Li-Fraumeni syndrome, clinical and molecular genetics

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Chapter 6

Discussion and future perspectives

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The main objective of this thesis was to evaluate Li-Fraumeni syndrome in the Netherlands and propose recommendations for *TP53* mutation analysis and surveillance of *TP53* mutation carriers.

When should TP53 mutation analysis be performed?
One of the aims of this thesis was to present an overview of all families who have been tested for *TP53* germline mutations in the Netherlands and to determine which families carried a *TP53* germline mutation.
In most study populations published to date, the LFS[1]- and LFL[2]-criteria have been used for initiating *TP53* mutation analysis. More recently, in 2001, Chompret et al. proposed criteria for mutation analysis, in which multiple primary cancers and certain sporadic tumours were included as well[3]. These criteria were updated in 2009 by including lung bronchoalveolar cancer in the LFS tumour spectrum and sporadic choroid plexus carcinoma, irrespective of family history. In addition, the age limits were revised [4].

As described in Chapter 2, we tested 180 index patients for *TP53* germline mutations and identified 24 mutation-positive families (13%). One hundred and five families fulfilled the revised Chompret criteria, 11 families the LFS criteria and 36 the LFL criteria. The 105 families fulfilling the revised Chompret criteria included 10 of the 11 classical LFS families and 32 of the 36 LFL families. In total 70 of the 180 families did not fulfil any of these three criteria, two carried *TP53* germline mutations (2.9%).
Based on our data and data from literature we recommend the revised Chompret criteria for DNA testing, because these criteria give the highest sensitivity for mutation detection, compared to using the LFS/LFL criteria. In addition, a reasonable mutation detection rate of 21% was reached. With the revised Chompret criteria, 105 families would have been tested (105/180, 21%) and 22 of the 24 mutation-positive families in the Netherlands would have been detected (sensitivity 92%). With the LFS and LFL criteria, 18 of the 24 mutation families would have been detected (sensitivity 75%). No mutations were found in the 5 LFS/LFL families which did not fulfil the revised Chompret criteria. The only two families that would have been missed with the revised Chompret criteria are the families of a child who developed a rhabdomyosarcoma at 4 years of age and a woman who developed breast cancer at 24 years of age, respectively. In both families a second-degree relative was affected with cancer: the grandfather of the child with rhabdomyosarcoma died of cancer at the age of 69 years (type of tumour unknown), the grandmother of the woman who developed breast cancer died of breast cancer at 37 years of age. Five years after detecting the *TP53* germline mutation in the patient who developed breast cancer at 24 years of age, the mother of the patient developed a sarcoma at 61 years of age and turned out to be a carrier of the *TP53* germline mutation as well. In literature, the mutation detection rate for sporadic childhood sarcoma was reported to be 3-9% [5-7], for women with breast cancer before 36 years of age 0-7% [4, 8, 9]. On the basis of these data we suggest to consider *TP53* germline mutation testing for children with sarcoma and women with breast cancer before 30 years of age (without a *BRCA1* or *BRCA2* mutation). In 2008 Bougeard et al. [10] suggested including sporadic breast cancer before 36 years of age as part of the Chompret criteria, but it was not included in the revised Chompret criteria 2009 [4] due to the low mutation detection rate (4%). Recently, 95 women who developed breast cancer before 30 years of age were tested for *TP53* germline mutations; no mutations were found [8].
In summary, the *TP53* mutation detection rate for sporadic early onset breast cancer is very low. However, the number of young women who developed breast cancer and were tested for *TP53* germline mutations is small, in our series only 13 women with breast cancer under 36 years of age were included. In addition, breast cancer is one of the tumours most often found in *TP53*

mutation carriers (24.8%-35% of all tumours in *TP53* mutation carriers [9, 11]). Larger series of young women with breast cancer should be tested to determine the true mutation detection rate.
In our series, collecting bias is conceivable, since only families were included who had been referred to a clinical genetics centre and had been offered and accepted *TP53* mutation testing. The number of families who did not seek, nor had been offered or refused genetic counselling and *TP53* mutation testing was not known. Therefore, our findings should be used with caution in different settings.
The question remains whether the potential benefits of knowing that one is a *TP53* mutation carrier outweighs the possible disadvantages. The psychological distress that might be induced by *TP53* genetic testing and the low mutation detection rate were the reasons breast cancer under 36 years of age was not included in the 2009 version of the Chompret criteria [4]. On the other hand, a delay in the diagnosis of a possible second malignancy and the exposure to radiation can be avoided for these young women. Therefore, it would be interesting to know the actual psychological distress that is imposed on these women when *TP53* genetic testing is offered.

Psychological impact of TP53 germline mutation testing
So far, limited data on the uptake of presymptomatic testing for *TP53* mutation families and the psychological impact of *TP53* germline mutation testing and the knowledge of being a *TP53* germline mutation carrier is available, due to the small number of *TP53* mutation carriers detected worldwide. In three studies on psychological consequences of *TP53* testing and the initiation of presymptomatic testing , the uptake varied between 25% and 40% [12-14], the populations studied, however, were small (16, 57 and 57 individuals, respectively). In the Dutch families the uptake was over 50% (personal communication, dr. E. Bleiker). About a quarter of the family members (with at least a 50% risk of being a mutation carrier) who participated in the psychological part of the Dutch study reported increased levels of distress. These increased levels of distress were present in all participants, mutation carriers (both affected and unaffected), non-carriers and the at risk group that did not undergo *TP53* mutation analysis. (Lammens et al. manuscript in preparation 2009). Dorval et al. [15] found that the participants were accurate in predicting their emotional reactions upon disclosure of their test results and that a correct prediction was associated with psychological adjustment when the test result was known.
The uptake for *TP53* mutation analysis in the Dutch series is higher than the uptake for mutation analysis in Huntington families ([16]) and comparable with the uptake of *BRCA1* or *BRCA2* mutation-positive families ([17])). On average, 2 to 3 individuals/*TP53*-positive family indeed sought presymptomatic mutation testing; in one family 38 individuals were included. When this family was excluded, 1.2 individual/*TP53*-positive family did seek presymptomatic mutation testing.

Other genes and LFS
Since in LFS/LFL the mutation detection rate is not 100%, a second aim of this thesis was to look for possible candidate genes for *TP53*-negative Li-Fraumeni syndrome families. To date, no mutations have been found in candidate genes tested in these *TP53*-negative families, i.e. *BAX*, *Bcl10*, *CDKN2A*, *PTEN*, *CHEK1* and *TP63* [18-25]. The *CHEK2* gene also does not seem to be an alternative major LFS gene, as discussed in Chapter 3. *CHEK2* gene mutations may, however, explain the occurrence of breast cancer and possibly other tumours in *TP53*-negative families which fulfil the LFS/LFL criteria for some of the affected family members. If these family members had not been affected, the family would not be suspected of LFS. Others showed linkage of one locus on chromosome 1q in 4 LFS families (LOD scores >3.00), in which the *TP53*-locus was excluded, but a causative gene has not yet been identified [26]. In the future, many more low-penetrance genes, which contribute to LFS/LFL, may be detected. Since no other LFS gene besides *TP53* has been found so far, it will be interesting to see whether the *TP53*-negative LFS/LFL families can, at least partly, be explained by low penetrance genes.

Variation in penetrance and expression

Some *TP53* germline mutations show different clinical expression in different families.
A possible explanation for the variation in penetrance and expression can be the involvement of modifier genes. Because it was recently shown that a single nucleotide polymorphism in the *MDM2* gene, SNP309 (T>G variation), was associated with an earlier age of tumour onset in LFS patients who carry a *TP53* germline mutation[27], we wanted to evaluate this finding in our study population (Chapter 4). To enlarge our study population, 11 Finnish *TP53* mutation carriers were included. Additionally, we investigated whether the SNP309 G allele plays a role in the Dutch *TP53* negative LFS and LFS-suspected patients. No difference was seen in the mean age of tumour onset in patients with either of the SNP309 alleles in *TP53*-negative families. However, this *TP53*-negative group did show a significantly higher percentage of SNP309 homozygotes (G/G) compared to the general population ($p = 0.02$), suggesting this allele contributes to cancer susceptibility in LFS and LFS-suspected *TP53*-negative families. For *TP53*-positive families, the presence of the SNP309 G allele led to a 16 year earlier age of onset compared to the absence of the SNP309 G allele. In addition, the *TP53*-72Arg polymorphism might be related to an earlier age of onset in *TP53* mutation carriers [28]. Since further confirmation is needed, these observations are not implemented in clinical practice yet.
In conclusion, some modifier genes seem to influence penetrance and expression in *TP53* mutation carriers. In the future, other genes might be identified which influence the phenotype of *TP53* mutation carriers.

Counselling and screening

Chapter 5 addresses the complexities in counselling *TP53* mutation families. A family with relatively late-onset common cancers in which a novel *TP53* germline mutation was detected is described in Chapter 5.1. A surveillance program was started based on the tumour types occurring in affected family members. As a consequence, in two mutation carriers kidney cancer was detected early by ultrasound screening. In chapter 5.2 a classical LFS family with two *TP53* germline mutations is described. One of these mutations, a missense mutation for which the pathogenicity remains unclear, was described before in the literature. In the family described, the missense mutation was found in two healthy family members and one affected family member. The affected family member also carried the other *TP53* germline mutation. In addition, a functional test showed normal p53 transcriptional activity and the missense mutation was found once in anonymous healthy controls. Therefore, we defined this specific *TP53* germline mutation, p.Asn235Ser, as a rare neutral variant or at best a low penetrance allele rather than a pathogenic mutation for LFS, which of course has great implications for clinical practice.

Screening *TP53* mutation families is complicated by the different sites and types of cancer found in these families and the difficulties of finding appropriate screening modalities. We proposed the following surveillance procedures and recommendations for *TP53* mutation families as described in the Addendum:

* Yearly surveillance is optional. Information about early signs of cancer should be given.
* Yearly breast cancer screening from 20-25 years. Because mammography might have adverse effects through radiation, although the dose is low, screening by MRI might be a good alternative [29-32]. However, in the Netherlands, there is no consensus on the use of mammography and MRI or MRI alone
* An individual screening program can be considered for each family, based upon the tumour types occurring in the *TP53* mutation carriers in that particular family.
* Avoidance of CT scanning, because of the relatively high radiation dose.
* Avoidance of radiotherapy whenever possible. Tumour development has been reported in the radiotherapy field used for treatment of the first tumour [33-35].

Currently, mammography and MRI are used as screening modalities for *TP53*-positive and *BRCA1/2*-positive families. In general, exposure to mammographic X-rays confers a risk of radiation-induced breast cancer. The risk is dependent on the age (younger age confers a higher risk) during exposure and the number of X-rays [30, 36]. It has not been established whether the risk is higher for *TP53* mutation carriers than the general population. These data are available for *BRCA1/2* mutation carriers as mentioned in chapter 1.7. Some of the studies showed an association between exposure to chest X-rays and breast cancer risk for *BRCA1/2* mutation carriers[37, 38], others did not [39, 40]. The next question will be, is MRI a good alternative for mammography in *TP53* mutation carriers. This may depend on the type of breast tumours in LFS. Mammography is the imaging study of choice to detect microcalcifications associated with ductal carcinoma in situ (DCIS). In our study population, 21 female mutation carriers developed 29 breast tumours: 19 invasive ductal carcinomas, 6 DCIS, 1 lobular carcinoma, 1 phyllodes carcinoma and two breast tumours of unknown histology. The proportions of the different histologies in *TP53* mutation carriers is comparable with the proportions in the general population. The 6 DCIS tumours in our study were all grade II or III; the higher grade of DCIS are likely to be detected with MRI. Kuhl et al. [41] found that 98% of high grade DCIS were detected with MRI alone, 52% were detected with mammography alone. But the 2 tumours missed with MRI (2/89) were detected by mammography.

Since LFS is a rare syndrome and many specialists are involved in the management of *TP53*-positive families, decision-making regarding diagnosis and management of Li-Fraumeni families is preferably done in multidisciplinary (family) cancer clinics.

Strengths and limitations of the Li-Fruameni cohort study

This study allowed comprehensive evaluation of 180 families who were counselled for LFS in the Netherlands between 1995 and 2008. Although this is likely to be only a proportion of all LFS and LFS-suspected families in the Netherlands, and we have no information on the extent of the group of families who did not seek counselling, the number of 180 families does allow us to draw some general conclusions. Thus, for instance, in this comprehensive overview we could for the first time assess the clinical usefulness of the recently established revised Chompret criteria [4]. Although intended, the size of the population studied still did not allow us to investigate the relationship between radiation exposure and increased risk for tumour development in *TP53* mutation carriers. Further international collaboration would allow investigations into, for instance, radiation and LFS.

Future perspectives

Our study on the usefulness of the revised Chompret criteria should be confirmed in different international study populations.

Screening of young breast cancer cases for *TP53* mutations is not generally included in the criteria used for *TP53* germline mutation testing, because of the low mutation detection rate, 0-7% [4, 8, 9] and the psychological distress induced by *TP53* germline mutation testing. On the other hand, breast cancer screening is a possibility and treatment options may differ for *TP53* mutation carriers. In addition, radiotherapy could be avoided for *TP53* mutation carriers and family members can be informed about the possibly increased cancer risks. So far, the mutation detection rate has only been determined for small groups of young women: 0%-7% for women under 36 years of age. It seems important to study further the proportion of *TP53* mutation carriers among these young patients, since this may affect their clinical management. Clearly, international collaboration is needed to acquire series of sufficient size to study this issue.

As mentioned above, the psychological impact of *TP53* mutation testing is largely unknown and therefore the results of an ongoing study that specifically assesses the psychological consequences in our Dutch *TP53*-positive study cohort (Dr. E. Bleiker, PhD C. Lammens, NKI-AVL) are of

great interest and will be published in the near future. Their findings should be confirmed in different study cohorts of sufficient size.
Furthermore, more data will become available on the possibly hazardous effects of mammography when mammographic screening is started at young age as well as the number of tumours that might be missed if mammography is no longer used as a screening tool. When these data become available, it will be possible to decide whether to use mammography and MRI or MRI alone for screening *TP53* mutation carriers.

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