Low rate of TP53 germline mutations in breast cancer/sarcoma families not fulfilling classical criteria for Li-Fraumeni syndrome

D G R Evans, J M Birch, M Thorneycroft, G McGown, F Lalloo, J M Varley

MATERIAL AND METHODS

Over the last 20 years our group has ascertained families with a history of early onset tumours in addition to sarcoma. In the last 10 years we have also received samples from families ascertained at other genetics and oncology centres in the UK. We have retrospectively analysed the outcome of TP53 germline mutation testing in families with a single proven sarcoma where that person or a first degree relative developed breast cancer by the age of 50 in the general population in the western world. In contrast to sarcoma and ACC, there are other more common inherited syndromes to account for familial aggregation of breast cancer.

Key points

- Mutations in the TP53 gene account for the great majority (circa 70%) of families fulfilling classical criteria for Li-Fraumeni syndrome and a significant portion of families falling just short of these criteria.
- We have undertaken a study to determine the contribution of TP53 germline mutations to families containing breast cancer and a single proven sarcoma, which fall short of classical criteria for LFS.
- Blood samples from a sarcoma patient or a first degree relative with breast cancer were analysed for mutations in TP53 by direct sequencing of all exons, the promoter, and 3′ untranslated region. Only one mutation was identified in 21 (5%) eligible families compared to 23/30 (77%) of families fulfilling classical Li-Fraumeni syndrome criteria.
- These results suggest that breast cancer on its own (in addition to a sarcoma) may not be a particularly strong marker for TP53 mutations and that this should be taken into account in genetic counselling. The addition of even early onset breast cancer to a sarcoma may not be sufficient to justify TP53 mutation testing.

Table 1 Diagnostic criteria for Li-Fraumeni syndrome and Li-Fraumeni-like syndrome

<table>
<thead>
<tr>
<th>Li-Fraumeni syndrome</th>
<th>Li-Fraumeni like syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proband &lt;45 years with a sarcoma</td>
<td>Proband with any childhood tumour, or sarcoma, brain tumour, or adrenocortical tumour &lt;45 years</td>
</tr>
<tr>
<td>Plus 1st degree relative &lt;45 years with any cancer</td>
<td>Plus 1st or 2nd degree relative in the same lineage with typical LFS tumour at any age or any cancer &lt;45 years</td>
</tr>
<tr>
<td>Plus additional 1st or 2nd degree relative in the same lineage aged &lt;45 years with any cancer or a sarcoma at any age</td>
<td>Plus another 1st or 2nd degree relative in the same lineage with any cancer &lt;60 years</td>
</tr>
</tbody>
</table>

RESULTS

Only one mutation was identified in the 21 breast/sarcoma families studied. This family (family 2252, table 2) only failed to meet LFS criteria as the sarcoma was diagnosed four years after the qualifying date (49 rather than <45 years). There is also a suggestion of a further sarcoma in the mother of the tested subject who died from an intra-abdominal malignancy aged 23 years that has not been possible to confirm.

B

breast cancer and sarcoma are key components of Li-Fraumeni syndrome (LFS). Sarcoma, particularly childhood osteosarcoma or rhabdomyosarcoma in addition to childhood adrenocortical carcinoma (ACC), is the strongest predictor of the presence of a TP53 mutation. However, while up to 80% of unselected series of ACC have TP53 germline mutations, only 3-10% of unselected sarcomas have been found to have such mutations. At least half of these would have been predicted on the basis of family history and many of the rest could have arisen de novo. While breast cancer is common in LFS and the penetrance of TP53 germline mutations in women for breast cancer may be as high as 56% by the age of 45 years (80% of female cancer incidence aged 23 years that has not been possible to confirm. The key component of TP53 mutations is often raised fairly strongly in addition to a sarcoma) may not be a particularly strong marker for TP53 mutations and that this should be taken into account in genetic counselling. The addition of even early onset breast cancer to a sarcoma may not be sufficient to justify TP53 mutation testing.

Table 2  Cancers in eligible families

<table>
<thead>
<tr>
<th>Family</th>
<th>LFL</th>
<th>Breast cancer</th>
<th>Other sarcoma (age)</th>
<th>Other LFS spectrum cancers</th>
<th>Other cancers</th>
</tr>
</thead>
<tbody>
<tr>
<td>729</td>
<td>Yes</td>
<td>42*, 52</td>
<td>Femur 9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2063</td>
<td>Yes</td>
<td>47/49*, 58</td>
<td>Femur 13</td>
<td></td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>No</td>
<td>51†</td>
<td>Femur 15</td>
<td>Ovary 59†</td>
<td>Cervix 35†</td>
</tr>
<tr>
<td>B</td>
<td>No</td>
<td>42†, 32</td>
<td>48</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>No</td>
<td>34†</td>
<td>Abdomen 66†</td>
<td></td>
<td>BCC 67†</td>
</tr>
<tr>
<td>D</td>
<td>No</td>
<td>55*</td>
<td>Fibrosarcoma 67</td>
<td></td>
<td>Colon 42, RCC 39</td>
</tr>
<tr>
<td>E</td>
<td>No</td>
<td>55†</td>
<td>Femur 18</td>
<td></td>
<td>Melanoma 31†</td>
</tr>
<tr>
<td>F</td>
<td>No</td>
<td>35†</td>
<td>Radius 40†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>G</td>
<td>No</td>
<td>29*, 40†</td>
<td>Abdomen 45†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>H</td>
<td>No</td>
<td>31*</td>
<td>Uterus 62</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>No</td>
<td>38†</td>
<td>Femur 18†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>J</td>
<td>No</td>
<td>42*, 62</td>
<td>Humerus 2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>K</td>
<td>No</td>
<td>45/54†, 73</td>
<td>Synovial 27</td>
<td></td>
<td>Oesophagus 57†</td>
</tr>
<tr>
<td>L</td>
<td>No</td>
<td>30, 44†</td>
<td>Pelvis 55†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>M</td>
<td>No</td>
<td>39†</td>
<td>Fibrosarcoma 33†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>No</td>
<td>37†</td>
<td>Femur 15†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2252‡</td>
<td>Yes</td>
<td>25, 26/40†</td>
<td>Leimyosarcoma butock 49†</td>
<td>Glialblastoma 15, PNET 7</td>
<td>Abdominal malignancy 23</td>
</tr>
<tr>
<td>338</td>
<td>Yes</td>
<td>36/44†</td>
<td>Chondrosarcoma 35†</td>
<td>PNET 7</td>
<td></td>
</tr>
<tr>
<td>80</td>
<td>Yes</td>
<td>35*, 29, 60</td>
<td>Liposarcoma 30*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>328</td>
<td>Yes</td>
<td>45</td>
<td>16*</td>
<td>Glioma 56</td>
<td></td>
</tr>
<tr>
<td>1799</td>
<td>Yes</td>
<td>37†</td>
<td>Soft tissue 37†</td>
<td></td>
<td>Stomach 48, 42</td>
</tr>
</tbody>
</table>

Cancers are those in the sarcoma patient and breast cancer patient and in their first degree relatives. *Indicates subject tested, †Individual multiple primaries in a single person in a family (eg family 2252 contains a female with bilateral breast cancer aged 26 and 40 and a leiomyosarcoma aged 49 years); 45/50 indicates bilateral disease. ‡Indicates only family with proven TP53 germline mutation. Numbered families are those classified as LFL, which are also previously published.

This as the second LFS gene, it now appears that the mutation is a modifier of risk for genes other than BRCA1 and BRCA2 rather than a high risk allele in its own right.

Although breast cancer is a very common feature in LFS and LFL families, it is probable that it is the presence of other characteristic tumours in addition to sarcoma that are the key predictors. It is of note that family 2252 (the only mutation positive LFL family) is the only one to contain at least two typical LFS tumours (PNET 10 years, glioblastoma 15 years) and that only two other families, 338 and 328, contained a single typical tumour with only one of these being childhood at onset. Three groups have now collectively analysed more than 800 unselected breast cancer patients for TP53 germline mutations. Among these cases, germline TP53 mutations were detected in only two (0.25%) so such mutations are clearly rare among apparently sporadic breast cancer.

We have now extended our survey of classical LFS families to 30 and detected mutations in 23 (77%). In LFL families, 10/25 (40%) had mutations. Excluding the seven LFL families in the current survey, mutations were detected in 9/18 (50%) compared to only 1/7 (14%) in the breast sarcoma set.

DISCUSSION

We have been rather surprised by the low rate of TP53 mutations detected in families fulfilling our breast/sarcoma criteria. It is possible that we may not always have been able to test the most appropriate person (the sarcoma case) and that testing their affected mother may have failed to show a mutation that had occurred after conception (mosaic) but nonetheless was passed down to the affected offspring. However, this mechanism could only account for families A, L, and 338 as all other tested subjects in multi-case families were in the second or third generation of affected subjects (unless the first generation was a phenocopy). Nonetheless the four isolated breast/sarcoma double primaries (families A, E, L, and M) could also have been mosaic for a TP53 mutation. It is unlikely that mosaicism would account for a significant miss rate in our study, as even in NF2 the rate of mosaicism in de novo cases is no higher than 20%. It is also possible that mutations in these families could have been missed owing to the sensitivity of the mutation techniques. However, given that mutations were detected in 77% of classical families, it is unlikely that more than one mutation would have escaped detection. It is possible that there may be another gene that accounts for Li-Fraumeni syndrome, which is more common in families with a predominance of breast cancer. However, recent evidence has shown that the CHK2 gene may not be a real Li-Fraumeni syndrome gene. While an original report of one of our families with a CHK2 mutation appeared to herald
woman developed breast cancer at 38 years following an osteosarcoma at 18 years. However, Malkin et al.\textsuperscript{11} reported TP53 germline mutations in only four of 59 children and young adults with second primary cancers and, indeed, this was later corrected to three out of the 59 (5%).

Chompret et al.\textsuperscript{12} have attempted to devise criteria to assess the sensitivity and positive predictive value of TP53 germline mutation testing. Including their previous study of childhood tumours, they added a series of 116 breast cancers aged less than 36 years at diagnosis out of a series of 275 eligible cases. They identified three mutations in this series with two occurring in the context of classical LFS. One of these patients appeared to represent an isolated case of breast cancer at 31 years, but no information on testing of relatives was mentioned and this may have been de novo. Using the stringent criteria in this analysis, we have identified 5/21 families with a incident breast cancer <36 years in which a first or second degree relative developed an un questioned LFS tumour (sarcoma, brain, breast cancer, ACC). Both the cases identified from the 116 incident breast cancer series had mutations if breast cancer was excluded as the cancer in the relative, but 0/21 had mutations if breast cancer was taken as the only relevant cancer. In contrast, we have identified only 1/5 (20%) of those fulfilling the stringent criteria in Chompret et al.\textsuperscript{12} (all our families fulfilled the breast cancer exclusion criteria as sarcoma was the main ascertainment criterion for our study). If we include the breast-sarcoma double primary cases (the sarcoma counted as a relative), this drops to 1/8 (12.5%) where the breast cancer was <36 years. Given that both the families in the French breast cancer series fulfilled LFS criteria (LFL criteria excluding breast cancer as the main other tumour), this drops to 1/8 (12.5%).

In summary, our report has pointed to a low detection rate for TP53 mutations in breast/sarcoma families not conforming to LFS. Indeed, it is questionable whether such testing should be initiated if the history does not even fulfill LFL criteria (LFL criteria excluding breast cancer as the main other tumour has a high positive predictive value, 50%). Certainly the 5% (1/21) mutation rate in the series as a whole is lower than the 10% guideline suggested by ASCO. Given the particularly difficult issues of genetic counselling and the low uptake of presymptomatic testing in TP53 families,\textsuperscript{11,12} it is debatable how strongly the possibility of a TP53 mutation should be raised, particularly in older onset breast/sarcoma families. While it is possible that such aggregations may be the result of other, as yet unidentified genes, the possibility that many of these could have occurred by chance should not be dismissed.

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doi: 10.1136/jmg.39.12.941

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