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Published in:
Medical Oncology

DOI:
[10.1007/s12032-013-0462-6](https://doi.org/10.1007/s12032-013-0462-6)

2013

[Link to publication](#)

Citation for published version (APA):

Kabir, N. N., Rönstrand, L., & Kazi, J. U. (2013). FLT3 mutations in patients with childhood acute lymphoblastic leukemia (ALL). *Medical Oncology*, 30(1), 462-462. <https://doi.org/10.1007/s12032-013-0462-6>

Total number of authors:
3

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"Letter to the editor"

FLT3 mutations in childhood acute lymphoblastic leukemia

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The type III receptor tyrosine kinase FLT3 is of importance in hematopoiesis. FLT3 is a frequently mutated gene in acute myeloid leukemia (AML) as well as prognostic marker. The most common mutation occurs in patients includes internal tandem duplication (ITD) in the juxtamembrane domain. Other point mutations in the kinase domain also identified in many patients. These mutations result in constitutive activation of receptor as well as uncontrolled activation of survival pathways. Although 30% of AML patients carry a mutation in FLT3 (Gilliland and Griffin, 2002), its expression is not limited to only those patients. It has also been found to be expressed in acute lymphoblastic leukemia (ALL) and several studies identified FLT3 mutations in a portion of ALL patients. This study will identify possible correlation in between FLT3 and childhood ALL patients.

With the search criteria depicted in figure 1A we retrieved 12 references that included 1213 childhood ALL patients with 76 patients (6.3%) carrying FLT3 mutations (Table S1). All 12 studies described FLT mutations. Further review of those references identified 89 patients with MLL-rearrangement and 196 patients with hyperdiploid ALL. Although 6.3% childhood ALL patients carried FLT3 mutations, 15.7 % of MLL-rearrangement and 14.4% of hyperdiploid childhood ALL patients carried FLT3 mutations (data not shown). Only 1% patients carried FLT3-ITD mutations (12/1213).

Childhood ALL patients with MLL-rearrangement displayed an overall odds ratio of 4.17 (95% CI=2.60-9.88, $p < 0.0001$) (Fig. 1B) and patients with hyperdiploid ALL showed an overall odds ratio of 4.03 (95% CI=2.18-7.95, $p < 0.0001$) (Fig. 1C). Studies with FLT3-ITD mutation (Fig. 1D) and FLT3-TKD mutations (Fig. 1E) showed that TKD mutations happened more frequently than ITD mutations. An increased rate of FLT3 mutations was observed in American population (Odds ratio=1.4, 95% CI= 0.85 to 2.29), while in Japanese and European population comparatively lower FLT3 mutations were identified (Fig. 1F).

The receptor tyrosine kinase FLT3 is frequently mutated in AML and activating FLT3 mutations cause poor prognosis in this disease (Gilliland and Griffin, 2002). Several FLT3 inhibitors display promising results in clinical trials. Although several studies described presence of FLT3 mutations in

childhood ALL, still we have limited knowledge in defining roles of FLT3 mutations. In this study, we carried out a meta-analysis to define the role of FLT3 mutations in childhood ALL.

All 12 studies analyzed in this study were mainly from three different populations that cover 1213 childhood ALL patients. The identification of 76 mutations in these populations suggests that FLT3 mutations in childhood ALL is less frequent than that of in AML. Although about 30% of FLT3-ITD mutations were reported in AML (Gilliland and Griffin, 2002), childhood ALL patients carry only 1% FLT3-ITD mutations suggesting that targeting FLT3-ITD will not be beneficial in pediatric ALL. It is likely that FLT3-TKD mutations other than FLT3-ITD mutations are more frequent. However, it is quite difficult to suggest a correlation between FLT3 mutations and ALL prognoses due to the insufficient studies, even though some studies described a relation between FLT3 mutations and ALL prognoses (Armstrong et al., 2004; Taketani et al., 2004).

The comparisons between sub-groups suggest that FLT3 mutations are more common in MLL-rearrangement ALL and hyperdiploid ALL suggesting that FLT3 mutation play a role in these sub-groups. Although one study suggest that patients with FLT3-mutations in both MLL-rearrangement and hyperdiploid ALL (Taketani et al., 2004), further studies are required to define the role.

Our study describes the FLT3 mutations in ALL using large number of patients data and suggests that FLT3 is frequently mutated in MLL-rearrangement and hyperdiploid ALL in compare to normal ALL.

Conflict of interest:

The authors declare no conflict of interest.

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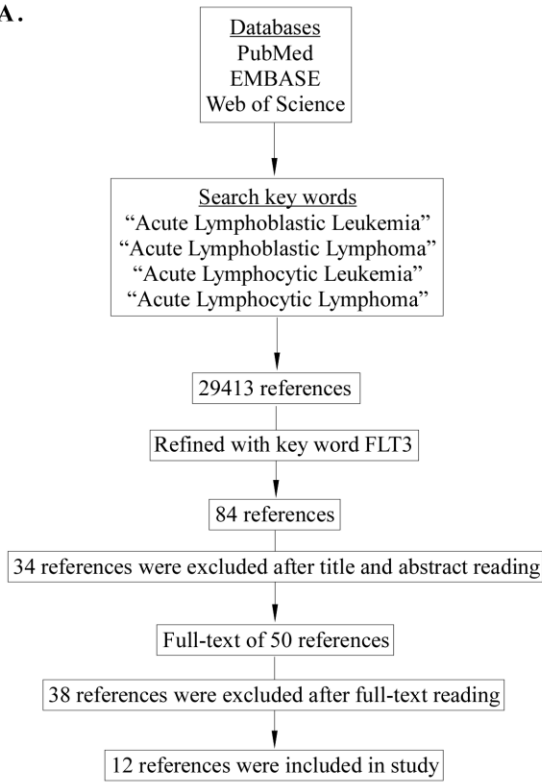
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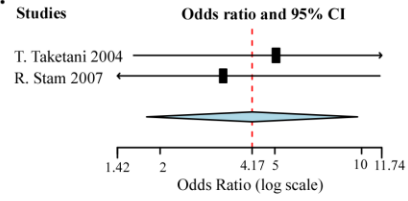
Figure Legends

Figure 1: (A) Flow diagram of study selection. (B) Meta-analysis of FLT3 mutations in MLL-rearrangement ALL. (C) Meta-analysis of FLT3 mutations in hyperdiploid ALL. (D) Meta-analysis of FLT3-ITD mutations in ALL. (E) Meta-analysis of FLT3-TKD mutations in ALL. (F) Meta-analysis of FLT3 mutations in different populations

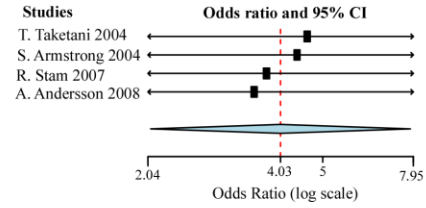
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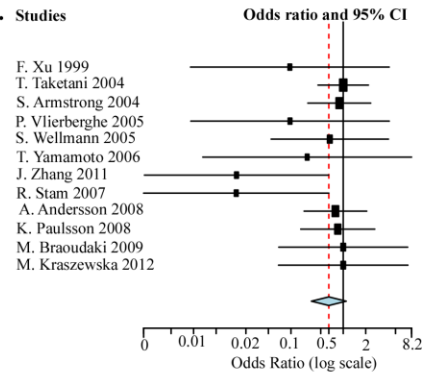
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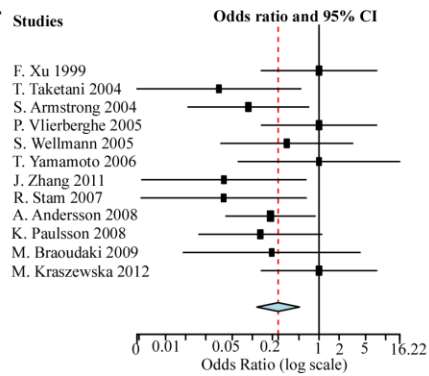
C.



D. Studies



E.



F.

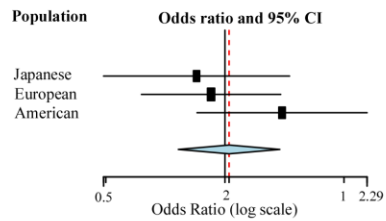


Table S1. List of studies included in the analysis

First Author	Publication Year	Country	ALL Patients	Flt3-mutation	Flt3-ITD
F. Xu	1999	Japan	60	2	2
T. Taketani	2004	Japan	162	14	
S. Armstrong	2004	USA	71	10	1
P. Vlierberghe	2005	Netherlands	72	2	2
S. Wellmann	2005	Germany	134	3	1
T Yamamoto	2006	Japan	95	1	1
R. Stam	2007	Netherlands	75	11	
A. Andersson	2008	Sweden	128	10	2
K. Paulsson	2008	Sweden	78	7	1
M. Braoudaki	2009	Greece	86	2	
J. Zhang	2011	USA	187	12	
M. Kraszewska	2012	Poland	65	2	2