift mutations, and three nonsense mutations. Median VAF was 0.47 (range=0.10-0.696). TMB markedly varied (median: 1.6 mutations/Mb, range=0-69.8). An analysis of co-occurring genomic alterations showed recurrent mutations in several cancer-associated genes, as visualized in the accompanying heatmap (Figure 1).

Among the cases analyzed, one harbored concurrent pathogenic variants in *MSH6* and *RB1* genes. A panel-specific analysis showed 36 cases detected through NOP and 7 through TOP, with similar variant detection rates between platforms.

Treatment outcomes and comparisons with wild-type TP53 cases. In the gTP53v cohort, 37 patients received first-line chemotherapy, achieving an objective response rate of 62% (CR=3, PR=11 among 25 evaluable patients). This response rate was significantly higher than that of *TP53* wild-type cases (Table II) in the database (n=6515, ORR 32%, p=0.02). The best overall response in the gTP53v cohort (Table III) was six complete responses and 14 partial responses, with six patients maintaining

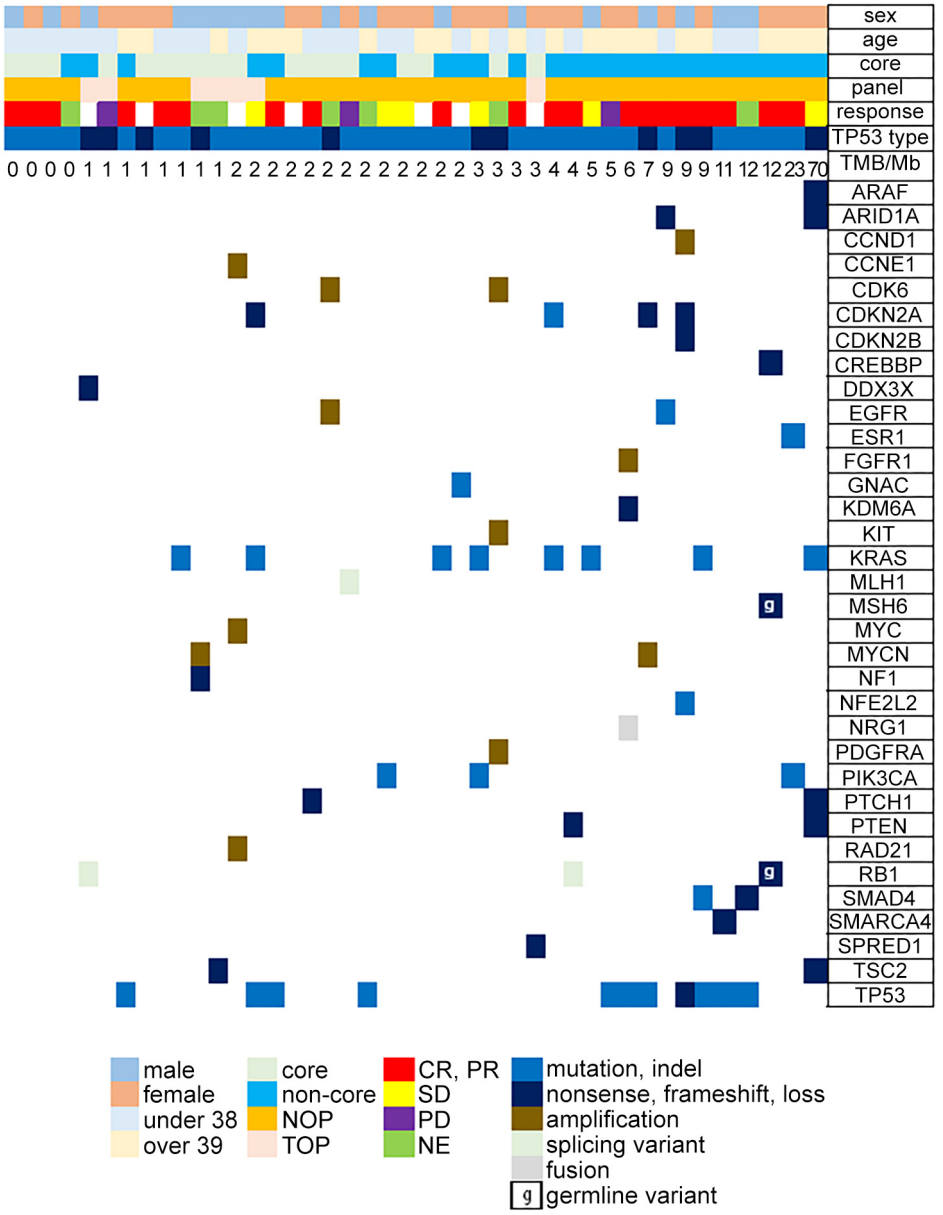

Figure 1. *Genomic profiling results and treatment responses in patients with germline TP53 alterations. NOP, NCC Oncopanel System; TOP, GenMine TOP Cancer Panel; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; NE, not evaluated; core, central nervous system, soft tissue, adrenal, bone.*

stable disease. The *TP53* wild-type cohort (n=6,515) had similar baseline characteristics in terms of age distribution, the performance status, and tumor types; however, detailed matching was not performed due to the retrospective nature of the analysis.

Case presentation. To illustrate the challenges associated with interpreting incidentally detected germline *TP53* variants, we present a case of a female patient diagnosed with synchronous colorectal tumors. The initial presentation suggested colorectal cancer; however, an

Table II. *Characteristics of all registered cases and patients with germline wild-type TP53.*

All cases (n=80,329)	
Primary site	
Colorectal	13.376
Pancreas	12.207
Bile duct	7.010
Breast	5.229
Esophagus/Stomach	4.937
Prostate	4.912
Lung	4.776
Ovary/Fallopian tube	4.507
Soft tissue	3.197
Uterus	2.775
Others	17.403
Sex	
Male	40.447
Female	39.877
Unknown	5
Cancer Genomics Panel	
FoundationOne CDx	57.085
FoundationOne Liquid CDx	12.184
NCC Oncopanel System	8.016
GenMine TOP Cancer Panel	1.853
Guardant360 CDx	1.191
Age group (years)	
70-79	23.252
60-69	22.630
50-59	16.846
40-49	8.661
80-89	3.528
0-29	2.840
20-29	949
10-19	849
0-9	718
90-	56

Wild-type germline *TP53* cases with treatment evaluation (n=6,515)			
Sex		Cancer Genomics Panel	
Male	3.352	NCC Oncopanel System	5.539
Female	3.163	GenMine TOP Cancer Panel	976

The study period for each genomic profiling test was as follows: NCC Oncopanel® System (June 1, 2019 to August 15, 2024), FoundationOne® CDx (June 1, 2019 to August 19, 2024), FoundationOne® Liquid CDx (August 1, 2021 to August 17, 2024), Guardant360® CDx (July 24, 2023 to August 16, 2024), and GenMineTM TOP Cancer Panel (August 1, 2023 to August 16, 2024).

Table III. *Genomic testing results and molecular tumor board recommendations for patients with germline TP53 alterations.*

Druggable variants: Expert Panel review	
No	14
Yes, treatment not administered	10
Yes, treatment administered	4*
Not registered	15
Tumor mutational burden (/Mbase)	
Low (<5)	31
Intermediate (5-10)	7
High (>10)	5
Germline pathogenic variant without *TP53*	
No	42
Yes	1
Treatment response (Best response)	
CR	6
PR	14
SD	6
PD	3
NE	7
Treatment response (First line)	
CR	3
PR	11
SD	6
PD	5
NE	12

*Pembrolizumab administered in 2 cases with a high tumor mutational burden; treatment details unavailable for the remaining 2 cases. CR, Complete response; PR, partial response; SD, stable disease; PD, progressive disease; NE, not evaluated.

immunohistochemical analysis revealed an unusual profile that was more consistent with a gynecological origin. However, a thorough gynecological evaluation showed no evidence of ovarian or fallopian tube malignancy. The patient lacked a significant family history of cancer and presented at an age atypical for classical LFS. CGP revealed a germline *TP53* variant with an allele frequency of 0.31, raising important considerations regarding the possibility of mosaicism, *de novo* mutations, or CHIP. This case exemplifies the complex nature of interpreting germline *TP53* variants detected through routine CGP, particularly in patients who do not meet the classical LFS criteria.

Discussion

The widespread implementation of CGP has led to an increase in the detection of gTP53v in patients who do not meet the classical LFS criteria (12, 13, 18, 19). Our analysis of 43 cases with gTP53v identified through comprehensive genomic profiling demonstrated that

these cases exhibit considerable heterogeneity in their clinical presentations and molecular characteristics, while also suggesting potentially favorable treatment outcomes in these patients. The clinical characteristics of our cohort challenge the traditional understanding of LFS. While some patients presented with classical LFS-associated tumors at young ages with strong family histories, others had notably atypical features. The median age of 39 years and the predominance of non-core LFS tumors (58.1%) in our cohort markedly differ from classical LFS descriptions (20). This heterogeneity raises important questions about the spectrum of TP53-associated cancer predisposition syndromes and their clinical interpretation.

The molecular landscape of these cases provides additional complexity to their interpretation. VAF in our cohort ranged between 0.10 and 0.696, with a median of 0.47. While frequencies of approximately 0.5 are consistent with heterozygous germline variants, lower frequencies raise important considerations about mosaicism or CHIP. As illustrated by our case presentation, the interpretation of germline *TP53* variants becomes particularly challenging in patients with atypical presentations and intermediate VAF. These cases necessitate the careful consideration of multiple possibilities including *de novo* mutations, mosaicism, and CHIP, with each carrying distinct implications for patient management.

Our observation of favorable treatment responses in this cohort is noteworthy. The objective response rate of 62% to first-line chemotherapy was significantly higher than that observed in *TP53* wild-type cases (p=0.02). This result appears counterintuitive given the traditional association of *TP53* mutations with a poor prognosis in various cancer types (21). Several hypotheses may explain this observation. The complete loss of *TP53* function may increase sensitivity to DNA-damaging agents due to compromised cell cycle checkpoints (22). Furthermore, the germline nature of these variants, as opposed to somatic mutations, may result in distinct biological behaviors (23). However, these hypotheses require further validation in larger cohorts and molecular studies.

The clinical implications of our results extend beyond the traditional framework of LFS management. The identification of germline *TP53* variants through CGP requires a nuanced approach to genetic counseling and clinical decision-making. In patients with typical LFS presentations, standard-of-care management approaches, including established comprehensive cancer surveillance protocols, need to be followed. However, the management of patients with atypical features, as observed in our case presentation, poses unique clinical challenges. The presence of mosaicism or CHIP introduces additional complexity to a risk assessment and surveillance planning, representing an emerging area in clinical practice.

The favorable treatment outcomes observed in our cohort suggest that the presence of gTP53v is not necessarily a negative prognostic factor. This contrasts with the established poor prognostic implications of somatic *TP53* mutations (21). However, concerns regarding therapy-related adverse events and secondary malignancies in *TP53* variant carriers remain valid (24). While our analysis did not reveal increases in severe adverse events, the short follow-up period limits definitive conclusions regarding long-term safety.

Recent evidence suggests relationships between the germline *TP53* status and responses to immune checkpoint inhibitors (16). Although our cohort included a limited number of cases treated with immunotherapy, this therapeutic approach warrants further investigation. The complex interplay between germline *TP53* variants, tumor immunogenicity, and treatment responses requires dedicated prospective studies.

Study limitations. The retrospective nature and small sample size limit definitive conclusions, particularly regarding treatment outcomes. Furthermore, the potential selection bias inherent in analyzing cases identified through CGP may not represent the full spectrum of germline *TP53* variant carriers. Moreover, the heterogeneity of tumor types and treatment regimens complicates direct comparisons of therapeutic outcomes. In addition, a longer follow-up is

needed to fully assess the implications of these results for patient care.

Future research directions need to include a prospective validation of treatment outcomes in larger cohorts, molecular studies to elucidate the mechanisms underlying potentially enhanced chemotherapy sensitivity, and the development of specific guidelines for managing patients with atypical presentations. The establishment of international registries and collaborative networks will be crucial for advancing our understanding of this complex patient population.

In conclusion, the present results highlight the evolving landscape of germline *TP53* variant interpretations in the era of CGP. The heterogeneity of clinical presentations and the potentially favorable treatment outcomes observed in our cohort challenge traditional paradigms and emphasize the need for individualized approaches to patient care. As CGP becomes increasingly routine, a sophisticated understanding of these complexities will be essential for optimal patient management.

Conclusion

CGP has revealed a broader spectrum of gTP53v carriers than previously recognized through classical LFS criteria, including cases with atypical presentations requiring careful interpretation of mosaicism, *de novo* mutations, and clonal hematopoiesis. While the present results suggest potentially favorable treatment outcomes in these patients, further prospective studies are needed to optimize the clinical management of this unique patient population.

Conflicts of Interest

This work was supported by the Yamagata University Center of Excellence [YU-COE(M)] for Genetic Research.

Authors' Contributions

Conceptualization: Y.S. and S.S.; Data curation: Y.S. and S.S.; Formal analysis: Y.S. and S.S.; Funding acquisition: M. Sato., M. Seino, M.K., and S.S.; Investigation: Y.S. and S.S.; Methodology: Y.S. and S.S.; Project administration: Y.S. and S.S.; Resources: M. Sato., M. Seino., M.K., and S.S.; Software: Y.S. and S.S.; Supervision: S.S.; Validation: Y.S. and S.S.; Visualization: S.S.; Roles/Writing - original draft: Y.S. and S.S.; Writing - review & editing: Y.S., Y.H., M. Sato, M. Seino, N.W., M.K., and S.S.

Acknowledgements

The Authors would like to express their gratitude to the staff of the Center for Cancer Genomics and Advanced Therapeutics (C-CAT) for their support in data acquisition and management. We are grateful to Professor George Delinasios, Managing Editor of Cancer Genomics and Proteomics, for the invitation to submit this manuscript. The Authors acknowledge Anthropic's Claude, Grammarly, and DeepL for their assistance in improving the readability and clarity of the manuscript in English.

Funding

This work was supported by the Yamagata University Center of Excellence (YU-COE(M)) for Genetic Research.

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