Identification of a TPM3-PDGFRB fusion transcript and its chromosomal breakpoints by RNA-Seq in a case of Chronic Eosinophilic Leukemia

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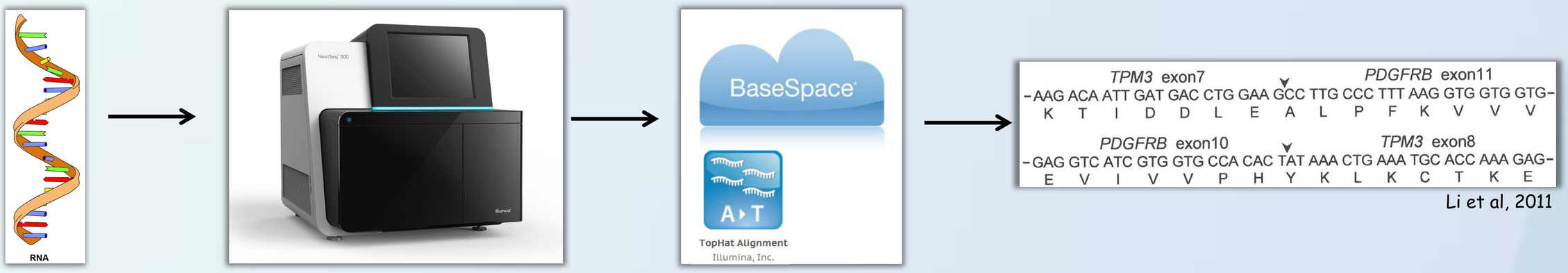
Introduction

We received a bone marrow from a 77-year old patient presenting with hypereosinophilia. FIP1L1-PDGFRA fusion was not detected, but cytogenetic analysis revealed a t(1;5)(q21;q33), with locus 5q33 corresponding to *PDGFRB*. This was in accordance with a diagnosis of Chronic Eosinophilic Leukemia (CEL), a rare subtype of myeloproliferative neoplasm, frequently characterized by rearrangements involving *PDGFRA/B* or *FGFR1* genes.

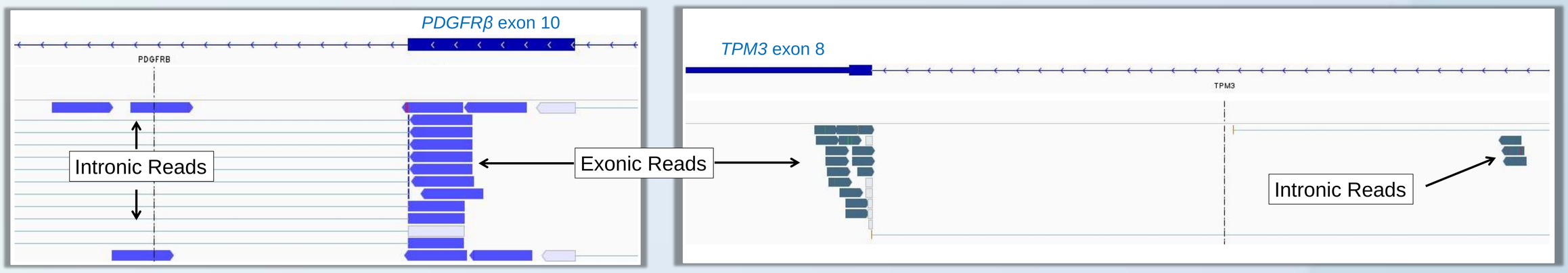
As FISH couldn't identify the fusion partner of *PDGFRB*, we performed a whole transcriptome sequencing (or RNA-Seq).

Identification of the fusion transcripts



- RNA-Seq was performed using polyA selection. The run was analysed using a cloud version of TopHat aligment in BaseSpace.
- TPM3 was found to be the fusion partner.
- The two fusion transcripts identified have already been described in two cases of childhood CEL (Li et al. 2011, Rosati et al. 2006)

Identification of the chromosomal breakpoints by RNA Seq – Confirmation by PCR



- By looking at the reads in IGV viewer, we could identify « mate-pair » reads aligning to intronic regions of *TPM3* and *PDGFRB*.
- We then performed a PCR with primers annealing upstream of the intronic reads, and were able to localize the genomic breakpoints more precisely

PDGFRβ intron 10.11 - CATATACTATATGTATGTCGTAAGCCATGTACA**TGAGCATGCCTGTTCCTTGAA**CATAGGTGCAAATCCTCTGTGTGTAGATATGTAAATCGTCTA

Intronic reads identified by RNA-Seq

TPM3 intron 7.8 - **CTTGTATCAGGAATGCTTGCTAAA**TTGTCCTT - - (90bp) - - CATCTAGCCATGAGCAACTGTGGCCTGTTGTAGCTGGGCTT

The chromosomal breakpoints are located ~6kb (*TPM3*) and ~1,5kb (*PDGFRB*) further than those previously published.

Conclusion

We describe here a third case of TPM3-PDGFRB fusion
- With the same fusion transcripts previously described but not concerning a childhood CEL
- With chromosomal breakpoints differing from those previously described

The patient was treated with imatinib therapy, responded well, and was in hematological remission at his last follow-up.

RNA-Seq allows for a rapid screening of fusion transcripts and can identifiy the rare ones, for which no diagnostic test is developed for routine work.

In addition to the « transcriptome » information, we used the « genome » information present in the data to identify the chromosomal breakpoints.

This methodology was more time-efficient than performing a screening by PCR, and more cost-efficient than performing a whole genome sequencing.

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