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ORIGINAL ARTICLE

Transmission ratio distortion of germline *TP53* variants in Li–Fraumeni syndrome families

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Abstract

Background: Li–Fraumeni syndrome (LFS) is a rare autosomal-dominant cancer-predisposition syndrome caused by germline pathogenic or likely pathogenic variants (P/LPVs) in the *TP53* gene. Classical autosomal-dominant inheritance predicts a 50% transmission rate of *TP53* P/LPV from each carrier parent to their offspring. However, clinical observations suggest higher-than-expected carrier proportions, indicating a potential transmission ratio distortion (TRD). The objective of this study was to investigate TRD in Israeli LFS families.

Methods: Data from families with an LFS diagnosis who were followed at Sheba Medical Center between 2015 and 2024 were reviewed. Families that had complete clinical data and offspring were included. Pedigree analyses classified carriers as confirmed, obligate, or probable. Observed carrier proportions were compared with the expected 50% rate using one-sample *t*-tests.

Results: Among 171 individuals from 20 families, 100 (58.5%) were identified as *TP53* P/LPV confirmed or obligatory carriers, significantly exceeding the expected 50% inheritance rate ($p = .027$). A second analysis, which included 11 probable carriers, resulted in a carrier proportion of 64.9% ($p < .001$). TRD was observed across all phenotypic groups. No significant differences in TRD were observed by sex or variant type.

Conclusions: This study revealed significant TRD in *TP53* P/LPV inheritance among Israeli LFS families. A potential mechanism involves the role of *TP53* in the cell cycle, in which reduced TP53 function may enhance embryonic cell proliferation, offering a survival or implantation advantage. TRD in LFS has implications for genetic counseling, reproductive decision making, and clinical management. These findings underscore the need for further research to validate TRD across diverse populations and elucidate the underlying mechanisms.

KEYWORDS
hereditary cancer syndromes, Li–Fraumeni syndrome, TP53, transmission ratio distortion

INTRODUCTION

Li–Fraumeni syndrome (LFS; Online Mendelian Inheritance in Man identifier 151623) is a rare autosomal-dominant (AD) cancer-predisposition syndrome primarily caused by germline pathogenic or likely pathogenic variants (P/LPVs) in the *TP53* gene.[1] The estimated prevalence of LFS is between 1 in 3000 and 1 in 10,000 individuals in the general population, with certain founder mutations identified among specific groups, including Brazilian, Ashkenazi Jewish, and Palestinian populations.[2–5] LFS is associated with a wide spectrum of malignancies, manifesting in both childhood and adulthood, including sarcomas, breast cancer, brain tumors, and adrenocortical carcinomas.[6–8]

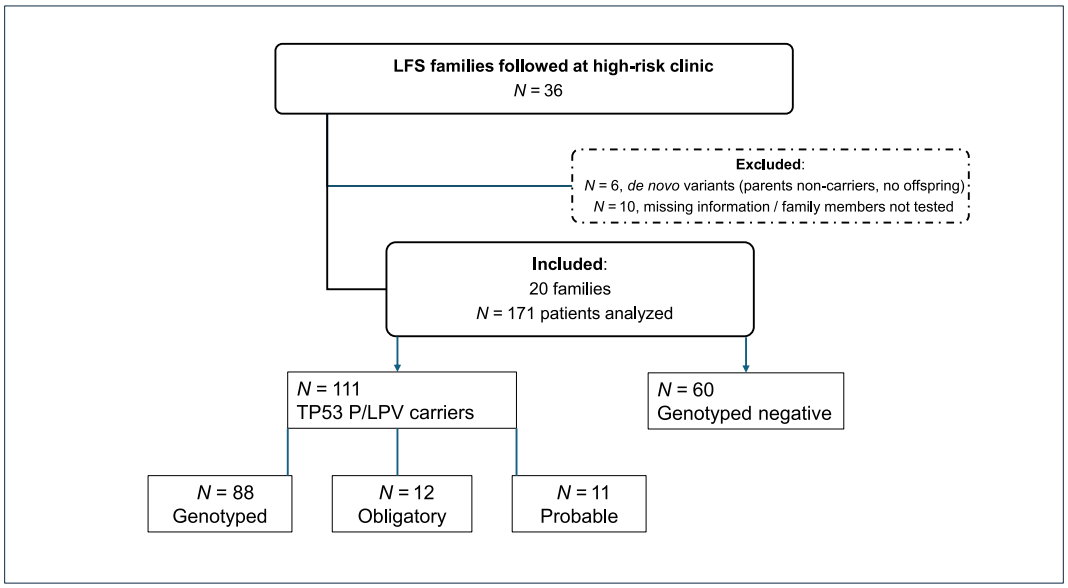
Although the syndrome is clinically heterogeneous, it is characterized by high penetrance, with females typically presenting with cancer at a younger age compared with males (33.7 and 45.0 years, respectively).[8] However, recent studies have suggested that earlier estimates of penetrance may have been inflated because of selection bias in early series, which primarily included families with severe clinical manifestations.[5,8–11] The increased use of next-generation sequencing (NGS) and multigene panels has identified *TP53* P/LPV carriers who do not meet the classic clinical criteria for LFS, leading to refined classifications, such as *attenuated* Li–Fraumeni syndrome (ALFS).[6,9,12] This phenotype encompasses *TP53* P/LPV carriers with a history of cancer who do not meet the traditional diagnostic criteria for LFS and typically have no malignancy onset before age 18 years.[9,12] Such insights underscore the variability in the presentation of LFS, necessitating nuanced approaches to diagnosis and management.

The classical AD inheritance pattern of LFS predicts a 50% risk of transmission to offspring from affected carriers. However, observations in Israeli LFS families suggest a higher-than-expected prevalence of *TP53* P/LPV carriers among offspring, raising questions about deviations from Mendelian inheritance. This phenomenon, known as *transmission ratio distortion* (TRD), has been described in other genetic disorders.[13–15] The proposed biologic mechanisms underlying TRD are thought to involve fertilization or early embryonic development.[13] Studies conducted in mice and humans suggest that variations in TP53 may influence gamete function as well as embryo implantation.[16–18]

The objective of this study was to investigate the presence of TRD in Israeli families affected by LFS, offering new insights into the inheritance dynamics of this syndrome and its implications for genetic counseling and risk assessment.

MATERIALS AND METHODS

For this study, we reviewed clinical and genetic data from families with at least two generations harboring a known *TP53* P/LPV who were followed at the High-Risk Clinic at Sheba Medical Center between 2015 and 2024. The clinic serves as a reference center; consequently, the majority of LFS carriers in Israel are monitored and



LFS, Li-Fraumeni Syndrome; P/LPV, pathogenic / likely-pathogenic

FIGURE 1 Participant flowchart: criteria and outcomes.

TABLE 1 Clinical and molecular characteristics of the cohort.

Family	Germline variant	Protein NM_000546.6	Exon	Functional classification—TA class[a]	DNE/LOF class[b]	Phenotype[c]	Total no. of individuals analyzed[d]	Total no. of carriers[e]	Carriers ratio[f]	No. of obligatory carriers	No. of probable carriers[g]	No. of healthy carriers[h]	No. of male carriers
1	c.97-2delA	NA	3-intron	No data	No data	LFS	21	13	0.62	1	3	6	8
2	c.659A>G	Y220C	6	Nonfunctional	DNE/LOF	Classic LFS	10	10	1.0	1	2	5	3
3	c.638G>A	R174Q	6	Nonfunctional	DNE/LOF	ALFS	5	3	0.6	1	0	1	0
4	c.365_366delTG	V122fs	4	No data	No data	LFS	5	2	0.4	0	0	0	0
5	c.733G>A	G245S	7	Nonfunctional	DNE/LOF	Classic LFS	5	5	1.0	1	1	2	2
6	c.1000G>C	G334R	10	Functional	Not DNE/not LOF	ALFS	4	2	0.5	0	0	1	1
7	c.818G>A	R273H	8	Nonfunctional	DNE/LOF	Classic LFS	14	12	0.86	0	1	6	9
8	c.1000G>C	G334R	10	Functional	Not DNE/not LOF	LFS	14	6	0.43	0	0	4	2
9	c.754_763del	L252fs	7	No data	No data	ALFS	2	1	0.5	0	0	1	0
10	c.473G>A	R158H	5	Nonfunctional	DNE/LOF	Classic LFS	19	10	0.53	3	1	7	5
11	c.97-2A>G	NA	3-intron	No data	No data	Classic LFS	9	7	0.78	2	2	2	5
12	c.799C>T	R267W	8	Nonfunctional	Unclassified	ALFS	13	9	0.69	1	0	7	5
13	c.1176_1179del4	*394Ilefs	11	No data	No data	Classic LFS	9	6	0.67	0	0	6	3
14	c.733G>A	G245S	7	Nonfunctional	DNE/LOF	ALFS	5	3	0.6	0	0	2	3
15	c.434T>A	L145Q	5	Nonfunctional	DNE/LOF	LFS	4	2	0.5	0	0	1	1
16	c.1000G>C	G334R	10	Functional	Not DNE/not LOF	ALFS	5	3	0.6	0	0	3	1
17	c.1009C>T	R337C	10	Nonfunctional	Not DNE/LOF	Classic LFS	5	3	0.6	0	1	1	2
18	c.393C>A	N131K	52	Partial function	Not DNE/not LOF	LFS	11	7	0.64	2	0	6	5

(Continues)

TABLE 1 (Continued)

Family	Germline variant	Protein NM_000546.6	Exon	Functional classification—TA class[a]	DNE/LOF class[b]	Phenotype[c]	Total no. of individuals analyzed[d]	Total no. of carriers[e]	Carriers ratio[f]	No. of obligatory carriers	No. of probable carriers[g]	No. of healthy carriers[h]	No. of male carriers
19	c.473G>A	R158H	5	Nonfunctional	DNE/LOF	ALFS	8	5	0.62	0	0	4	2
20	c.638G>A	R213Q	6	No data	No data	ALFS	3	2	0.67	0	0	2	2
Total							171	111	0.65	12	11	67	59

Abbreviations: ALFS, attenuated Li–Fraumeni syndrome; del, deletion; DNE, dominant-negative effect; LFS, Li-Fraumeni syndrome; LOF, loss of function; NA, nonapplicable; TA, transcriptional activity.

[a]As described by Kato et al.[20]

[b]As described by Giacomelli et al.[21]

[c]Phenotype classification as described in Materials and Methods.

[d]Includes the analysis as described in Materials and Methods (individuals who tested negative, confirmed carriers, obligatory carriers, and probable carriers).

[e]Includes confirmed, obligatory, and probable carriers.

[f]Total number of carriers (including confirmed, obligatory, and probable carriers) among the tested individuals.

[g]As defined in Materials and Methods.

[h]Cancer-free carriers at the time of mutation detection.

followed at this facility. Inclusion criteria required knowledge of the carrier status of all offspring of a specific individual along with the availability of demographic data and information on the presence or absence of malignancies. Data on malignancies were confirmed based on pathology reports for patients who were actively followed in the clinic and on pedigree information for individuals who died. Data collection was conducted under an Institutional Review Board-approved protocol.

We provided each *TP53* variants' functional data and their dominant-negative activity based on the TP53 Database.[19–21]

Pedigree analyses were conducted to assess the carrier status of offspring from confirmed carriers (genotyped individuals carrying *TP53* P/LPVs), obligatory carriers (individuals whose offspring and another family member [sibling, nephew, niece, etc.] tested positive for *TP53* P/LPVs), and probable carriers (individuals diagnosed with a malignancy before age 30 years who are a first-degree relative of a confirmed or obligatory carrier).

Based on clinical and genetic criteria, families were categorized into three distinct phenotypic groups: (1) classic LFS included *TP53* P/LPV carriers who met traditional clinical diagnostic criteria for LFS[6]; (2) Chompret criteria–based LFS[7,22]; and (3) ALFS, comprised of *TP53* P/LPV carriers with a history of cancer who did not meet LFS testing criteria and had no cancer diagnosis before age 18 years.[12] The observed proportion of *TP53* P/LPV carriers among offspring was compared with the expected 50% inheritance rate predicted for AD conditions. We performed a one-sample *t*-test to determine whether the observed carrier proportions deviated significantly from the Mendelian expectation. Statistical analysis was conducted using Stata/IC software version 16.0 (StataCorp).

RESULTS

In total, 171 individuals from 20 distinct families met the study criteria (Figure 1, Table 1).[20,21] Among them, 100 patients (58.5%) were identified as *TP53* P/LPV confirmed or obligatory carriers, significantly exceeding the expected 50% inheritance rate for AD conditions ($p = .027$). A second analysis, which included 11 probable carriers (Table 2), increased the carrier proportion to 64.9% ($p < .001$).

The average number of individuals tested per family was 8.5 (range, 3–21), whereas the average number of carriers per family was 5.5 (range, 2–13). Two families (10%) exhibited a carrier proportion below 50% (40% and 43%, both with a phenotype of LFS), and three families (15%) displayed the expected 50% inheritance rate (two with ALFS phenotype and one with LFS phenotype). Among identified carriers, 67 individuals (60.0%) were cancer-free at the time of genotyping, and 59 (53.1%) were males. We analyzed the inheritance ratio based on the parent's sex and observed no significant difference: the carrier rate was 61% when inherited from the mother and 66.6% when inherited from the father (p = not significant). Moreover, no clear correlation was identified in our cohort between the functional classification of the variants, their dominant-negative activity, and the severity of either the phenotype or the TRD.

TABLE 2 Probable carriers' characteristics and malignancies.

Probable carrier[a]	Sex	Malignancy	Age at diagnosis, years
1a	Female	Adrenocortical	4
1b	Male	Pancreaticobiliary	16
1c	Male	Liver	21
2a	Male	Brain	29
2b	Female	Breast	25
5a	Male	Unknown	11
7a	Male	Neuroblastoma	3
10a	Male	Sarcoma	6
11a	Male	Sarcoma	2
11b	Male	Medulloblastoma, leukemia	10,12
17	Male	Brain	10

[a]The number indicates the family to which the probable carrier belongs, and the letter is the individual identifier.

Pedigrees of the three families that exhibited significant TRD are presented in Figure 2.

DISCUSSION

This study identifies a significant TRD in *TP53* P/LPV inheritance in Israeli LFS families, with a higher-than-expected prevalence of carriers among offspring. To our knowledge, this phenomenon has not been previously reported in LFS. TRD has been described in several other hereditary syndromes, such as hereditary paraganglioma-pheochromocytoma, long-QT syndrome, and hereditary retinoblastoma.[14,15,23] Although this has not been explicitly described in the literature for LFS, exploring the pedigrees presented in previous publications might support our findings.[4,24]

One potential explanation for why this phenomenon has not been reported in other non-Israeli cohorts may be demographic differences. The average number of children per family in Israel is 2.9, which is the highest among Organization for Economic Cooperation and Development countries, compared with fewer than two children in most other Organization for Economic Cooperation and Development nations.[25] Larger family sizes increase the likelihood of detecting deviations from Mendelian inheritance ratios, making TRD more apparent in the Israeli population.

From a biologic perspective, the role of *TP53* in regulating the cell cycle and apoptosis may contribute to the observed TRD. Reduced levels of functional TP53 protein in mouse embryos have been associated with enhanced cell proliferation during early embryonic development, potentially conferring a selective advantage that improves embryonic survival or implantation success.[17] Building on this, it may be hypothesized that certain *TP53* variants influence mitochondrial function, promoting embryonic survival under hypoxia or pseudohypoxia conditions. In addition, the permissive state for mutation and recombination observed in *TP53* carriers might confer an advantage during mitosis, favoring skewed inheritance patterns that align with early theories of TRD.[13] Although these mechanisms remain speculative, they suggest potential pathways by which *TP53* variants might affect early embryogenesis and inheritance distortion, although elucidating the precise etiology of TRD in *TP53* mutation carriers is beyond the scope of the current study.

Genetic explanations, such as founder effects, appear less likely to explain our findings. Whereas rare founder mutations, such as the Brazilian p.R337H variant[3] and the Ashkenazi Jewish p.G334R variant,[4] have been documented, only three families in our cohort carried the Ashkenazi variant, exhibiting variable inheritance rates of 60%, 50%, and 40%. In addition, the absence of consanguinity across our cohort rules out inbreeding as a contributing factor.

Several limitations of this study should be acknowledged. The cohort included 20 families, limiting the generalizability of the findings. Nonetheless, the large number of carriers per family provides robust statistical power within the cohort. Referral bias toward families with severe phenotypes also is a consideration. However, the inclusion of ALFS families (eight families) and the proportion of cancer-free and male carriers reduce the likelihood of significant bias.

Phenotypic variability further complicates interpretation. Families with classical LFS consistently exhibited inheritance rates above 50%, whereas ALFS families mostly had rates above 50% (six of eight families) or exactly 50% (two families). In contrast, families classified under broader Chompret criteria exhibited more variability in inheritance patterns.

If validated in larger, ethnically diverse LFS cohorts, the observed TRD could have implications for genetic counseling and risk assessment. Traditional AD inheritance models assume a 50% transmission rate, which forms the basis of counseling for families. Skewed inheritance introduces uncertainty, particularly in reproductive decision making, in which the observed patterns may lead to overestimation or underestimation of risk.

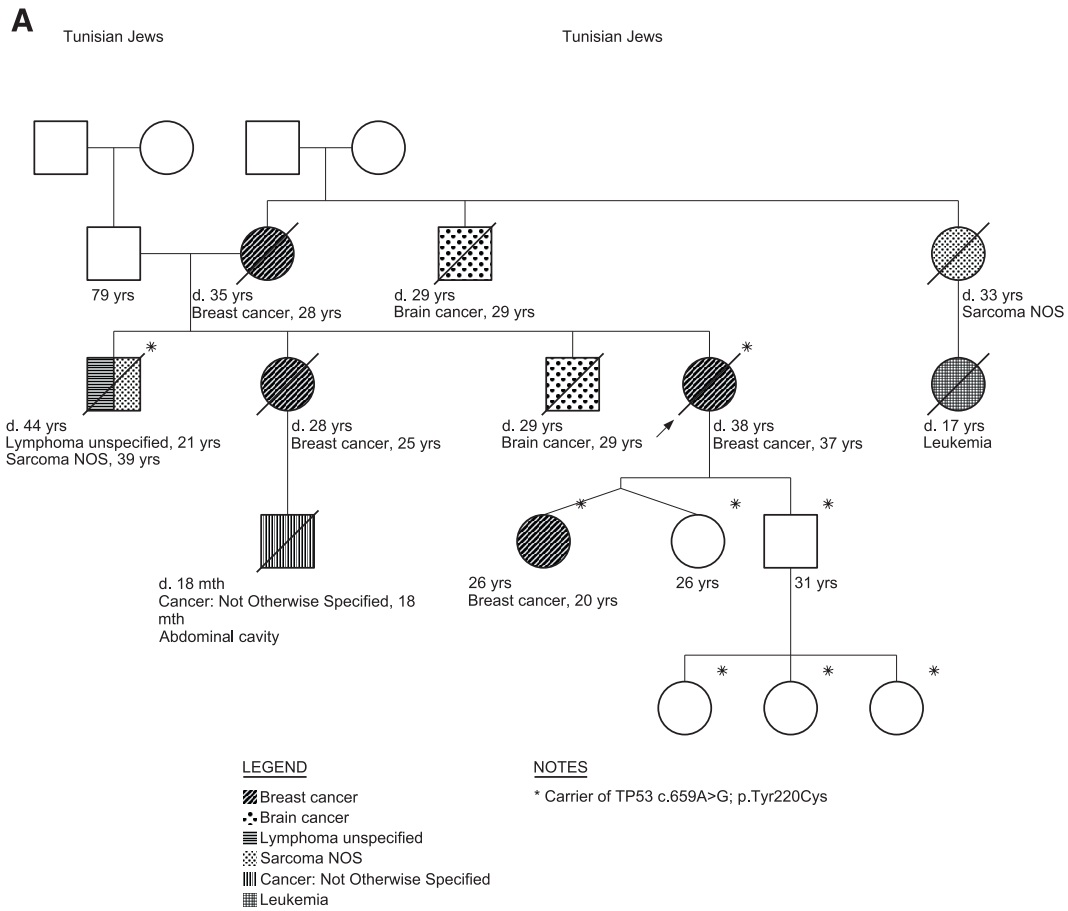


FIGURE 2 Pedigrees of three families exhibiting significant transmission ratio distortion. (A) Pedigree of family 2. (B) Pedigree of family 7. (C) Pedigree of family 12. CA-NOS indicates carcinoma, not otherwise specified; d, death; DCIS, ductal carcinoma in situ; mth, months; NOS, not otherwise specified; yrs, years.

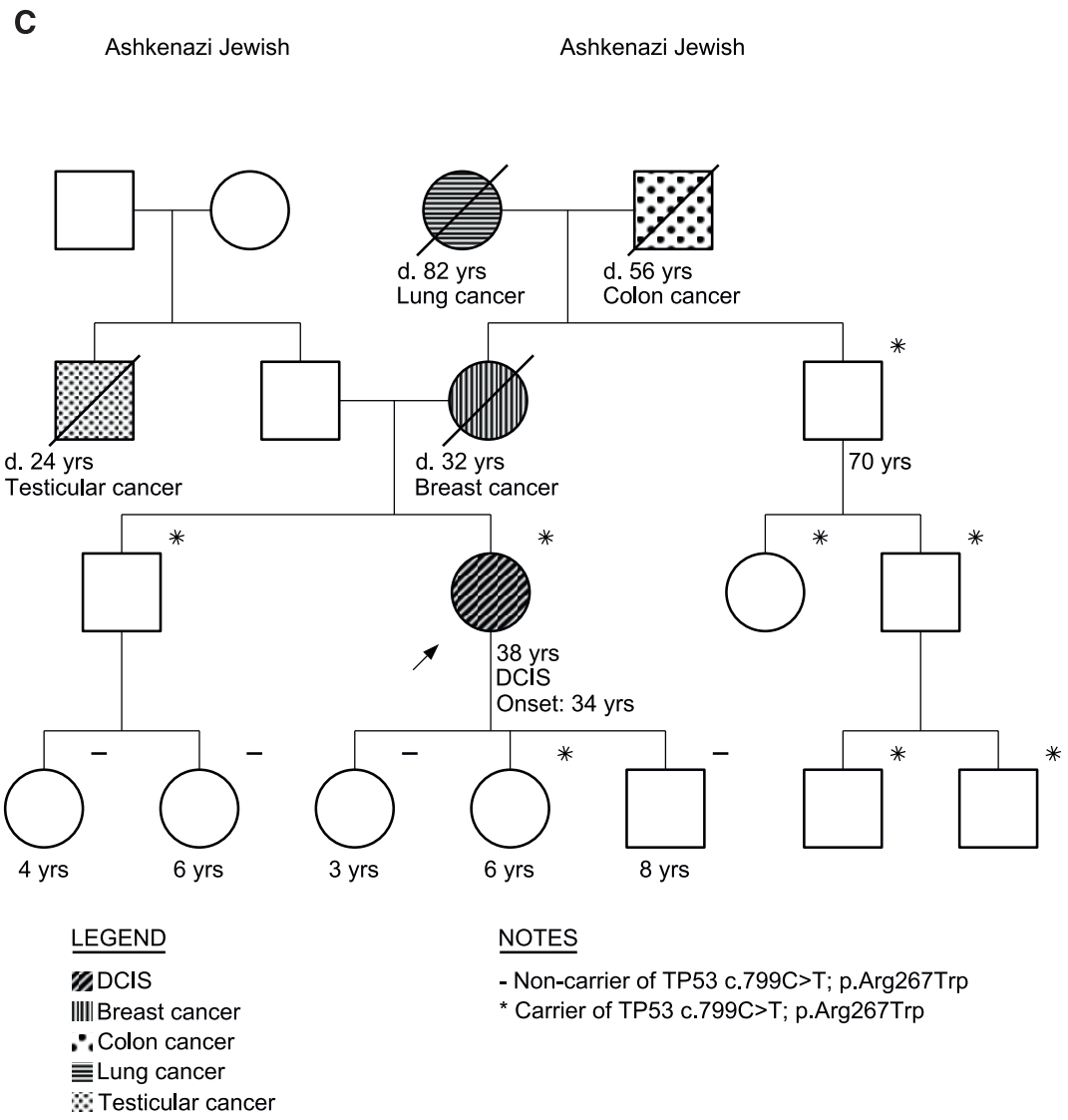


FIGURE 2 (Continued)

CONCLUSION

This study underscores a novel aspect of *TP53* inheritance in LFS, with potential implications for genetic counseling and clinical management. Our findings provide a foundation for future research into TRD in LFS and possibly in other genetic syndromes. Validation in larger, ethnically diverse cohorts and exploration of the underlying biologic mechanisms are critical next steps.

AUTHOR CONTRIBUTIONS

Naama Halpern: Conceptualization; investigation; writing—original draft; methodology; validation; visualization; writing—review and editing; project administration; data curation; supervision; and resources. **Iris Kventsel**: Conceptualization; investigation; writing—original draft; methodology; supervision; and writing—review and editing. **Gal Strauss**: Data curation; project administration; resources; writing—review and editing; and investigation. **Yehudit Peerless**: Writing—review and editing; investigation; formal analysis; data curation; supervision; and resources. **Ben Boursi**: Conceptualization; investigation; writing—original draft; methodology; formal analysis; supervision; and writing—review and editing. **Michal Yalon**: Investigation; writing—review and editing; and project administration. **Yael Goldberg**: Investigation; writing—original draft; methodology; writing—review and editing; and supervision. **Inbal Kedar**: Investigation; writing—review and editing; resources; and data curation. **Hagit Shani**: Writing—review and editing; investigation; and supervision. **Eitan Friedman**: Conceptualization; investigation; writing—original draft; writing—review and editing; methodology; formal analysis; and supervision. **Rinat Bernstein-Molho**: Conceptualization; investigation; writing—original draft; methodology; validation; visualization; writing—review and editing; formal analysis; data curation; and supervision.

CONFLICT OF INTEREST STATEMENT

Rinat Bernstein-Molho reports travel support from Gilead Sciences Inc. and Pfizer and support for other professional activities from AstraZeneca outside the submitted work. The remaining authors disclosed no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data sets generated during and/or analyzed during the current study are available from the corresponding author upon reasonable request.

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