FREQUENCY OF *JAK2* AND *JAK3* MUTATIONS AND THEIR PROGNOSTIC ROLE IN ACUTE LYMPHOBLASTIC LEUKAEMIA

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Introduction

- Acute lymphoblastic leukaemia (ALL) is the most common haematological malignancy in paediatric patients, but it also occurs in adults.
- ALL has a heterogenic molecular profile characterized by sequential acquisition of genomic abnormalities that contribute to the leukaemogenic process (Figure 1).

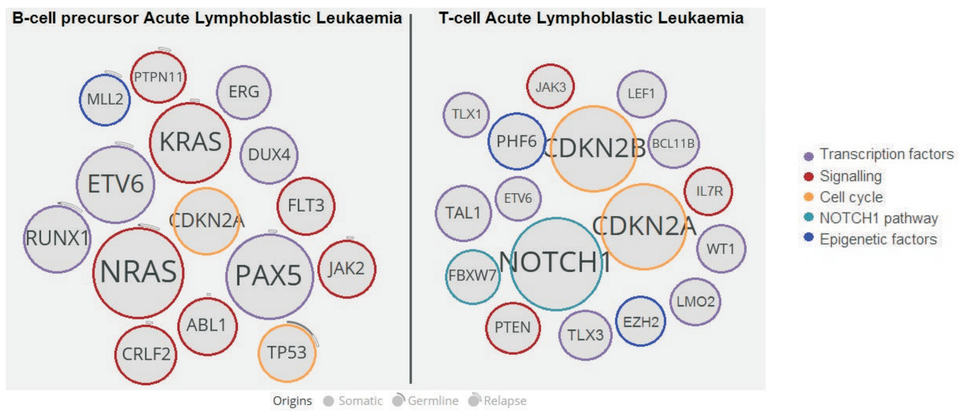


Figure 1. Genomic profile of acute lymphoblastic leukaemia (ALL). The schemes show the most frequently observed alterations in B-cell precursor and T-cell ALL, respectively. Alterations are coloured according to gene function, i.e. transcription factors, signalling, cell cycle, NOTCH1 pathway and epigenetic factors. The size of the circles represents the frequency of alterations affecting those genes. Both figures were adapted from 2015-2018 St. Jude Children's Research Hospital – **Ped**iatric **Ca**ncer Data Portal (**PeCan**).

- Mutations in genes of the JAK family are potential biomarkers to be used for risk stratification and therapeutic decisions.
- *JAK2* and *JAK3* mutations result in constitutive activation of JAK-STAT, PI3K/AKT and MAPK signalling pathways contributing to the malignant transformation of haematopoietic precursors (Figure 2).

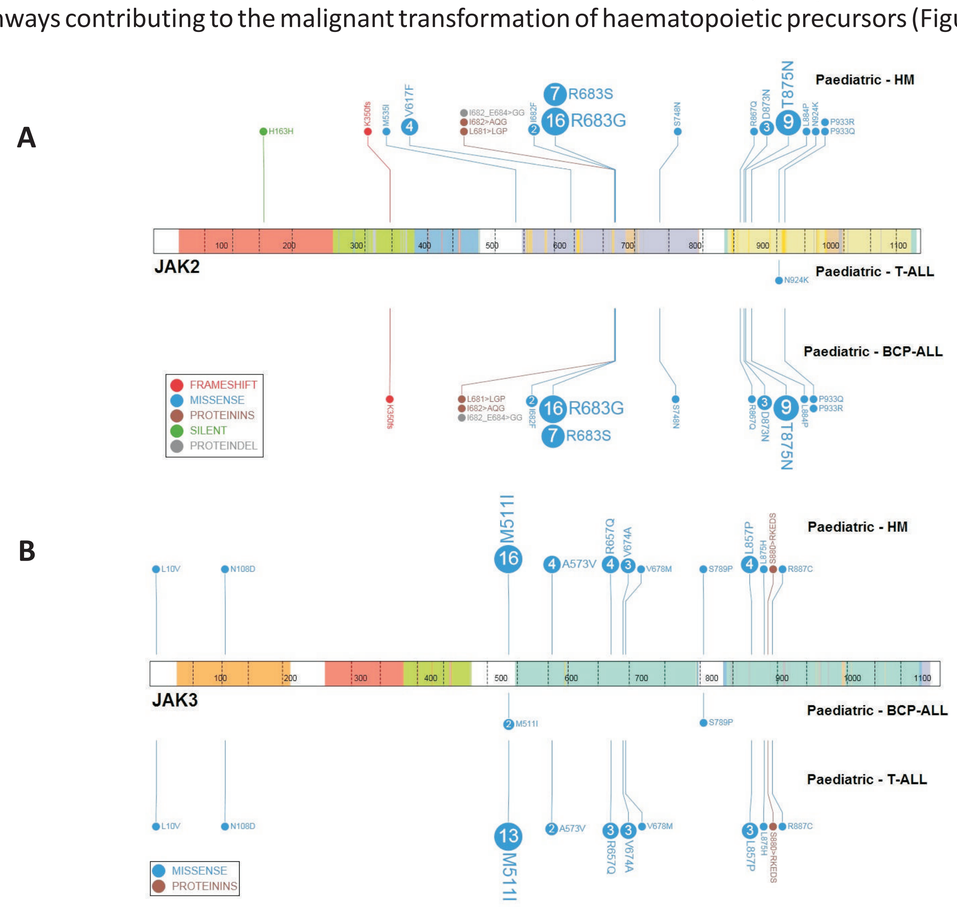
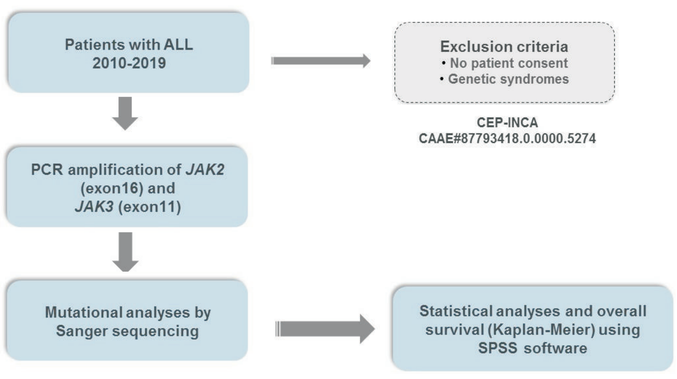


Figure 2. Recurrent mutations in JAK2 and JAK3 according to protein domains affected. A) R683_ is the most common mutation affecting *JAK2*, particularly in BCP-ALL. This mutation alters the pseudokinase (JH2) domain. **B)** In *JAK3*, SH2-pseudokinase (JH2) linker sequence is were the most common mutation (M511I) occurs particularly in T-ALL cases. Figures were modified from St. Jude PeCan Data Portal and the links for JAK2 and JAK3 mutational profile are https://pecan.stjude.cloud/proteinpaint/JAK2 and https://pecan.stjude.cloud/proteinpaint/JAK3, respectively.

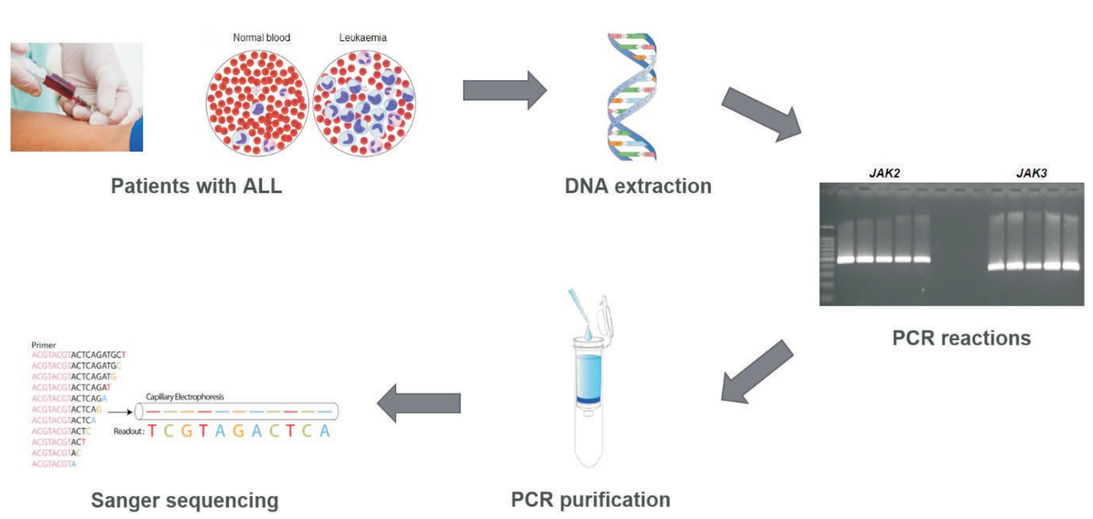
Aims

- The present proposal aims to determine the frequency of these mutations in a representative series of ALL and to investigate the potential prognostic impact of these markers on patient's overall survival (OS).

Study design



Methodology



Results

- We have, so far, analysed 16 leukaemic cases diagnosed in 2018 tracing potential mutations in *JAK2* and *JAK3*.
- Among those samples, 14 were classified as B-cell precursor ALL (BCP-ALL) and 2 as T-cell ALL (T-ALL). All 16 samples were wild-type for both *JAK2* e *JAK3* (Table 1).

Table 1. Clinical-laboratorial characteristics of ALL cases.

Patient ID	Leuk_Dx	AGE	GENDER	Material	WBC	MOLECULAR SUBGROUP	*JAK2* STATUS	*JAK3* STATUS
#ID01	BCP-ALL	10	F	BM	8000	*ETV6-RUNX1+*	WT	WT
#ID06	BCP-ALL	7	M	BM	4100	NA	WT	**SNP rs55883965**
#ID08	BCP-ALL	13	F	BM	70000	NA	WT	WT
#ID10	BCP-ALL	5 months	M	PB	345900	NA	WT	WT
#ID13	BCP-ALL	7	M	BM	39990	*TCF3-PBX1+*	WT	WT
#ID14	BCP-ALL	11	M	PB	29000	*ETV6-RUNX1+*	WT	WT
#ID15	BCP-ALL	12	M	BM	78000	*BCR-ABL1+*	WT	WT
#ID16	T-ALL	9	M	PB	700000	NA	WT	WT
#ID21	BCP-ALL	4	F	BM	2500	NA	WT	WT
#ID22	BCP-ALL	2	F	BM	10400	NA	WT	WT
#ID24	T-ALL	13	M	PB	26190	*JAK2*-r	WT	WT
#ID29	BCP-ALL	14	F	BM	4000	NA	WT	WT
#ID31	BCP-ALL	8	M	PB	335410	*BCR-ABL1+*	WT	WT
#ID40	BCP-ALL	4	M	PB	4000	NA	WT	WT
#ID45	BCP-ALL	5	F	PB	33920	NA	WT	WT
#ID48	BCP-ALL	5	M	BM	56000	NA	WT	WT

- In one of the BCP-ALL cases, we found a SNP, which was already described in the dbSNP database as rs55883965 (Figure 3).

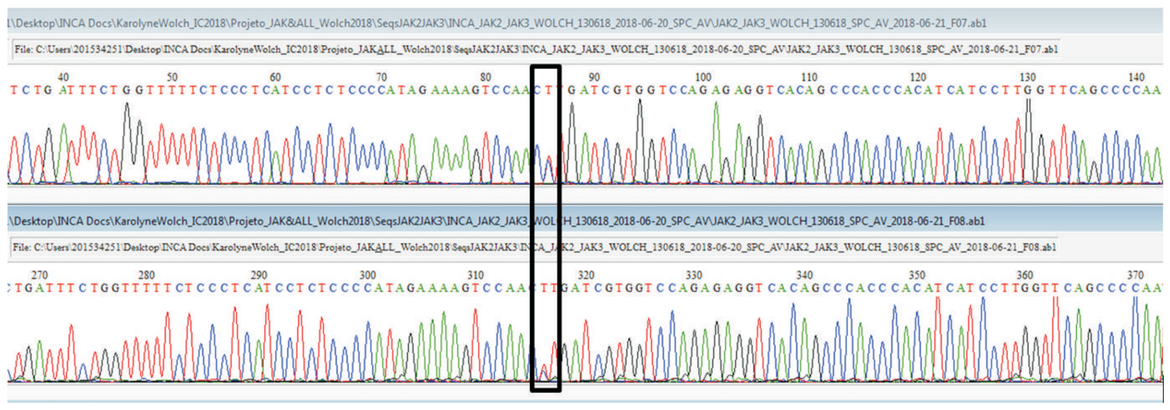


Figure 3. Sequencing of *JAK3* for the ALL case harbouring the SNP rs55883965. Sequencing results of *JAK3* exon 11 showed the c.1553C> T; p.L485L (rs55883965) in a BCP-ALL patient.

Conclusion

- These partial results are part of an ongoing investigation, therefore we intend to include more cases (retrospectively and prospectively) in order to answer the aforementioned aims. In summary, due to the preliminary nature of the current data we are still unable to draw any definitive conclusion.

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Projeto Gráfico: Setor de Edição e Informação Técnico-Científica / INCA

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