A next-generation sequencing approach for the simultaneous study of Wilms tumors and parathyroid tumours

Catarina Silva[1], Dina Carpinteiro[1], Branca Cavaco[2], Luís Vieira[1]

1. Unidade de Tecnologia e Inovação, Departamento de Genética Humana, Instituto Nacional de Saúde Dr. Ricardo Jorge, Lisboa

2. Unidade de Investigação de Patobiologia Molecular, Instituto Português de Oncologia de Lisboa Francisco Gentil (IPOLFG), Lisboa

Wilms Tumor (WT), also known as nephroblastoma, is a rare kidney condition which affects 1 in ~10.000 infants and children. This tumor is of complex etiology with underlying causes still incompletely understood. The majority of known mutations in WT are of somatic origin, with approximately one-third of patients displaying mutations in *WT1*, *CTNNB1*, *AMER1* (*WTX*) and/or *TP53* genes. In contrast, familial predisposition mutations are very rare. Recently, we used Next-Generation Sequencing (NGS) technology and a customized amplicon panel (TruSeq Custom Amplicon, Illumina) to detect somatic mutations of *WT1*, *AMER1*, *TP53* and *CTNNB1* (exon 4) genes, and identified mutations in 11 of 36 patients (30.5%). These results prompted us to design a new sequencing panel which incorporates a larger set of genes and addresses the problems encountered with low or inexistent coverage for some amplicons. In addition to those 4 genes, the new panel also includes genes involved in the SIX1/SIX2 pathway, which are frequently mutated in WT patients with blastemal-type histology(1), microRNA-processing genes (*DROSHA, DICER1*, *DGCR8*, *XPO5* and *TARBP2*), which were found to be mutated in over 10% of WT patients(2), as well as other genes (*e.g.*, *MYCN*) previously known to be involved in Wilms tumorigenesis. Moreover, we included 6 other genes (*CDC73*, *CTR9, PAF1, LEO1, RTF1* and *WDR61*), which encode subunits of the PAF1 complex. Among these genes, *CTR9* is already known to be a WT-predisposition gene(3), and *CDC73* is associated with the pathogenesis of the hereditary hyperparathyroidism-jaw tumour syndrome, and is also frequently mutated in sporadic parathyroid carcinomas. Using this new sequencing approach it will be possible to sequence genes involved in different types of familial cancer syndromes and sporadic tumours, simultaneously. Moreover, this strategy may also lead to identification of novel mutations of PAF1 complex genes, not yet known to be implicated in WT and parathyroid tumour development.