UNIWERSYTET MEDYCZNY W ŁODZI

International Doctoral School
Medical University of Lodz

The influence of ETV6 gene mutations on acute lymphoblastic leukemia treatment outcome and complications

Introduction: The ETV6 protein is a transcription factor, belonging to the ETS family, which is known for its involvement in leukemogenesis and hematopoesis. Latest research indicates, however, that ETV6 plays a more prominent role in a whole plethora of different signalling pathways, responsible for tissue differentation. It is proposed, that ETV6 mutations may influence patients diagnosed with acute leukemias response to treatment and likelihood to develop complications and side-effects.

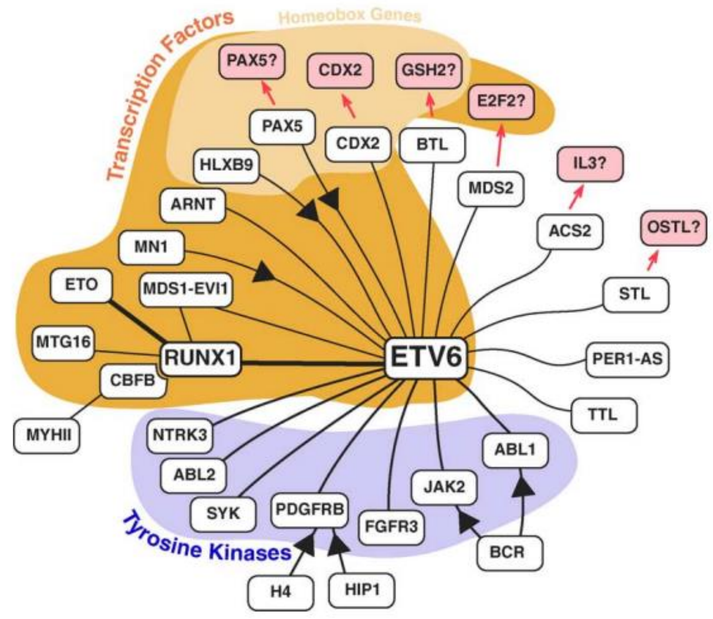
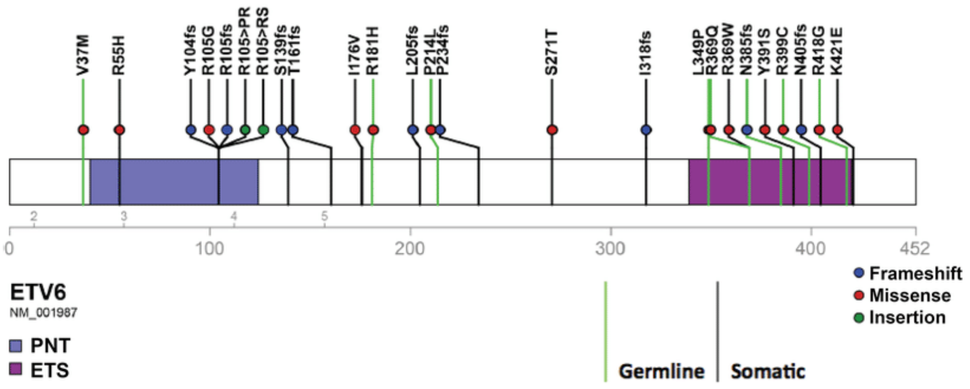


Fig.1 *Signalisation pathways discovered so far in which ETV6 transcription factor is involved*

Fig.2 *Diagram of known germinal and somatic mutations of ETV6 gene and proposed visualisation of interaction between the protein and its target DNA sequence*

Methods: We analysed the clinical course of acute leukemia in patients with a germline mutation through a systematic review of literature data, obtained from PubMed and Scopus databases, in order to identify mutation carriers and their pedigree. The study covered record data (in particular, age at the time of mutation diagnosis, current age, follow-up time), test results at the time of diagnosis, coexistence of other diseases, clinical course of these diseases, signs of treatment toxicity. The next stage of the study will be the active identification and diagnosis of patients with a hereditary ETV6 mutation, presenting thrombocytopenia preceding the development of cancer.

A



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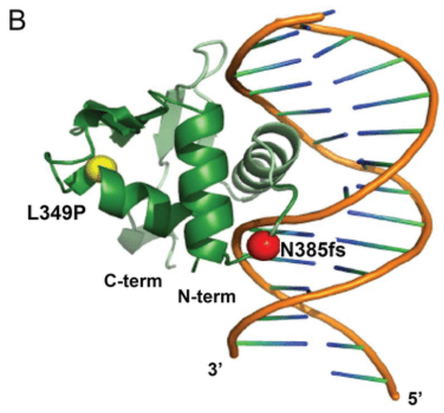

Acknowledgement: *I would like to thank MD PhD Sabine Topka et al. for the lollipop diagram of discovered ETV6 mutations and the 3D visualisation of interaction between transcription factor and target DNA sequence*

Results: 93 people with a germline mutation of the ETV6 gene have been identified worldwide. A number of missense and frame-shift point mutations were identified in the described patients, most of which concerned the DNA-binding domain, however, the most common mutation occurred within the region responsible for the conformation of the protein – P214L (25 cases, 26%). 82 people from this population developed thrombocytopenia during their lives (~88%). 21 patients (26% of patients with diagnosed thrombocytopenia) developed acute leukemia, most often lymphoblastic type B (18 cases), 1 case of leukemia with a mixed phenotype and 1 of acute myeloid leukemia M0. In most patients, thrombocytopenia was reported before the onset of leukemia, not after initiation of treatment.

Conclusion: Further collection of data regarding patients studied so far is essential in establishing long-term complications stemming from ETV6 mutation. As gathered evidence suggests, ETV6 transcription factor is involved in numerous cel-differentiation pathways, therefore its influence on their gene expression, combined with the mutagenic properties of cytostatic drugs used in chemotherapy regiments cannot be ignored. Additionally, somatic mutations of ETV6 need to be explored as well to have as broad picture of its mechanism of action as possible.

Patients age on admission (years)	Platelet count on admission (10^3/µl)	*ETV6* mutation	Neoplasm	Age of onset (years)	Complications/side-effects
83	221	t(12;14)(p13.2;q23.1)	-	-	-
64	212	t(12;14)(p13.2;q23.1)	-	-	-
40	309	t(12;14)(p13.2;q23.1)	-	-	-
19	260	t(12;14)(p13.2;q23.1)	B-Cell ALL	8	Bilateral osteonecrosis
16	262	t(12;14)(p13.2;q23.1)	-	-	-
16	280	t(12;14)(p13.2;q23.1)	B-Cell ALL	12	Bilateral osteonecrosis, vincristine neuropathy, osteoporis, compression fractures
2	240	t(12;14)(p13.2;q23.1)	-	-	-

Table 1. *A particularly interesting pedigree of a family from Finland with inheritable ETV6 mutation, where members of family did not develop thrombocytopenia, some of tchem however, did develop acute lymphoblastic leukemia, complicated with serious adverse reactions. Additionaly it is worth noting, that the mutation is not a point mutation, but a transolocation of a whole chromosome fragment*