

A novel deadly variant in the TP53 gene causing Li-Fraumeni Syndrome.

The importance of clinical awareness and the contribution of molecular diagnosis in active prevention within families with multiple tumor incidents at a young age.

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Background

- Li-Fraumeni Syndrome (LFS) is an autosomal dominant hereditary cancer syndrome associated with germline pathogenic variants in the TP53 gene and high risk of a broad range of childhood-onset or adult-onset malignancies.
- The 70-77% of LFS associated tumors are breast cancer, soft-tissue sarcoma, brain tumor, osteosarcoma and adrenocortical carcinoma.
- However, also ovarian, pancreatic and gastrointestinal track tumors are LFS-related. The patients with LFS have high percentages of a second and third primary tumor at a young age.

Case presentation

- A 15-month old girl (generation V) was referred to our center because of clitoromegaly 1.5 cm and pubic hair.
- An adrenal ultrasound detected a large adrenal tumor at the left side. No other tumors were detected.
- Left total adrenalectomy was performed confirming adrenocortical carcinoma.
- Before a family history with multiple cancers in both families, we examined clinically the mother aged 24 and prescribed an extensive laboratory workup which revealed bilateral breast cancer for which she was operated immediately with bilateral total mastectomy and adjuvant chemotherapy.

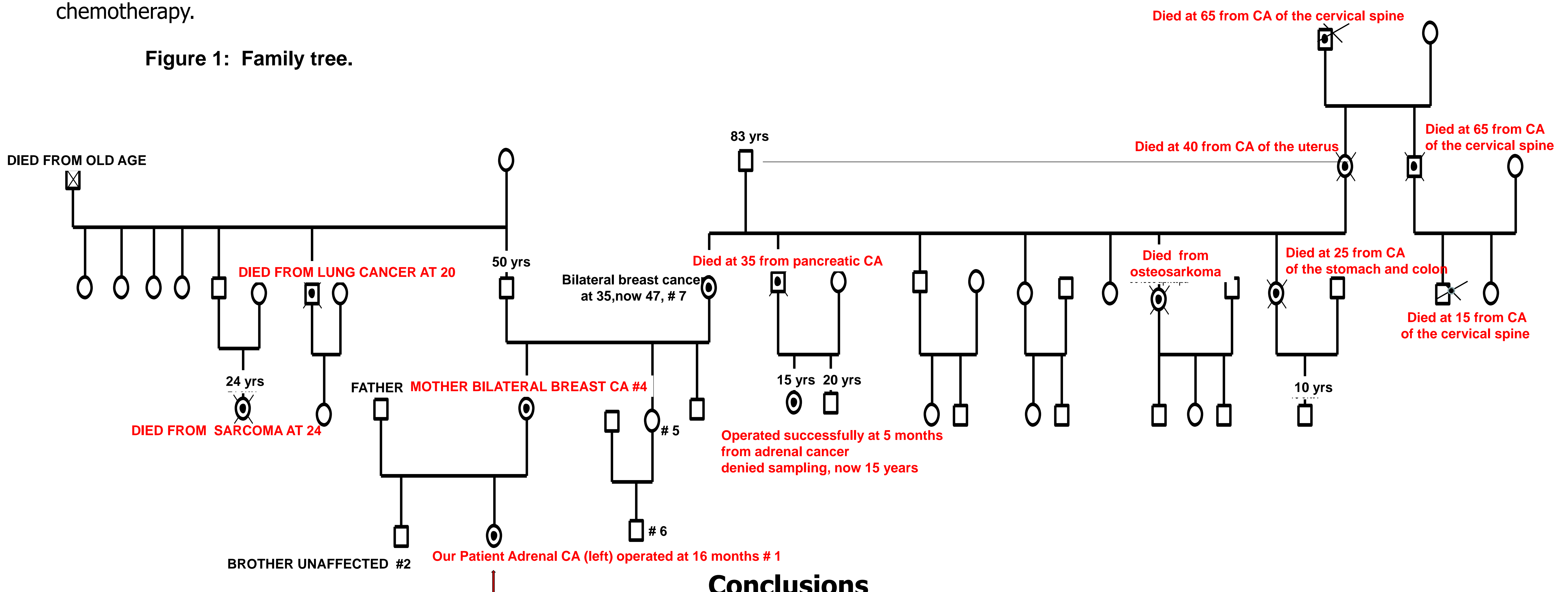
Genetic analysis:

- Considering the family history, with a maternal cousin operated of adrenocortical tumor at the age of 5 months and the maternal grandmother with a diagnosis of bilateral breast cancer at the age of 35 yrs, we performed genetic testing to all the available family members (mother, father, brother, maternal grandmother, maternal aunt, maternal cousin - not the one with adrenocortical tumor in the past), as a genetic dominant trait seemed most probable. Our hypothesis was supported also by the fact that other family members of the maternal family tree experienced tumors like osteosarcoma (generation III), tumors of the cervical spine (generation I, II and III) and pancreas (generation III) and died before the age of 30 yrs. the genetic dominant trait seemed most probable.
- Whole genome sequencing (WGS) was performed to all the available family members (mother, father, brother, maternal grandmother, maternal aunt, maternal cousin).

Results

- The referred child, the mother and the maternal grandmother were positive for a novel variant (c. 892delGinsTTT, p. Glu298PhefsX48, NM_0005464) in the TP53 gene.
- This variant is predicted to cause loss of normal protein function either through protein truncation or non-sense mediated mRNA decay.
- Considering the current data, this variant is most probably a pathologic variant.

Figure 1: Family tree.



Conclusions

- **Clinical awareness and the detailed family history resulted in a timely diagnosis of adrenocortical tumor in the child and in early detection of a bilateral breast cancer in a very young mother.**
- **Affirming the molecular diagnosis allows for appropriate genetic counselling and planning an intensive follow-up of the affected members, considering the high probability of a second and a third primary tumor.**

References:

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