Results from London Regional Clinical Genetics Services over a five year period on germline *TP53* testing in women diagnosed with breast cancer at <30 years

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Abstract

Background

The most common cancer diagnosed in germline *TP53* pathogenic variant (PV) carriers is premenopausal breast cancer. An increased rate of breast tumour HER2-positivity has been reported in this group. Screening for breast/other cancers is recommended in PV carriers.

Objectives

1. To assess the frequency of germline *TP53* PVs reported diagnostically in females with breast cancer <30 years
2. To evaluate the impact of personal/family history and HER2 status on the likelihood of germline *TP53* PV/likely pathogenic variant (LPV) identification

Methods

Genetic test results from patients undergoing diagnostic germline *TP53* tests between 2012-2017 in the four London Regional Clinical Genetics Services were reviewed. Clinical/pathology data and family history were extracted from Genetics files for females diagnosed with breast cancer <30.

Results

The overall germline *TP53* PV/LPV variant detection rate was 9/270=3.3% in all females diagnosed with breast cancer <30 and 2/171=1.2% in those with no second/subsequent cancer diagnosis or family history of *TP53*-spectrum cancers. Breast cancers were significantly more likely to be HER2-positive in *TP53* PV/LPV carriers than in non-carriers (p=0.00006).

Conclusions

Germline *TP53* PVs/LPVs are uncommon amongst females diagnosed with breast cancer <30 without other relevant personal or family cancer history but have an important clinical impact when identified.

Introduction

Germline pathogenic variants (PVs) in *TP53* have a pan-ethnicity population frequency of approximately 1/3555-1/5476[1]. The classic "Li Fraumeni syndrome" caused by such variants involves a proband diagnosed with a sarcoma at <45 years, as well as sarcoma or early onset cancer diagnoses in at least two first or second degree relatives[2]. As exemplified by the Chompret criteria and terms such as "TP53-Related Heritable Cancer Syndrome", phenotypic associations with germline *TP53* PVs have now expanded to include rare cancer types, such as adrenocortical carcinomas and rhabdomyosarcomas, as well as increased frequencies of more common cancers, such as brain cancer and premenopausal breast cancer[3,4].

The penetrance of germline *TP53* PVs is generally considered to be high (particularly in combination with environmental risk factors, such as radiation exposure), at approximately 40% by 18 years of age and close to 100% by 70 years[3,5]. The management of germline *TP53* PV carriers includes additional surveillance for early cancer detection, consideration of prophylactic interventions such as risk-reducing bilateral mastectomy and the avoidance of ionising radiation during cancer treatment,

with the aim of improving survival[4,6]. Breast cancer represents one of the most frequently diagnosed cancers in adults with a germline PV in *TP53*[4]. HER2 receptor amplification is often reported in this group[7]. The *de novo* rate of *TP53* germline PVs is estimated to be approximately 7-20%, indicating that a lack of relevant family history does not rule out PV presence[8].

The identification of a *TP53* PV has important genetic counselling implications for probands and their relatives. Probands' offspring each have a 50% chance of inheriting the PV. The patient cohort included in this study are of child-bearing age and if found to carry a *TP53* PV may, therefore, wish to consider prenatal diagnosis or preimplantation genetic diagnosis. Additionally, predictive testing could be offered to their children to determine those that might benefit from surveillance for childhood cancers[4,6]. Other close relatives may also be offered predictive testing, followed by options for additional screening and prophylactic interventions if also found to carry the PV.

Previous studies investigating germline *TP53* testing in patients diagnosed with early onset breast cancer have found variable PV detection rates, ranging from 0 to 8.5%[9-13]. This range can largely be explained by differences between study populations, including thresholds for age at diagnosis and whether family history and tumour histology were considered during case selection. This retrospective study examines rates of germline *TP53* PVs in women diagnosed with breast cancer at <30 years from the diverse population served by Regional Clinical Genetics Services in London, UK[14].

Study aims

1. To review the results of germline clinical diagnostic *TP53* tests conducted in females diagnosed with breast cancer at <30 years across Regional Clinical Genetics Services in London in a 5 year period
2. To evaluate the impact of personal/family history and tumour HER2 expression on the likelihood of *TP53* PV/likely pathogenic variant (LPV) detection in this group

Methods and materials

Patients and setting

Data was collected from the four Regional Clinical Genetics Services in London (North East, North West, South East and South West Thames Regional Clinical Genetics Services). Lists of patients for whom a clinical report had been issued for diagnostic germline *TP53* testing during the 5 year period 2012-2017 were collated from regional laboratory and/or clinical service databases.

Clinical Genetics staff collected clinical and pathological information from the genetics files for each patient on the list relating to their personal and family history of cancer. Where performed, the results of diagnostic tests in *BRCA1*, *BRCA2* and *PALB2* were also recorded.

The identification of a variant classified as pathogenic (PV) or likely pathogenic (LPV) by the reporting UKAS-accredited NHS diagnostic laboratory was designated as "positive" diagnostic test result.

Data review

Personal and family history data were reviewed to determine whether patients had family histories of a "*TP53*-spectrum cancer" in a first or second degree relative (FDR/SDR) and whether family cancer histories included only breast cancer diagnoses. *TP53*-spectrum cancers were defined as:

- Sarcoma at any age
- Brain cancer at any age
- Any cancer diagnosed at <18 years
- Breast cancer diagnosed at <50 years

The HER2 status amongst those diagnosed with breast cancer at <30 years in *TP53* PV/LPV carriers and non-carriers was compared using a Fisher's exact two-tailed test.

Data analysis was performed using STATA v12.1.

Results

Between 2012 and 2017, germline *TP53* clinical diagnostic reports were issued for 376 females with breast cancer under the care of the four Regional Genetics Services, constituting 376/432=87.0% of the total diagnostic *TP53* reports issued. Of these females, 270/376 (71.8%) were diagnosed with breast cancer at <30 years.

TP53 PV/LPVs were found in 9 females diagnosed with breast cancer at <30 years and 5 variants of uncertain significance (VUS) were found in this group. Relevant clinical characteristics and variant details are shown in table 1 and supplementary table 1 respectively. Germline *PALB2* testing was conducted in 50/376=13.3% of females and *BRCA1/2* testing was conducted in 367/376=97.6% of females, identifying 13 *BRCA1*, 6 *BRCA2* and 1 *PALB2* PV/LPVs. One female had LPVs in both *BRCA2* and *TP53* and was included in the *TP53* PV/LPV carrier group as the *TP53* LPV would have contributed to her cancer phenotype.

1st cancer diagnosis	Age at 1st cancer diagnosis (years)	2nd cancer diagnosis	Age at 2nd cancer diagnosis (years)	Invasive breast cancer pathological features	Pathological features of associated DCIS (if present)	Family history
Breast	27			Grade 3 IDC, ER -ve, HER2 +ve	Present, grade unknown	Adrenocortical tumour and breast cancer
Breast	28			Grade 3 IDC, ER/PR -ve, HER2 +ve	High grade	None
Breast	23	Breast	25	Bilateral, both sides grade 3 IDC, L: ER/PR -ve, HER2 +ve R: ER/HER2 +ve	Both sides high grade	Prostate cancer
Osteosarcoma	18	Breast	27	Unknown	Presence/ absence unknown	None
Breast	22			Grade 3 IDC, ER/PR/HER2 +ve	High grade	Breast cancer
Breast	24			Grade 3 IDC, ER/HER2 +ve	High grade	Brain cancer and leukaemia
Breast	21			Grade 3 IDC, ER/HER2 +ve	High grade	Non-Hodgkin's lymphoma and breast cancer >50
Breast	23			Grade/type unknown, ER/PR/HER2 +ve	Presence/ absence unknown	Breast cancer <50 including 2 x bilateral breast cancer diagnoses
Astrocytoma	24	Breast	26	Grade 2 IDC, ER/HER2 +ve	High grade	Multiple primary tumours and bilateral breast cancer <50

Table 1: Clinical characteristics of females diagnosed with breast cancer at <30 years in whom a germline *TP53* pathogenic (PV)/likely pathogenic variant (LPV) was reported. IDC: invasive ductal carcinoma, DCIS: ductal carcinoma in situ, +ve: positive, -ve: negative.

The detection rate of *TP53* PV/LPVs in females diagnosed with breast cancer at <30 years overall was 9/270=3.3%. It was 9/251=3.6% if individuals with *BRCA1*, *BRCA2* or *PALB2* pathogenic variants causative of their phenotype were excluded.

Of the patients diagnosed with breast cancer at <30 years, excluding those with causative pathogenic *BRCA1*, *BRCA2* or *PALB2* variants, 59/251=23.5% had a family history of a *TP53*-spectrum cancer diagnosis in a FDR/SDR, 184/251=73.3% did not, and for 8/251=3.2%, the family history was not available in the genetics file, and was therefore recorded as unknown. Of the 59 patients with a relevant family history, the cancer diagnoses were of breast cancer only in 35/59=59.3% of cases.

225/251=89.6% of women had a single cancer diagnosis, 20/251=8.0% had two cancer diagnoses, 5/251=2.0% had three cancer diagnoses and 1/251=0.4% had four cancer diagnoses.

The detection rate of *TP53* PV/LPVs in those with no family history of *TP53*-spectrum cancers in a FDR/SDR was 5/184=2.7%. Once the patients with a second or subsequent cancer diagnosis (other than a second breast cancer) were excluded, the detection rate fell to 2/171=1.2%. The detection rate in those with a family history in FDR/SDR consisting of breast cancer only was 3/35=8.6%.

A comparison of the HER2 status of women diagnosed with breast cancer at <30 years in whom a *TP53* PV/LPV was detected (n=9) and was not detected (n=242), excluding women with causative pathogenic *BRCA1*, *BRCA2* or *PALB2* variants, are shown in table 2.

	***TP53* pathogenic/likely pathogenic variant present**	***TP53* pathogenic/likely pathogenic variant absent**	**Total**
HER2 positive	8	42	**50 (31.1% of tumours where HER2 status known)**
HER2 negative	0	111	**111 (68.9% of tumours where HER2 status known)**
HER2 status unknown	1	89	**90 (35.9% of all tumours)**
Total	**9**	**242**	**251**
Two-tailed Fisher's exact test result: p=0.00006 (unknown HER2 status excluded)			

Table 2: HER2 status by *TP53* result for women diagnosed with breast cancer at <30 years

Discussion

Between 2012-2017, a diagnosis of breast cancer at <30 years was by far the most common clinical indication for germline *TP53* testing amongst the four London Regional Clinical Genetics Services (376/432=87.0%). With the introduction of the NHS England National Genomic Test Directory, the number of patients offered testing under an early onset breast cancer indication will increase as eligibility criteria become more permissive, from testing any individual with breast cancer at <30 years (previous regional practice) to any breast cancer at ≤30 years or triple positive breast cancer at ≤35 years[15]. Determining the utility of this testing is therefore crucial to ensure appropriate resource allocation. Possible clinical benefits of PV/LPV identification must be balanced against potential anxiety or other harm occurring through unnecessary testing, particularly if a VUS is identified.

The detection rate of *TP53* PV/LPVs in those diagnosed with breast cancer at <30 years, excluding those with causative pathogenic *BRCA1*, *BRCA2* or *PALB2* variants, was 3.6%, in keeping with the findings of previous studies[10,11]. If the proband had no FDR/SDR with a *TP53*-spectrum tumour diagnosis, the detection rate was lower at 2.7%. The detection rate was lower still at 1.2% if limited to probands with breast cancer diagnoses only. This is similar to the proportion of patients found to have a PV in the largest study of *TP53* testing in patients with very early onset breast cancer and no significant family history to date[12]. In this study, conducted in the Netherlands, 2/233 (0.9%) of

patients with breast cancer at <30 years and no sarcoma, brain tumour or adrenocortical carcinomas in their personal or family history were found to have a germline pathogenic *TP53* variant[12].

In our study, the detection rate in women diagnosed with breast cancer at <30 years and a family history of premenopausal breast cancers but no other *TP53*-spectrum cancers was higher at 3/35=8.6%. However, the small number of patients in this group in the study necessitates caution in drawing inferences from this result.

The finding that HER2 positivity was significantly more likely in breast tumours diagnosed at <30 years amongst *TP53* PV/LPV carriers than non-carriers (p=00006) is in keeping with previous studies[7]. This supports the incorporation of tumour characteristics into *TP53* testing eligibility criteria[15]. As ER/PR status data collection was incomplete in this study and therefore not presented, no conclusions regarding triple positive breast cancers can be drawn. Tumour ER status in *TP53* PV/LPV carriers was mixed (table 1).

The grade/presence of ductal carcinoma in situ (DCIS) was not collected for a large enough proportion of the cases to allow meaningful comparisons between *TP53* PV/LPV carriers and non-carriers. However, it is notable that high grade DCIS was reported in all *TP53* PV/LPV carriers with known DCIS status (table 1), consistent with the findings of a recent study of histopathological features of breast cancer in germline *TP53* PV carriers[16].

One female had germline LPVs in both *TP53* and *BRCA2*. In a recent study, 110/379=29.0% of females diagnosed with breast cancer at ≤30 years carried a germline PV/LPV in *BRCA1/BRCA2*[11]. There may be an argument for conducting parallel testing of breast cancer susceptibility genes in cases of early onset breast cancer, since sequential testing could lead to delays in reaching a molecular diagnosis and failure to detect clinically relevant PV/LPVs in other genes.

For one female with early onset breast cancer and no relevant family history, the *TP53* LPV found in the proband was confirmed as *de novo* when parental testing was conducted to assist with variant classification. Parental testing data was unavailable for other patients in whom a germline *TP53* PV/LPV was found, as is often the case for adult patients. However, collecting parental testing data would provide further information regarding the proportion of *TP53* PVs which are *de novo,* thereby improving our understanding of the role of cancer family history in assessing the likelihood of germline *TP53* PV detection.

Limitations of this study included the fact that *PALB2* testing was only conducted in a minority of the probands included, so there may be undiagnosed *PALB2* PV carriers within this cohort. Other breast cancer predisposition genes, such as *CHEK2, ATM, RAD51 and RAD51D,* were also not tested for[17]. However, this may be less significant, since finding a pathogenic variant in one of these genes in isolation may not entirely explain why the patient developed cancer at such a young age. We have demonstrated that all of the *TP53* PV/LPVs identified during 2012-2017 could now be classified as PV/LPV using the American College of Medical Genetics/Association for Medical Pathology (ACMG/AMP) guidance (supplementary table 1)[18]. However, further work in this field could include a prospective study of young women with breast cancer to assess the PV/LPV/VUS detection rates following the incorporation of the ClinGen TP53 expert guidance into routine laboratory practice[19].

Concluding remarks

The likelihood of finding a *TP53* PV/LPV in patients diagnosed with breast cancer at <30 years with no relevant family history and no second (non-breast) cancer diagnosis is approximately 1%. Breast tumours in *TP53* PV/LPV carriers are significantly more likely to be HER2-positive than in non-carriers.

The implications of identifying a *TP53* PV in a young woman are potentially very significant. Despite their rarity, we believe it important to identify *TP53* PVs in this patient group in order to influence cancer treatment/screening/prophylaxis in the proband and for genetic counselling on risks to offspring and other family members.

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Raw data available on request

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