Welcome to the UKCGG-National Cancer Genetics MDT meeting

October 15th 12.30-13.45
Li-Fraumeni syndrome to heritable $TP53$-related cancer (h$TP53$rc) syndrome

Dr Helen Hanson
Consultant in Cancer Genetics
St Georges Hospital, London
Overview

- Background
- Clinical phenotype
- Cancer Risk
- Low penetrance variants
- Pathogenicity/ variant classification
- Surveillance
- Clinical considerations
Li-Fraumeni syndrome?

**Li-Fraumeni Syndrome**

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

Classic LFS Criteria

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

Constitutional TP53 mutations (IARC database R14 2009)

Hotspots 175, 245, 248, 275, 282
Expanding clinical phenotype

<table>
<thead>
<tr>
<th>Chompret Criteria 2015</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>FAMILIAL PRESENTATION</strong></td>
</tr>
<tr>
<td>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) &lt; 46 years or any solid childhood cancer and one first-degree or second-degree relative with LFS tumour &lt; 56 years (excluding two cases of breast cancer).</td>
</tr>
<tr>
<td><strong>MULTIPLE TUMOURS</strong></td>
</tr>
<tr>
<td>ii) Proband with multiple primary tumours (except multiple primary breast cancers), two of which belong to LFS tumour spectrum and the first occurred &lt; 46 years.</td>
</tr>
<tr>
<td><strong>RARE TUMOURS</strong></td>
</tr>
<tr>
<td>iii) Proband with adrenocortical carcinoma, choroid plexus tumour, rhabdomyosarcoma of anaplastic subtype at any age irrespective of family history.</td>
</tr>
<tr>
<td><strong>EARLY ONSET BREAST CANCER</strong></td>
</tr>
<tr>
<td>iv) Breast cancer &lt; 31 yrs</td>
</tr>
</tbody>
</table>

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
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
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?

- 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
Stringent TP53 variant classification guidelines

PS3 - Use data from functional studies; Kato and Giacomelli

PP3 - can use as moderate, specify in-silico 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?

<table>
<thead>
<tr>
<th>PS4 Evidence Strength</th>
<th># of Points Required</th>
</tr>
</thead>
<tbody>
<tr>
<td>PS4</td>
<td>4 or more points</td>
</tr>
<tr>
<td>PS4_Moderate</td>
<td>2-3 points</td>
</tr>
<tr>
<td>PS4_Supporting</td>
<td>1 point</td>
</tr>
</tbody>
</table>

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

PM2_Supporting Absent from population databases

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

- Clonal haematopoiesis of indeterminate potential - form of mosaicism restricted to haematopoietic 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)
New surveillance guidelines for Li-Fraumeni and hereditary TP53 related cancer syndrome: implications for germline TP53 testing in breast cancer

D. Gareth Evans¹ · Emma R. Woodward¹

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

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; Payyal P. Khincha, MD; Jennifer T. Loud, RN; June A. Peters, MS; Maria Isabel Achatz, MD; Rubens Chopeia, MD; Alexandre Balloiro da Costa, MD; Karina Miranda Santiago, MS; Judy Garber, MD, MPH; Allison F. O’Neill, MD; Rosalind A. Ekeles, PhD; D. Gareth Evans, MD, FCRP; Eveline Bleiker, PhD; Gabe S. Sonkie, MD; Marielle Ruijs, MD; Claudette Loo, MD; Joshua Schifman, MD; Anne Raumer, MS; Wendy Kohlmann, MS; Louise C. Strong, MD; Jasmina Bogdajeva, MS; David Malkin, MD; Sonya P. Redman, MD; Elena M. Stoffel, MD, MPH; Enija Kooppe, 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

CCP PEDIATRIC ONCOLOGY SERIES

Cancer Screening Recommendations for Individuals with Li-Fraumeni Syndrome
UKCGG Consensus Group guidelines for the management of patients with constitutional *TP53* pathogenic variants

Helen Hanson, Angela F Brady, Gillian Crawford, Rosalind A Eeles, Sarah Gibson, Mette Jorgensen, Louise Izatt, Aslam Sohaib, Marc Tischkowitz, D Gareth Evans, Consensus Group Members

**Table 1** Agreed surveillance recommendations for *TP53* carriers

<table>
<thead>
<tr>
<th>Tumour</th>
<th>Screening recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACC</td>
<td>Abdominal USS 3–4 monthly birth:18 years</td>
</tr>
<tr>
<td></td>
<td>Biochemistry (17 OH-progesterone, total testosterone, DHEAS, androstenedione) should only be performed where there is an unsatisfactory USS.</td>
</tr>
<tr>
<td>Breast cancer</td>
<td>Annual dedicated MRI from age 20–70 years</td>
</tr>
<tr>
<td>(women only)</td>
<td>Consider risk-reducing mastectomy from age 20 years</td>
</tr>
<tr>
<td>Brain tumour</td>
<td>Annual dedicated brain MRI from birth (first MRI with contrast)</td>
</tr>
<tr>
<td>Sarcoma</td>
<td>Annual WB-MRI† from birth*</td>
</tr>
<tr>
<td>Haematological</td>
<td>Routine FBC are not indicated due to lack of evidence that these detect haematological malignancy at an early stage.</td>
</tr>
<tr>
<td>Colon</td>
<td>Colonoscopy only indicated when family history of colorectal cancer or polyposis†; consider investigation for, possibly co-inherited, 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).</td>
</tr>
<tr>
<td>Gastric</td>
<td>Recommend <em>Helicobacter pylori</em> testing and eradication if required</td>
</tr>
<tr>
<td></td>
<td>Endoscopy not indicated due to lack of evidence</td>
</tr>
<tr>
<td>Skin</td>
<td>Annual dermatology review from 18 years (general practitioner or dermatology)</td>
</tr>
<tr>
<td></td>
<td>General advice on use of high protection factor sunscreen and covering up in sun</td>
</tr>
<tr>
<td>Physical examination</td>
<td>Full physical examination 3–4 monthly in children (including blood pressure, anthropometric measurements, signs of virilisation and neurological exam)</td>
</tr>
<tr>
<td></td>
<td>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</td>
</tr>
<tr>
<td>Other</td>
<td>Recommend detailed discussion of red flag symptoms in both children and adults and provide information on relevant resources. Discourage importance of making positive lifestyle choices (e.g., not smoking, eating a healthy diet, limiting alcohol consumption, sun protection, keeping physically active and providing appropriate resources).</td>
</tr>
</tbody>
</table>
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
helen.hanson6@nhs.net
helen.hanson@stgeorges.nhs.uk