Early-onset breast cancer patients in the South and Southeast of Brazil should be tested for the *TP53* p.R337H mutation

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Abstract

Germline *TP53* mutations are associated with Li-Fraumeni syndrome (LFS), a disease that predisposes carriers to a wide variety of early onset tumors. In southern and southeastern Brazil, a high frequency of a germline *TP53* mutation, p.R337H, was diagnosed in 0.3% of the population due to a founder effect. Carriers are at risk for developing cancer but the penetrance is lower than in typical DNA binding domain mutations. To date, only a few families were detected and diagnosis of carriers remains a challenge. Therefore, the inclusion of additional criteria to detect p.R337H carriers is necessary for the Brazilian population. We assessed the A.C. Camargo Cancer Center Oncogenetics Department database in search of common characteristics associated with p.R337H families that did not fulfill LFS/LFL clinical criteria. Among 42 p.R337H families, three did not meet any LFS/LFL criteria. All cases were young female patients with breast cancer diagnosed before age 45 and with no family history of LFS linked-cancers. Our results suggest that screening for the germline *TP53* p.R337H mutation should be indicated, along with *BRCA1* and *BRCA2* genetic testing, for this group of patients, especially in the South and Southeast of Brazil.

Keywords: Breast cancer, Li-Fraumeni syndrome, p.R337H, *TP53*.

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Li-Fraumeni syndrome (LFS, OMIM #151623) is a rare autosomal dominant genetic disorder inherited by germline *TP53* mutations (Malkin et al., 1990). Carriers are predisposed to the development of a wide variety of early onset tumors, especially to those denominated as LFS core tumors: premenopausal breast cancer, soft-tissue sarcoma (STS), central nervous system tumors (CNS), and adrenocortical carcinomas (ADR) (Li and Fraumeni, 1969a, b).

In order to identify at-risk families who carry these mutations, different criteria for clinical diagnosis have been established (Table 1). Since its publication, classical criteria have been modified due to the presence of families which, although not fulfilling the definition, were positive for germline *TP53* mutations. This group of patients belongs to a variant form of LFS, named Li-Fraumeni-like (LFL), which is defined by either more inclusive parameters or additional criteria (Birch et al., 1994; Chompret et al., 2001; Eeles, 1995; Tinat et al., 2009).

Interestingly, a specific germline *TP53* mutation (NC_000017.9: c.1010G > A; p.R337H) was reported as highly associated with LFS/LFL families in Brazil (Achatz et al., 2007). It is present in 0.3% of the local population from southern and southeastern regions of the country (Palmero et al., 2008; Custódio et al., 2013) due to a founder effect (Pinto et al., 2004; Garritano et al., 2010). One of the hypotheses to explain why this deleterious mutation has persisted is based on its relatively reduced penetrance, which confers a tumor risk of 30% before the age of 30, while lifetime cancer risk is similar to other *TP53* mutations (Garritano et al., 2010). Thus, most carriers may have their children before developing cancer, spreading the mutation throughout generations. Also, the tumor profile among Brazilian carriers is similar to that of DNA-binding domain mutations found elsewhere in the world, but with some age difference and a higher risk for other types of tumors. In spite of its elevated prevalence, appropriate criteria to identify carriers, as well as guidelines to facilitate and direct genetic testing are still missing and, therefore, the number of carriers may be underestimated. Hence, our aim was to investigate the family history of p.R337H carriers who did not fulfill any of the LFS/LFL criteria, and define when individuals without criteria would benefit from testing for p.R337H.

This study is based on the A.C. Camargo Cancer Center Oncogenetics Department’s database. The department...
has been following patients at high-risk for cancer development since 1999 and currently comprises 7,059 individuals from 607 families. For each family we obtained a detailed family history regarding tumor diagnosis and clinical data for both index patients and their relatives. Patients eligible for either \( TP53 \) sequencing or point-mutation directed genetic testing are also registered in this database. From 348 families tested for germline \( TP53 \) mutations, 42 were found to carry the p.R337H mutation.

Table 2 shows the number of families that fulfilled each of the LFS/LFL criteria. From the 42 families identified as p.R337H carriers, three did not meet any of the LFS/LFL criteria. According to their respective pedigrees (Figure 1), family Y0347 (Figure 1A) presented only two cases of malignancy: the proband with an invasive ductal carcinoma (IDC) diagnosed at the age 41 and her paternal uncle with prostate cancer at the age 60, which is not considered as an LFS-core tumor. Family Y0348 (Figure 1B) also presented cases of early-onset breast cancer; an IDC and a ductal carcinoma in situ (DCIS) diagnosed in the proband at the ages of 42 and 46, respectively, in addition to a breast cancer diagnosed in her mother at the age 61. Finally, the pedigree of family Y0349 (Figure 1C) includes a proband diagnosed with breast cancer at the age of 29 and cases of uterus and prostate cancers in her second- and third-degree relatives.

Altogether, we identified three different p.R337H families that did not fulfill any of the clinical criteria for LFS diagnosis. The main common observations in these families were the cases of breast cancer, diagnosed before age 45, irrespective of family history.
It has been suggested that women diagnosed with breast cancer before age 30, along with a family history of one or more core LFS cancers in a first- or second-degree relative should also be considered for TP53 genetic testing. Under this premise, Gonzalez et al. (2009) found a likelihood of 100% (5 of 5) individuals harboring a germline TP53 mutation. In contrast, the authors did not detect any mutation carrier in the group composed by 15 women diagnosed with invasive ductal carcinoma between the interval of 30-49 years and who did not have any core LFS tumor in the family history. Similar results were described later (Mouchawar et al., 2010), and the probability of identifying a germline TP53 mutation in women diagnosed with early onset breast cancer and who have a negative family history was defined as ranging from 5% to 8%, (McCuaig et al., 2012).

The three families detected in our study presented some features that should be carefully interpreted based on specific p.R337H characteristics. Different from the findings described by Gonzalez et al. (2009), two positive cases (Y0347T000 and Y0349T000) did not have any core LFS tumor in their first- or second-degree relatives. In addition, although the family Y0348 includes two cases of breast cancer, it did not meet any of the LFS criteria due to the relatively older age at tumor diagnosis of the proband’s mother. These particularities could be consequences of the low penetrance presented by the p.R337H mutation, especially before the age of 30 (Garritano et al., 2010), which raises the possibility of later-than-expected ages at cancer development when compared to those described in currently applied LFS clinical criteria. Therefore, this might be a plausible explanation for both the absence of other affected individuals in the pedigree, as well as a slightly older age at cancer onset.

The indication of simultaneous genetic testing for BRCA1/BRCA2 and TP53 has been proposed especially for women with breast cancer diagnosed before age 35 who have a family history of LFS-linked cancers (Lee et al., 2012). Conversely, Tinat et al. (2009) suggested TP53 testing only for women diagnosed with early onset breast cancer who are negative for mutations in BRCA1 and BRCA2, irrespective of family history. Nonetheless, the authors state that it should be avoided in those who do not present a family history of cancer or multiple primary tumors, mainly due to the low estimated prevalence of positive cases in this category (less than 5%) and the psychosocial burden induced by a TP53 genetic testing. In accordance with our observations, Gomes et al. (2012) described two p.R337H carriers diagnosed with breast cancer before the age 40 in an unselected breast cancer-cohort with 390 participants (0.5%), indicating that the genetic testing for the p.R337H mutation could potentially be included in existing screening panels. Similarly, Giacomazzi et al. (2014) investigated the prevalence of the p.R337H mutation in two different Brazilian groups of women diagnosed with breast cancer: one composed by affected individuals with a family history compatible with hereditary breast cancer but no LFS/LFL features and another one, by women unselected for family history. The authors found mutation frequencies of 3.4% and 8.6% for each group, respectively. Due to this frequency, they proposed that this mutation may play an important role in the incidence of breast cancer in Brazil.

These findings, along with ours, strengthen the importance of suggesting concomitant TP53 testing for women affected by breast cancer before age 45, irrespective of family history, particularly in the South and Southeast of Brazil, where the prevalence of a germline TP53 is considerably higher than elsewhere in the world. The inclusion of this group of patients would potentially avoid LFS/LFL underdiagnosis and inappropriate genetic counseling.

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References

Achatz MI, Olivier M, Le Calvez F, Martel-Planche G, Lopes A, Rossi BM, Ashton-Prolla P, Giugliani R, Palmiero EI, Vargas FR, et al. (2007) The TP53 mutation, R337H, is associated with Li-Fraumeni and Li-Fraumeni-like syndromes in Brazilian families. Cancer Lett 245:96-102.

Birch JM, Hartley AL, Tricker KJ, Prosser J, Condie A, Kelsey AM, Harris M, Morris Jones PH, Binchy A, Crowther D, et al. (1994) Prevalence and diversity of constitutional mutations in the p53 gene among 21 Li-Fraumeni families. Cancer Res 54:1298-1304.

Chompret A, Abel A, Stoppa-Lyonnet D, Brugières L, Pagés S, Feunteun J and Bonaïti-Pellié C (2001) Sensitivity and predictive value of criteria for p53 germline mutation screening. J Med Genet 38:43-47.

Custódio G, Parise GA, Kiesel Filho N, Komechen H, Sabbaga CC, Rosati R, Grisa L, Parise IZ, Pianovski MA, Fiori CM, et al. (2013) Impact of neonatal screening and surveillance for the TP53 R337H mutation on early detection of childhood adrenocortical tumors. J Clin Oncol 31:2619-2626.

Eeles RA (1995) Germline mutations in the TP53 gene. Cancer Surv 25:101-124.

Garritano S, Gemignani F, Palermo EI, Olivier M, Martel-Planche G, Le Calvez-Kelm F, Brugières L, Vargas FR, Brentani RR, Ashton-Prolla P, et al. (2010) Detailed haplotype analysis at the TP53 locus in p.R337H mutation carriers in the population of Southern Brazil: Evidence for a founder effect. Hum Mutat 31:143-150.

Giacomazzi J, Graudenz MS, Osorio CA, Koehler-Santos P, Palmero EI, Zagonel-Oliveira M, Michelli RA, Scapulatempo Neto C, Fernandes GC, Achatz MI, et al. (2014) Prevalence of the TP53 p.R337H mutation in breast cancer patients in Brazil. PLoS One 9:e99893.

Gomes MC, Kotsopoulos J, de Almeida GL, Costa MM, Vieira R, Filho FaC, Pitombo MB, F Leal PR, Royer R, Zhang P, et al. (2012) The R337H mutation in TP53 and breast cancer in Brazil. Hered Cancer Clin Pract 10:3.

Gonzalez KD, Noltner KA, Buzin CH, Gu D, Wen-Fong CY, Nguyen VQ, Han JH, Lowstuter K, Longmate J, Sommer SS, et al. (2009) Beyond Li Fraumeni syndrome: Clinical characteristics of families with p53 germline mutations. J Clin Oncol 27:1250-1256.

Lee DS, Yoon SY, Looi LM, Kang P, Kang IN, Sivanandan K, Ariffin H, Thong MK, Chin KF, Mohd Taib NA, et al. (2012) Comparable frequency of BRCA1, BRCA2 and TP53 germline mutations in a multi-ethnic Asian cohort suggests TP53 screening should be offered together with BRCA1/2 screening to early-onset breast cancer patients. Breast Cancer Res 14:R66.

Li FP and Fraumeni JF (1969a) Rhabdomyosarcoma in children: Epidemiologic study and identification of a familial cancer syndrome. J Natl Cancer Inst 43:1365-1373.

Li FP and Fraumeni JF (1969b) Soft-tissue sarcomas, breast cancer, and other neoplasms. A familial syndrome? Ann Intern Med 71:747-752.

Malkin D, Li FP, Strong LC, Fraumeni JF, Nelson CE, Kim DH, Kassel J, Gryka MA, Bischoff FZ and Tainsky MA (1990) Germ line p53 mutations in a familial syndrome of breast cancer, sarcomas, and other neoplasms. Science 250:1233-1238.

McCuaig JM, Armel SR, Novokmet A, Ginsburg OM, Demsky R, Narod SA and Malkin D (2012) Routine TP53 testing for breast cancer under age 30: Ready for prime time? Fam Cancer 11:607-613.

Mouchawar J, Korch C, Byers T, Pitts TM, Li E, McCredie MR, Giles GG, Hopper JL, and Southey MC (2010) Population-based estimate of the contribution of TP53 mutations to subgroups of early-onset breast cancer: Australian Breast Cancer Family Study. Cancer Res 70:4795-4800.

Palmero EI, Schulter-Faccini L, Caleffi M, Achatz MI, Olivier M, Martel-Planche G, Marcel V, Aguiar E, Giacomazzi J, Ewald IP, et al. (2008) Detection of R337H, a germline TP53 mutation predisposing to multiple cancers, in asymptomatic women participating in a breast cancer screening program in Southern Brazil. Cancer Lett 261:21-225.

Pinto EM, Billerbeck AE, Villares MC, Domencio S, Mendonça BB and Latronico AC (2004) Founder effect for the highly prevalent R337H mutation of tumor suppressor p53 in Brazilian patients with adrenocortical tumors. Arq Bras Endocrinol Metabol 48:647-650.

Tinat J, Bougeard G, Baert-Desurmont S, Vasseur S, Martin C, Bouvignies E, Caron O, Bressac-de Paillerets B, Berthet P, Dugast C, et al. (2009) 2009 version of the Chompret criteria for Li Fraumeni syndrome. J Clin Oncol 27:e108-9; author reply e110.

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