Welcome to the UKCGG-National Cancer Genetics MDT meeting

October 15th 12.30-13.45

St George's University Hospitals NHS
NHS Foundation Trust

Li-Fraumeni syndrome to heritable *TP53*-related cancer (h*TP53*rc) syndrome

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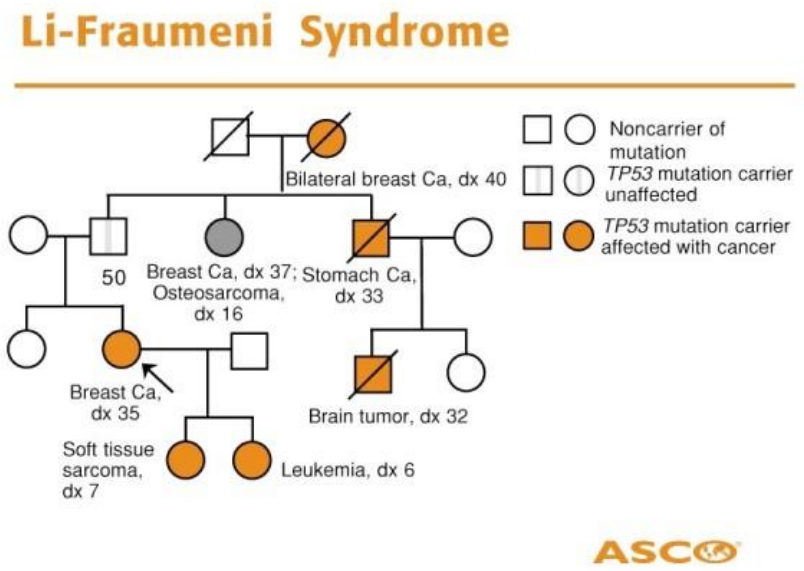
CanGene CanVar

Cancer Genetics Group

Overview

- Background
- Clinical phenotype
- Cancer Risk
- Low penetrance variants
- Pathogenicity/ variant classification
- Surveillance
- Clinical considerations

Li-Fraumeni syndrome?



Frederick Li and Joseph Fraumeni, 1991.

https://www.lfsassociation.org/founding-fathers/

Classic LFS Criteria

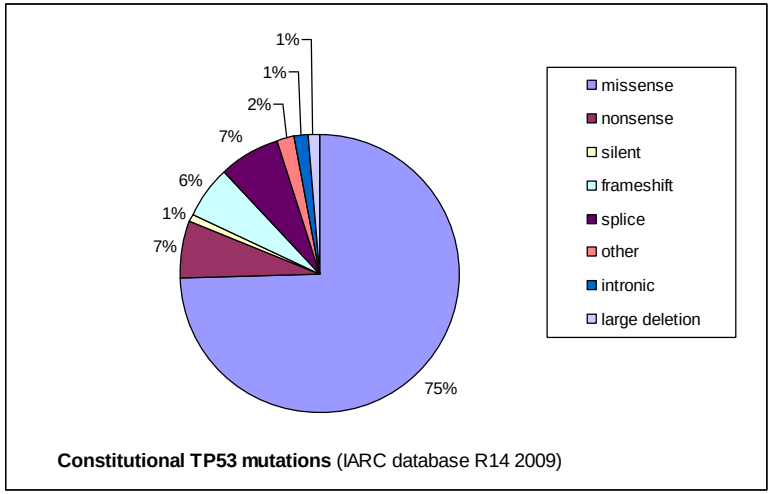
-Proband with sarcoma < 45 years

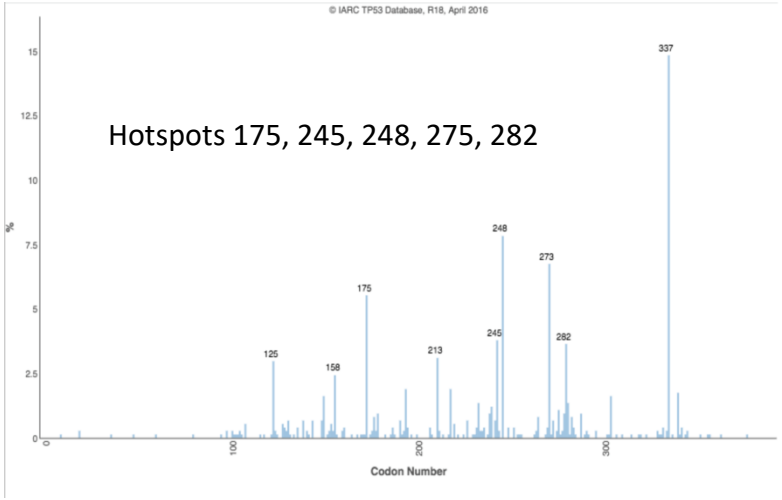
-First degree relative with cancer < 45 years

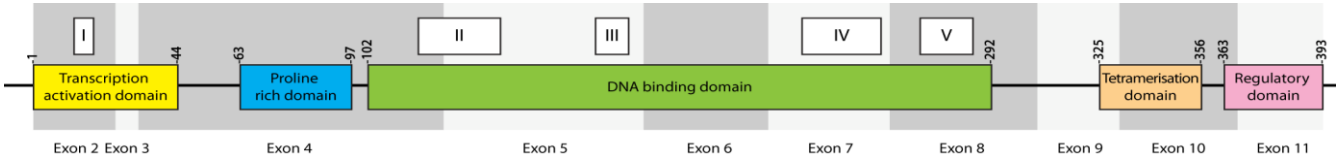
-First or second degree with cancer < 45 years or sarcoma any age

TP53 as cause of LFS

- *TP53* PV identified in five classic LFS families (Malkin, 1990)
- PV are identified in 50-75% of families fulfilling Classic LFS







Expanding clinical phenotype

Chompret Criteria 2015
FAMILIAL PRESENTATION **i) Proband with tumour belonging to LFS tumour spectrum (soft-tissue sarcoma, osteosarcoma, brain tumour, pre-menopausal breast cancer, adrenocortical carcinoma, leukaemia, lung bronchoalveolar cancer) < 46 years or any solid childhood cancer** **and** **one first-degree or second-degree relative with LFS tumour < 56years (excluding two cases of breast cancer).**
MULTIPLE TUMOURS **ii) Proband with multiple primary tumours (except multiple primary breast cancers), two of which belong to LFS tumour spectrum and the first occurred < 46 years.**
RARE TUMOURS **iii) Proband with adrenocortical carcinoma, choroid plexus tumour, rhabdomyosarcoma of anaplastic subtype at any age irrespective of family history.**
EARLY ONSET BREAST CANCER **iv) Breast cancer <31yrs**

Renaux-Petel et al (2017) Journal Medical Genetics; 328 patients with *TP53* PV, 40/328 de novo (12%)
Test directory: R216 (Li-Fraumeni syndrome) + R359 (childhood solid tumour)

Cancer risk for *TP53* carriers

- Limited studies –rarity and mortality
- Ascertainment basis
- **Lustbader et al. 1992 + Hwang et al. 2003**
  - 159 childhood sarcoma survivors
  - Penetrance 50% by 40 yrs, 90% by 70 yrs
  - Follow up of families
  - Penetrance 93% by 50 yrs for women, 68% by 50 years for men

VOLUME 33 · NUMBER 21 · JULY 20 2015

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Revisiting Li-Fraumeni Syndrome From *TP53* Mutation Carriers

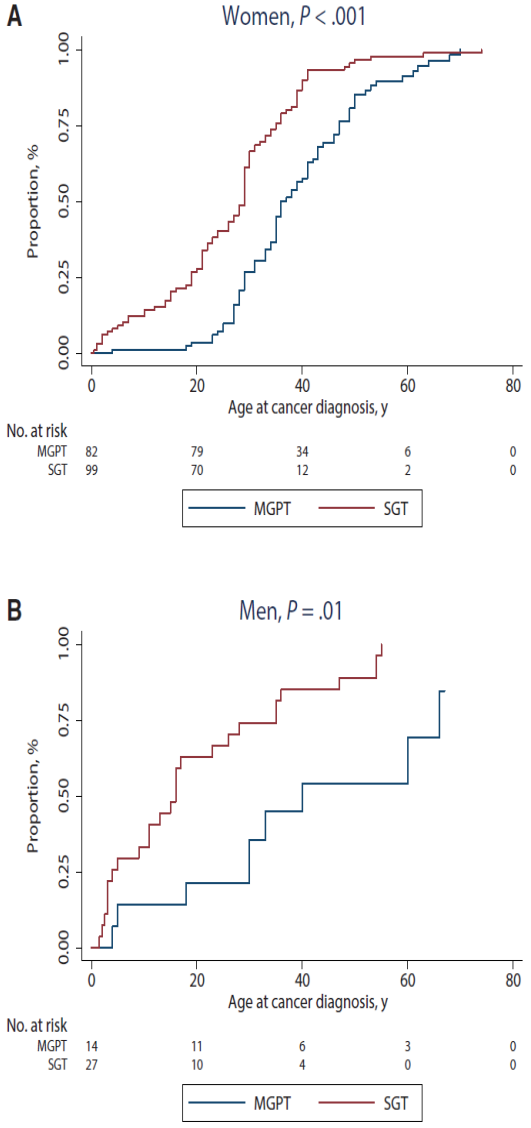
Gaëlle Bougeard, Mariette Renaux-Petel, Jean-Michel Flaman, Camille Charbonnier, Pierre Fermey, Muriel Belotti, Marion Gauthier-Villars, Dominique Stoppa-Lyonnet, Emilie Consolino, Laurence Brugières, Olivier Caron, Patrick R. Benusiglio, Brigitte Bressac-de Paillerets, Valérie Bonadona, Catherine Bonaïti-Pellié, Julie Tinat, Stéphanie Baert-Desurmont, and Thierry Frebourg

- Studied 415 carriers of *TP53* mutation of whom 322 developed cancer (total 552 tumours)
  - 22% developed cancer by age 5, 41% developed by age 18
  - Mean age mid 20s
  - 139/322 (43%) individuals with cancer developed a further primary cancer

- '**core cancers**' –breast cancer, sarcoma, ACC and brain tumours
- ***Childhood*** -osteosarcoma, adrenocortical tumours, brain tumours and soft tissue sarcomas
- ***Adults*** -breast cancer and soft tissue sarcoma

'Differences in TP53 Mutation Carrier Phenotypes Emerge from Panel-Based Testing' Rana et al (2018)

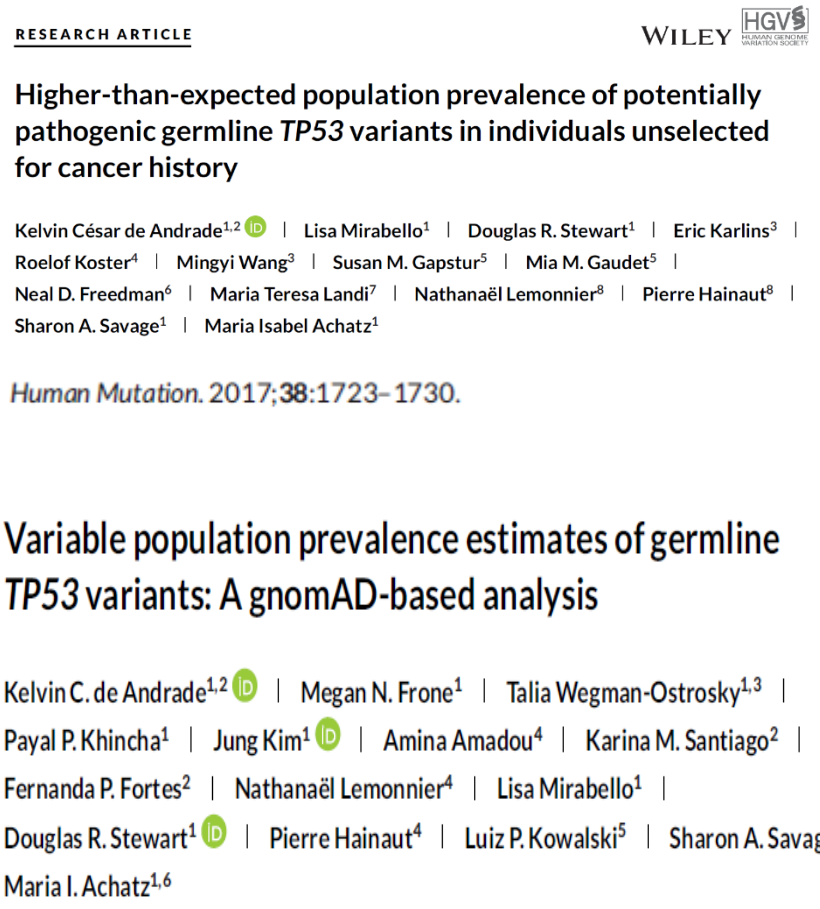
- Compared cancer risk in *TP53* carriers ascertained through single gene or multi-panel testing
- *TP53* PV were identified in 0.2% (102/40 885) vs 4.1% (132/ 3201) of individuals undergoing MGPT and SGT
- Those tested by panel were significantly older at age of cancer onset (36 v 28yrs – women and 40 v 15yrs -men)
- MGPT less likely to have a family history consistent with LFS compared to those who were ascertained through a traditional single gene test



Low penetrance variants

- R337H
- 1 in 300 individuals in South/South-Eastern Brazil
- Found in nearly all Brazilian children with ACC and CPC
- Families with R337H have a lower penetrance LI-Fraumeni-like phenotype (15-20% risk by 30 yrs v 50% risk)

Population studies – further evidence for lower penetrance variants?



RESEARCH ARTICLE

WILEY HGVS HUMAN GENOME VARIATION SOCIETY

Higher-than-expected population prevalence of potentially pathogenic germline *TP53* variants in individuals unselected for cancer history

Kelvin César de Andrade[1,2] | Lisa Mirabello[1] | Douglas R. Stewart[1] | Eric Karlins[3] | Roelof Koster[4] | Mingyi Wang[3] | Susan M. Gapstur[5] | Mia M. Gaudet[5] | Neal D. Freedman[6] | Maria Teresa Landi[7] | Nathanaël Lemonnier[8] | Pierre Hainaut[8] | Sharon A. Savage[1] | Maria Isabel Achatz[1]

Human Mutation. 2017;38:1723–1730.

Variable population prevalence estimates of germline *TP53* variants: A gnomAD-based analysis

Kelvin C. de Andrade[1,2] | Megan N. Frone[1] | Talia Wegman-Ostrosky[1,3] | Payal P. Khincha[1] | Jung Kim[1] | Amina Amadou[4] | Karina M. Santiago[2] | Fernanda P. Fortes[2] | Nathanaël Lemonnier[4] | Lisa Mirabello[1] | Douglas R. Stewart[1] | Pierre Hainaut[4] | Luiz P. Kowalski[5] | Sharon A. Savage[1] | Maria I. Achatz[1,6]

- *TP53* sequencing data from three pooled datasets (ExAC, FLOSSIES and series of cancer free individuals) n=63,983
- 10x greater prevalence than expected
- Follow up study using gnomAD (r2.0.2) n=138,632
- Prevalence 1 in 500 LP germline *TP53* variants by study criteria
- More stringent criteria 1 in 3,555–5,476 individuals

ClinGen *TP53* Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines Version 1

This version specified for the following genes: *TP53*

Expert Panel Page: https://www.clinicalgenome.org/affiliation/50013

- Stringent *TP53* variant classification guidelines
- PS3 - Use data from functional studies; Kato and Giacomelli
- PP3 -can use as moderate, specify in-sillico tools –Bayes Del and Align GVGD,
- PM2 used as supporting not moderate
- PS4 families –points system weighted for LFS phenotype
- Very stringent -are we missing causative lower variants?

- Proband meeting Chompret criteria = 0.5 point
- Proband meeting classic LFS criteria = 1 points

PS4 Evidence Strength	# of Points Required
PS4	4 or more points
PS4_Moderate	2-3 points
PS4_Supporting	1 point

PM2_Supporting **Absent from population databases**

- The variant must be absent from population databases. gnomAD is the prefe
  database at this time (http://gnomad.broadinstitute.org)

Clonal haematopoesis (CHIP)

- Clonal haematopoesis of indeterminate potential - form of mosaicism restricted to haematopoeitic cells without known haematological disease
- NGS can identify variants at lower VAF's, but VAF can be as high as 50%
- CHIP increases with age (estimates vary from ~9.5%-15% of those over 70yrs and 18.5-30% over 90yrs), but has been reported from age 30
- May also be increase in CHIP associated with exposure to cancer treatments

Two issues when undertaking hereditary gene panel analysis:

1) Mis- reporting of CHIP as "true *TP53* mosaicism"
2) Mis-reporting of CHIP variants with high VAF as classic germline TP53 variants

Recommendations:

- Consider further testing , particularly if personal/family history not suggestive.
- Need another tissue sample ; buccal or preferably, skin, normal tissue from biopsy/ surgery
- If previous DNA exists – can check to see if the newer sample has increased mutation load – indicative of expansion event
- Family studies – demonstrating presence in offspring of "mosaic" proband excludes CHIP – requires high level counselling based on the familial cancer risk and firm knowledge as to what a negative result means in the familial context (also potential predictive nature if positive)

Familial Cancer
https://doi.org/10.1007/s10689-020-00207-z

EDITORIAL

New surveillance guidelines for Li-Fraumeni and hereditary *TP53* related cancer syndrome: implications for germline *TP53* testing in breast cancer

D. Gareth Evans[1] · Emma R. Woodward[1]

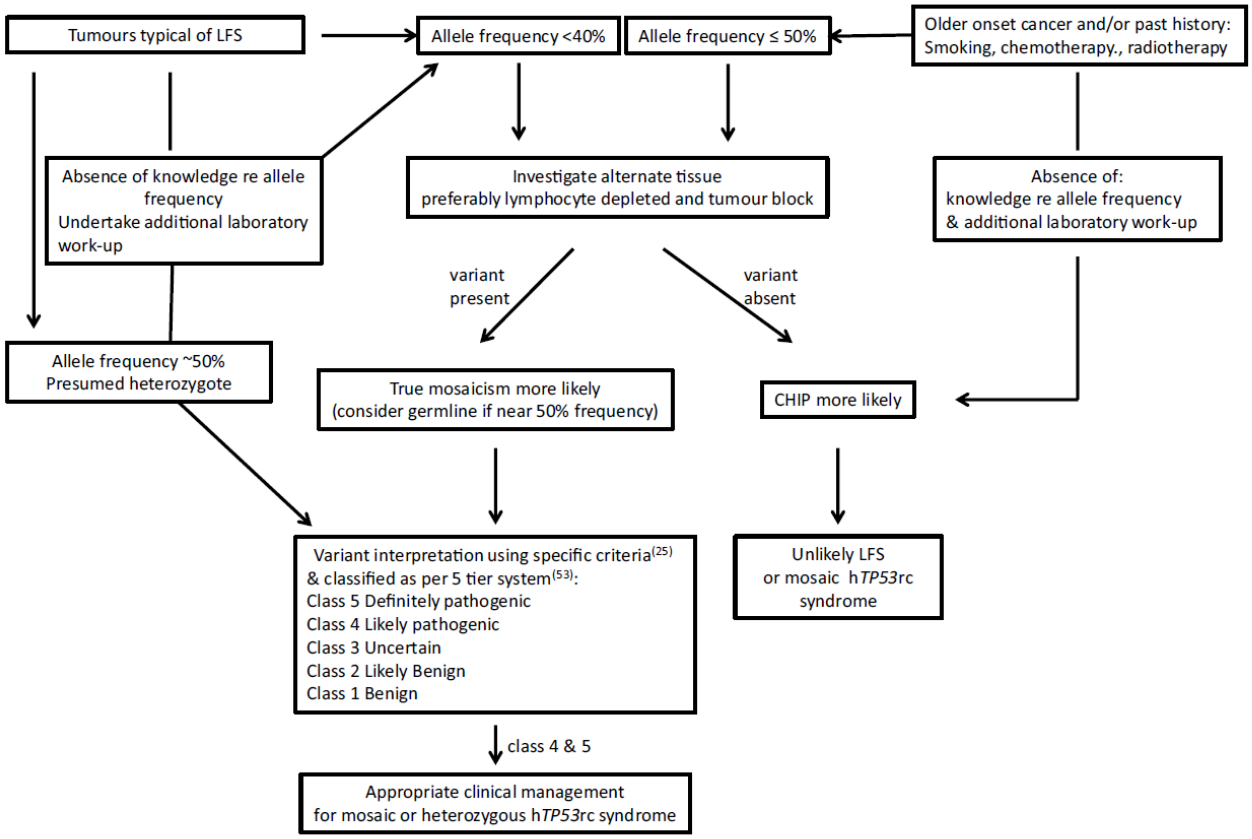


Fig. 1 Flow-chart to aid in distinguishing mosaicism from CHIP and subsequent variant interpretation

Surveillance

Villani et al. 2011 and 2016 (Toronto Protocol)

Lancet Oncol

Panel 1*: Surveillance strategy for individuals with germline *TP53* mutations

Children

Adrenocortical carcinoma
- Ultrasound of abdomen and pelvis every 3–4 months
- Complete urinalysis every 3–4 months
- Blood tests every 4 months: β-human chorionic gonadotropin, alpha-fetoprotein, 17-OH-progesterone, testosterone, dehydroepiandrosterone sulfate, androstenedione

Brain tumour
- Annual brain MRI

Soft tissue and bone sarcoma
- Annual rapid total body MRI

Leukaemia or lymphoma
- Blood test every 4 months: complete blood count, erythrocyte sedimentation rate, lactate dehydrogenase

Adults

Breast cancer
- Monthly breast self-examination starting at age 18 years
- Clinical breast examination twice a year, starting at age 20–25 years, or 5–10 years before the earliest known breast cancer in the family
- Annual mammography and breast MRI screening starting at age 20–25 years, or at earliest age of onset in the family
- Consider risk-reducing bilateral mastectomy

Brain tumour
- Annual brain MRI

Soft tissue and bone sarcoma
- Annual rapid total body MRI
- Ultrasound of abdomen and pelvis every 6 months

Colon cancer
- Colonoscopy every 2 years, beginning at age 40 years, or 10 years before the earliest known colon cancer in the family

Melanoma
- Annual dermatological examination

Leukaemia or lymphoma
- Complete blood count every 4 months
- Erythrocyte sedimentation rate, lactate dehydrogenase every 4 months

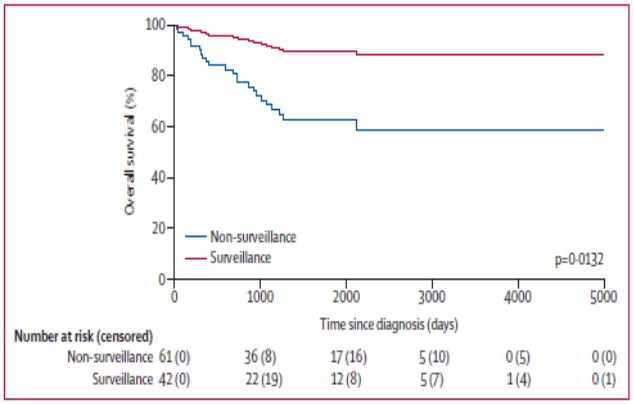


***Figure 1*: Overall survival in the surveillance and non-surveillance groups**
Number at risk refers to the number of tumours, not individuals.

JAMA Oncology | Original Investigation

Baseline Surveillance in Li-Fraumeni Syndrome Using Whole-Body Magnetic Resonance Imaging
A Meta-analysis

Mandy L. Ballinger, PhD; Ana Best, PhD; Phuong L. Mai, MD; Payal P. Khincha, MD; Jennifer T. Loud, RN; June A. Peters, MS; Maria Isabel Achatz, MD; Rubens Chojniak, MD; Alexandre Balieiro da Costa, MD; Karina Miranda Santiago, MS; Judy Garber, MD, MPH; Allison F. O'Neill, MD; Rosalind A. Eeles, PhD; D. Gareth Evans, MD, FCRP; Eveline Bleiker, PhD; Gabe S. Sonke, MD; Marielle Ruijs, MD; Claudette Loo, MD; Joshua Schiffman, MD; Anne Naumer, MS; Wendy Kohlmann, MS; Louise C. Strong, MD; Jasmina Bojadzieva, MS; David Malkin, MD; Surya P. Rednam, MD; Elena M. Stoffel, MD, MPH; Erika Koeppe, MPH; Jeffrey N. Weitzel, MD; Thomas P. Slavin, MD; Bita Nehoray, MS; Mark Robson, MD; Michael Walsh, MD; Lorenzo Manelli, MD; Anita Villani, MD; David M. Thomas, FRACP; Sharon A. Savage, MD

CCR PEDIATRIC ONCOLOGY SERIES

Cancer Screening Recommendations for Individuals with Li-Fraumeni Syndrome

Christian P. Kratz[1], Maria Isabel Achatz[2], Laurence Brugières[3], Thierry Frebourg[4], Judy E. Garber[5], Mary-Louise C. Greer[6], Jordan R. Hansford[7,8], Katherine A. Janeway[9], Wendy K. Kohlmann[10], Rose McGee[11], Charles G. Mullighan[12], Kenan Onel[13], Kristian W. Pajtler[14,15], Stefan M. Pfister[14,15], Sharon A. Savage[2], Joshua D. Schiffman[16], Katherine A. Schneider[5], Louise C. Strong[17], D. Gareth R. Evans[18], Jonathan D. Wasserman[19], Anita Villani[20], and David Malkin[20]

Cancer Genetics Group

UK Guidelines

The George Pantziarka TP53 Trust

Helping families with Li Fraumeni Syndrome and related conditions

UKCGG Consensus Group guidelines for the management of patients with constitutional *TP53* pathogenic variants

Helen Hanson [1], Angela F Brady,[2] Gillian Crawford,[3] Rosalind A Eeles,[4,5] Sarah Gibson,[6] Mette Jorgensen,[7] Louise Izatt,[8] Aslam Sohaib,[9] Marc Tischkowitz,[10] D Gareth Evans [11], Consensus Group Members

Table 1 Agreed surveillance recommendations for *TP53* carriers

Tumour	Screening recommendation
ACC	Abdominal USS 3–4 monthly birth:18 years Biochemistry (17 OH-progesterone, total testosterone, DHEAS, androstenedione) should only be performed where there is an unsatisfactory USS.
Breast cancer (women only)	Annual dedicated MRI from age 20–70 years Consider risk-reducing mastectomy from age 20 years
Brain tumour	Annual dedicated brain MRI from birth (first MRI with contrast)*
Sarcoma	Annual WB-MRI† from birth*
Haematological	Routine FBC are not indicated due to lack of evidence that these detect haematological malignancy at an early stage.
Colon	Colonoscopy only indicated when family history of colorectal cancer or polyposis‡; consider investigation for, possibly coinherited, causes if strong family history of colorectal cancer or polyposis The presence of microcytic anaemia should prompt investigation for a gastrointestinal tract malignancy (routine FBC not advised).
Gastric	Recommend *Helicobacter pylori* testing and eradication if required Endoscopy not indicated due to lack of evidence
Skin	Annual dermatology review from 18 years (general practitioner or dermatology) General advice on use of high protection factor sunscreen and covering up in sun
Physical examination	Full physical examination 3–4 monthly in children (including blood pressure, anthropometric measurements, signs of virilisation and neurological exam) Routine physical examination not recommended in adults; advise detailed discussion of 'red flag' symptoms and low threshold for fast track referral of persistent or unusual symptoms
Other	Recommend detailed discussion of red flag symptoms in both children and adults and provide information on relevant resources. Discuss importance of making positive lifestyle choices (eg, not smoking, eating a healthy diet, limiting alcohol consumption, sun protection, keeping physically active and providing appropriate resources).

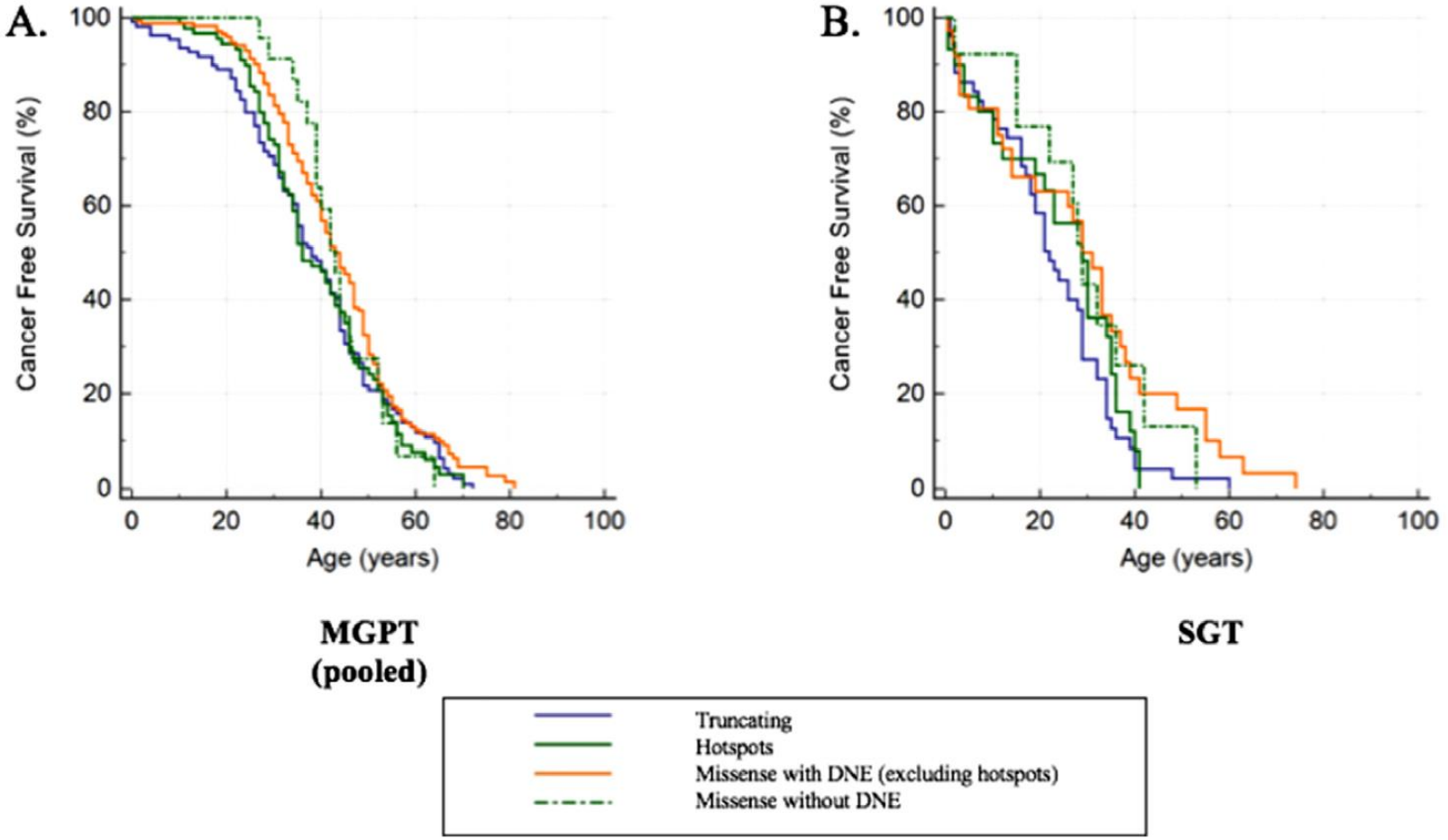


Fig. 2. Results for the cancer-free survival analysis using data from *TP53* carriers identified by multigene panel testing (MGPT) at two different diagnostic laboratories (A) and by single-gene testing (SGT) (B). DNE = Dominant-negative effect.

427 *TP53* carriers who had undergone MGPT, 154 *TP53* carriers SGT. Truncating/ hotspot variants might present with LFS cancers younger, but currently insufficient evidence to consider location and/or molecular effect of pathogenic variants in clinical management

WBMRI funding

- Guidelines discussed with NHSE, put forward by CRG in 2018/ early 2019
- CRG dissolved
- Specialised commissioning unable to support separate service
- Ongoing discussion with NHSE HSS
- Paper presented to RDAG July 2020
- Possible outcome - supportive of signposting patients to trusts that can undertake scanning, reimburse them for this activity and establish specific reporting arrangements building on existing infrastructure and arrangements

Remaining clinical dilemmas

- 30 yrs since *TP53* discovered…
- Is our current understanding of cancer risk for *TP53* been influenced by high degree of selection for genetic testing?
- What is really the true cancer risk and cancer spectrum for a *TP53* carrier?
- Have we got variant classification right? Are there lower penetrance variants? Should they be managed differently?
- Creation of patient anxiety by identifying *TP53* in families with no significant history?

Final thoughts

- Treat pathogenic *TP53* variants found in atypical clinical settings with caution!
- Need detailed counselling of risk with *TP53* families, move away from diagnosis of LFS
- European guidelines suggest renaming LFS to “heritable *TP53* related cancer hTP53rc”
- Suggest reviewing variants with new ClinGen criteria before recommending surveillance
- Agreed same surveillance approach for all families with *TP53* PV–may change in future
- As for most cancer predisposition genes, further comprehensive, collaborative approaches are required to fully understand prevalence, penetrance and pathogencity

Next meeting
December 17th 12.30-13.45
Mixed cases
MS Teams invite to follow

Feedback, suggestions or cases to

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