Novel germline mutations in *DICER1* gene in patients with different paediatric hereditary tumors

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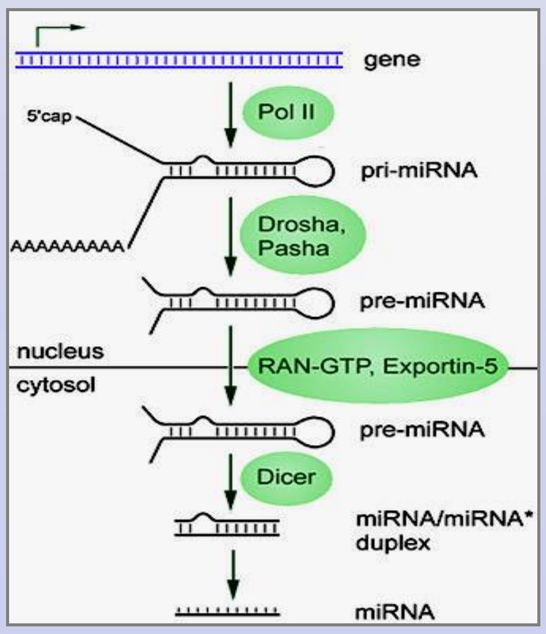
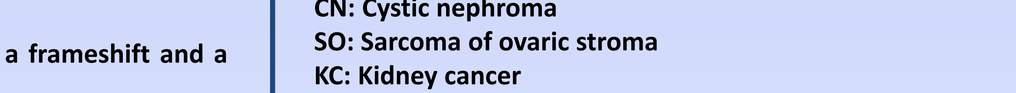
INTRODUCTION

Carriers of germline *DICER1* mutations are predisposed to a rare cancer syndrome, the DICER1 syndrome, associated with tumors such as pleuropulmonary blastoma (PPB), ovarian Sertoli-Leydig cell tumors (SLCT), multinodular goiter (MNG), cystic nephroma (CN), embryonal rhabdomyosarcoma (ERMS) or primitive neuroectodermic tumor.

DICER1 is involved in the generation of microRNAs (miRNAs), short, double-stranded, non-coding RNAs that modulate gene expression at the posttranscriptional level. Germline mutations in *DICER1* would cause an alteration in miRNAs processing deregulating target oncogenes and leading to elevated risk of tumorigenesis.



In humans, *DICER1* is located on chromosome 14q32.13, contains 1922 amino acids and is comprised of 26 coding exons. DICER1 is a multidomain protein, it is composed a ATPasa/DexD helicase domain, a PAZ domain, two RNase III domains and two dsRNA binding domains.



In most reported cases, there is an heterozygous germline mutation described and a somatic second hit mutation in the wild type allele. Therefore it is very important also to analyze tumoral samples.

AIM

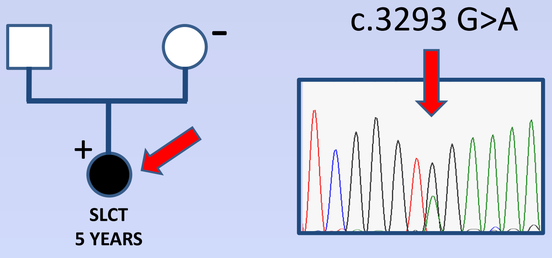
To analyze the presence of *DICER1* germline gene alterations in 4 patients with paediatric tumors associated with DICER1 spectrum. To investigate the presence of somatic *DICER1* mutations when a sample tissue is available.

METHODS

Automated sequencing of *DICER1* gene from gDNA extracted from blood of affected subjects and relatives. (ABI PRISM 3130 Genetic Analizer capillary DNA Sequencer, Applied Biosystems)

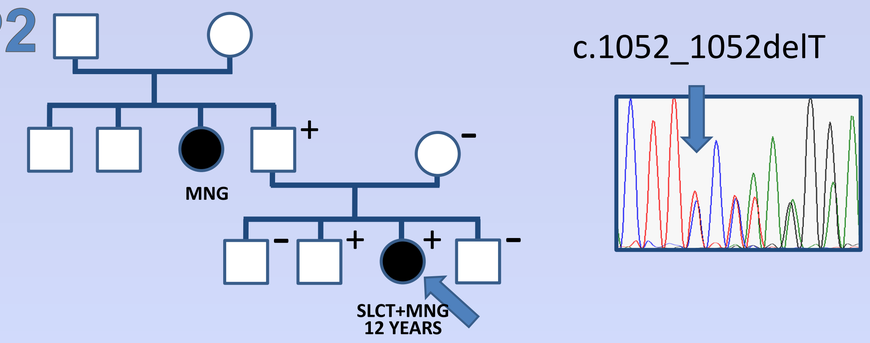
RESULTS

P1

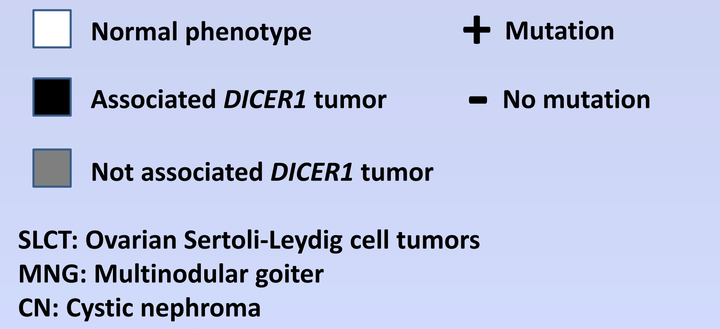


A novel heterozygous nonsense mutation in exon 21 (p.Trp1098*) was found.

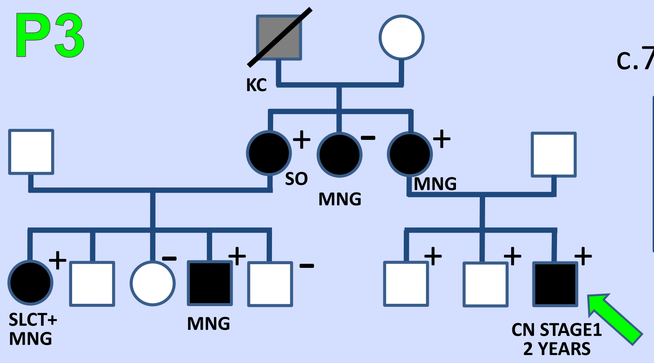
P2



A novel heterozygous deletion in exon 8 that causes a frameshift and a premature stop codon (p.Phe351fs*1) was found.

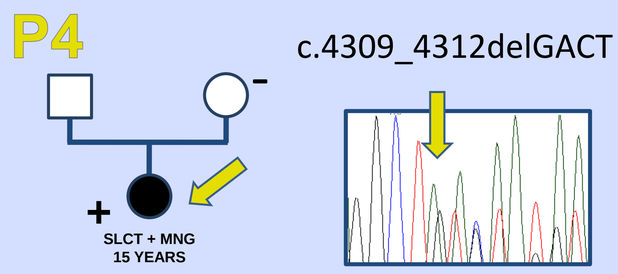


P3



A novel heterozygous deletion in exon 6 that causes a frameshift and a premature stop codon (p.Asp244Glyfs*27) was found.

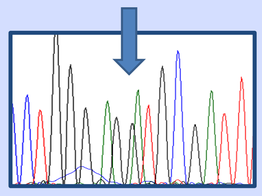
P4



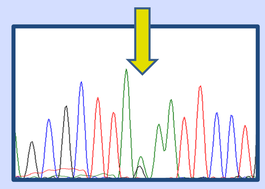
A previously described heterozygous deletion in exon 23 that causes a frameshift and a premature stop codon (p.Asp1437Metfs*16) was found.

SOMATIC MUTATIONS

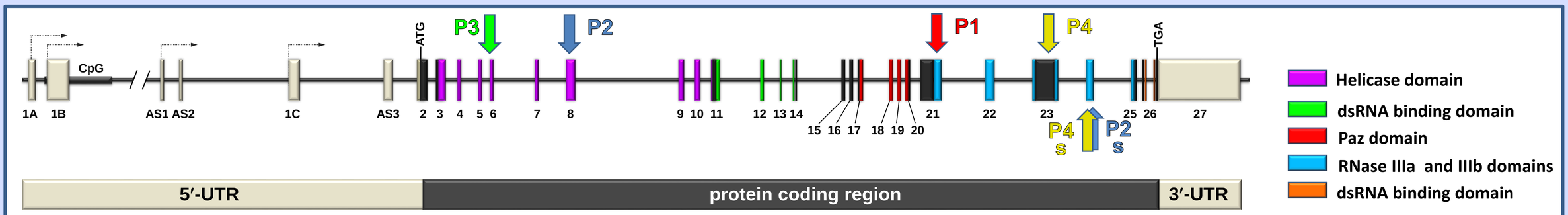
P2 MNG tissue
c.5126 A>G



P4 MNG tissue
c.5113 G>A



Two described heterozygous missense mutations in exon 24 (p.Asp1709Gly p.Glu1705Lys) were found. No malignant lesion was found by histological studies.



It is predicted that p.Phe 351fs*1, p.Trp1098* and pAsp244Glyfs*27 mutations would lead to a truncated protein above the RNase IIIa and RNase IIIb domains that includes metal-binding sites, and therefore without catalytic enzyme activity if translated.

CONCLUSIONS

In this study we report three novel heterozygous frameshift mutations in the *DICER1* gene. We also found two somatic RNase IIIb hotspot mutations in two MNG tissue samples. This findings confirm that a second hit event is involved in the mechanism of MNG development, as it was very recently described. MNG is a benign condition in which *DICER1* germline and somatic RNase IIIb mutations coexist. Molecular analysis of *DICER1* gene allows identification of high-risk families, to perfom an early diagnosis and to offer a genetic counselling about familial recurrence risk.

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