LI-FRAUMENI SYNDROME: UPDATE ON MOLECULAR BASIS AND CLINICAL MANAGEMENT

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and French LFS working group
1. A proband aged **under 45 years** with a **sarcoma** and
2. A **first degree relative under 45 years** with **any cancer** and
3. Another **first- or second-degree relative** in the same lineage with **any cancer under 45 years** or a **sarcoma** at **any age**

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**I. THE HISTORICAL LFS DEFINITION**

*Li and Fraumeni, Annals of Internal Medicine 1969*  
*Li et al., Cancer Research 1988*

641 children with **rhabdomyosarcoma**
II. THE MOLECULAR LFS DEFINITION

TP53

Malkin et al., Science 1990; Strivastava et al., Science 1990
TP53: GARDIAN OF THE GENOME AND ANTIONCOGENE

I. G1 cell cycle arrest
   - DNA repair
   - BRCA1
   - PCNA
   - GADD45
   - p21

II. DNA damage
   - Accumulation
   - Stabilisation
   - Activation
   - Cyclin
   - CDK
   - E2F
   - Rb
   - 14-3-3σ

   - Cytoplasmic sequestration
   - Cyclin B
   - Cdc2
   - p53

III. Oncogene activation
   - MDM2
   - Proteasomal degradation of p53
   - Apoptosis
   - KILLER
   - PIG3
   - BAX
   - Induction of target genes
   - TP53: GARDIAN OF THE GENOME AND ANTIONCOGENE
   - Cyclin B
   - Cdc2

II. G2 cell cycle arrest
   - Oncogene activation
   - Mitosis
   - p53

III. TP53:
   - DNA damage
   - MDM2
   - Proteasomal degradation of p53
   - Apoptosis
   - KILLER
   - PIG3
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   - Induction of target genes
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II. G2 cell cycle arrest
   - Oncogene activation
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   - p53

II. G2 cell cycle arrest
   - Oncogene activation
   - Mitosis
   - p53
I. A proband with a LFS tumour
(soft-tissue sarcoma, osteosarcoma, brain tumour, adrenocortical carcinoma, breast cancer, leukaemia, bronchoalveolar lung cancer)
under 46 years
and
One first- or second-degree relative with a LFS tumour (except breast cancer if the proband has a breast cancer) under 56 years or with multiple tumours

II. A proband with multiple primary tumours (except multiple primary breast cancers), two of which belonging to the narrow LFS spectrum, the first being developed before 46 years

III. A proband with adrenocortical carcinoma or choroid plexus cancer irrespective of the family history

Mutation detection rate = 29%
(Sensitivity = 82%)
(Specificity = 58%)
Astrocytoma 25

Breast cancer 25

p. Arg273Cys

Medulloblastoma 2
IV. AGE OF FIRST TUMOUR ONSET IN MALES AND FEMALES

Cumulative nb of patients

Age of first tumour onset

252 affected TP53 mutation carriers

French LFS consortium, 2012
### IV. MEAN AGE OF TUMOUR ONSET

<table>
<thead>
<tr>
<th>Tumour Type</th>
<th>Number of Tumours</th>
<th>Mean Age (years)</th>
<th>Age Range (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast cancer</td>
<td>143</td>
<td>34</td>
<td>20-69</td>
</tr>
<tr>
<td>Soft-tissue sarcoma</td>
<td>75</td>
<td>31</td>
<td>&lt;1-70</td>
</tr>
<tr>
<td>Osteo/chondrosarcoma</td>
<td>47</td>
<td>20</td>
<td>6-55</td>
</tr>
<tr>
<td>Brain tumour</td>
<td>36</td>
<td>15</td>
<td>&lt;1-67</td>
</tr>
<tr>
<td>Adrenocortical carcinoma</td>
<td>31</td>
<td>6</td>
<td>&lt;1-32</td>
</tr>
</tbody>
</table>

252 affected TP53 mutation carriers

French LFS consortium, 2012
V. FREQUENCY OF MULTIPLE PRIMARY TUMOURS IN LFS

- Sarcoma 2
- Adrenocortical carcinoma 6
- Osteosarcoma 14
- Left breast cancer 22
- Right breast cancer 25

p.Pro152Leu
V. FREQUENCY OF MULTIPLE PRIMARY TUMOURS IN LFS

252 affected TP53 mutation carriers

French LFS consortium, 2012
VI. RISK OF RADIOThERAPY IN LFS PATIENTS

Avoid radiations if possible
VII. LATE ONSET LFS ASSOCIATED TO TP53 NULL MUTATION

c.991>T, p.Gln331X, exon 9
VII. LATE ONSET LFS ASSOCIATED TO TP53 NULL MUTATION

Uterus leiomyosarcoma 44
Renal cell adenocarcinoma 68
Colon leiomyosarcoma 69

Leiomyosarcoma 32

Liposarcoma 57

c.375G>A, splicing mutation
VII. IMPACT OF THE TYPE OF *TP53* ALTERATION ON THE AGE OF FIRST TUMOUR ONSET

<table>
<thead>
<tr>
<th>Type of mutation</th>
<th>Nb of mutation carriers (n=252)</th>
<th>Median age of first tumour onset (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Missense</td>
<td>157</td>
<td>25</td>
</tr>
<tr>
<td>Null mutations</td>
<td>95</td>
<td>29</td>
</tr>
</tbody>
</table>
A NEW P53 FUNCTIONAL ASSAY TO ASSESS THE IMPACT OF GERMLINE HETEROZYGOUS TP53 MUTATIONS

EBV-immortalized lymphocytes
+/- Doxorubicine 8h at 37°C

41 000 probes - 19 596 RNA
Comparative transcriptomic analysis
+/- Doxorubicin

Number of probes (fold induction >2)

<table>
<thead>
<tr>
<th></th>
<th>Number of Probes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control 1</td>
<td>392</td>
</tr>
<tr>
<td>Control 2</td>
<td>390</td>
</tr>
<tr>
<td>Control 3</td>
<td>363</td>
</tr>
<tr>
<td>p.T231Pfs*16</td>
<td>344</td>
</tr>
<tr>
<td>Pro-ex1 del</td>
<td>335</td>
</tr>
<tr>
<td>Comp. del</td>
<td>234</td>
</tr>
<tr>
<td>p.R175H</td>
<td>119</td>
</tr>
<tr>
<td>p.R248W</td>
<td>89</td>
</tr>
<tr>
<td>p.R273H</td>
<td>79</td>
</tr>
</tbody>
</table>

Null mutations

Missense mutations

Drastic effect of the missense mutations on the p53 mediated response to DNA damage
Functional analysis in yeast of mutant TP53 cDNA:
Loss of transcriptional activity

LFS : Loss of p53 function

But the drastic effect of missense mutations on the response to DNA damage, probably resulting from the trans-dominant activity of the mutant over the wild-type, explains their predominance in LFS patients.

VIII. MOLECULAR BASIS OF THE LI-FRAUMENI SYNDROME IN 2012

QMPSF :
Detection of genomic deletions
IX. MEDICAL BENEFITS OF TP53 TESTING IN LFS

- Avoid a delay to the diagnosis of another tumour
- Annual clinical review by an informed clinician
- Systematic MRI screening only for breast from 20 years on an annual basis
- Avoid radiations (sarcoma and breast cancer) if possible
- Prenatal diagnosis
X. EVALUATION OF THE CLINICAL MANAGEMENT OF LFS

The Lifscreen Project (2012-2014)
Olivier Caron - Institut Gustave Roussy
11 French centers

100 TP53 mutation carriers
Follow-up during 2 years

Arm A
Every year
✓ Clinical exam
✓ Brain MRI
✓ Abdominal ultrasound
✓ Breast MRI and ultrasound in women since 20 years

Arm B
Every year
✓ Clinical exam
✓ Brain MRI
✓ Abdominal ultrasound
✓ Breast MRI and ultrasound in women since 20 years
✓ + Total body MRI

Efficiency and acceptance
PRENATAL DIAGNOSIS IN LFS

- Young age of onset of the LFS tumours
- Prognosis of some tumours
- Impossibility to ensure an efficient early detection
- Risk for mutation carriers to develop multiple primary tumours

Pre-implantation testing
# XI. *TP53* TESTING IN CHILDREN

<table>
<thead>
<tr>
<th></th>
<th>Adults</th>
<th>Children</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Positive testing</strong></td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>in affected subjects</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Presymptomatic testing</strong></td>
<td>Yes</td>
<td>Must be very carefully considered</td>
</tr>
<tr>
<td>unaffected relatives</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Note: Presymptomatic testing in unaffected relatives must be conducted very carefully.*
CASE 1: BRCA OR TP53?

Breast cancers 53 and 62

Head and neck tumour

Breast cancer 76

Testis cancer 59

Rhabdomyosarcoma 9

Breast cancer 47

Breast cancers 46 and 48

12y  8y  4y

BRCA OR TP53?
CASE 1: BRCA OR TP53?

Breast cancers 53 and 62

Head and neck tumour

Breast cancer 76

Testis cancer 59

Complete Mastectomy
No radiotherapy

TP53: c.286_288del, p.ser98del, exon 4

Incomplete penetrance

TP53: c.286_288del, p.ser98del, exon 4

12y  8y  4y
CASE 2: TP53 PRE-SYMPTOMATIC TESTING?

Médulloblastoma 14
Wt/His 179 Tyr

TP53: p.His179Tyr
CASE 2: TP53 PRE-SYMPTOMATIC TESTING?

Incomplete penetrance

Médulloblastoma 14
Wt /His 179 Tyr

Fibrosarcoma 1
Wt /His 179 Tyr

19 years
3 years
CASE 2: *TP53* PRE-SYMPTOMATIC TESTING?

**Médulloblastoma 14**
- **Wt /His 179 Tyr**

**Fibrosarcoma 1**
- **Wt /His 179 Tyr**

19 years

3 years

**Wt /His 179 Tyr**
CASE 3: TP53 PRE-SYMPTOMATIC TESTING?

Breast cancer 33

Brain tumour 39

Choroid plexus tumour 9

pArg282Trp

Medulloblast 14
Angiosarcoma 22
Breast cancer 22

12y 7y 5y 2y
CASE 3: TP53 PRE-SYMPTOMATIC TESTING?

Breast cancer 33

Brain tumour 39

Choroid plexus tumour 9

Medulloblast. 14
Angiosarcoma 22
Breast cancer 22

Wt/Arg282Trp

Breast cancer 32

Breast cancer 44

?
CASE 3: TP53 PRE-SYMPTOMATIC TESTING?

Breast cancer 33

Brain tumour 39

Breast cancer 32

Choroid plexus tumour 9

Medulloblast. 14
Angiosarcoma 22

Breast cancer 22

Osteosarcoma 12*
Wt/Arg282Trp

? ? ?
CASE 3: TP53 PRE-SYMPTOMATIC TESTING?

Breast cancer 33

Brain tumour 39

Breast cancer 32

Choroid plexus tumour 9

Medulloblast. 14
Angiosarcoma 22
Breast cancer 22

Osteosarcoma 12
Wt/Arg282Trp
CASE 3: TP53 PRE-SYMPTOMATIC TESTING?
CASE 4: TP53 PRE-SYMPTOMATIC TESTING?

Adrenocortical tumour
3 years
Wt /Mt

TP53: c783-1G>A

Loss of weight
Inflammatory syndrome

14 years
CASE 4: TP53 PRE-SYMPTOMATIC TESTING?

TP53: c783-1G>A

Adrenocortical tumour
3 years
Wt /Mt

Loss of weight
14 years
Inflammatory syndrome

Wt /Mt

Incomplete penetrance

*
CASE 4: TP53 PRE-SYMPTOMATIC TESTING?

Adrenocortical tumour
3 years
Wt/Mt

Loss of weight
Inflammatory syndrome
14 years
Wt/Mt*

Wt/Mt
CASE 4: TP53 PRE-SYMPTOMATIC TESTING?

Adrenocortical tumour

3 years

Wt / Mt

Loss of weight

14 years

Inflammatory syndrome

Wt / Mt

Total body MRI

TP53 PRE-SYMPTOMATIC TESTING?
CASE 4: *TP53* PRE-SYMPTOMATIC TESTING?

Angiomatoid fibrous histiocytoma

Surgical resection
TP53 TESTING IN LFS

- Annual clinical review by an informed clinician
- Systematic annual MRI screening for breast from 20 years
- Presymptomatic testing and evaluation of MRI-based follow-up
- Psychological supports
- Avoid radiations (sarcoma and breast cancer)
- Prenatal diagnosis