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UNIWERSYTET MEDYCZNY W ŁODZI

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The influence of ETV6 gene mutations on acute lymphoblastic leukemia treatment – current landscape of germinal ETV6 mutations in Poland and globally

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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.

Methods: We have gathered data on currently known cases of germinal *ETV6* mutations through publications obtained through searching through PubMed and SCOPUS databes. Concerning data (age, diagnosis, outcome, accompanying diseases, toxicities) were gathered in a database for analysis. Concurrently, both retrospective analysis of AIEOP BFM study and prospective of cALL-Pol study were performer to identify patients in Polish population with germline *ETV6* mutations. We have also reached out to authors of publications to obtain follow-up on already diagnosed patients

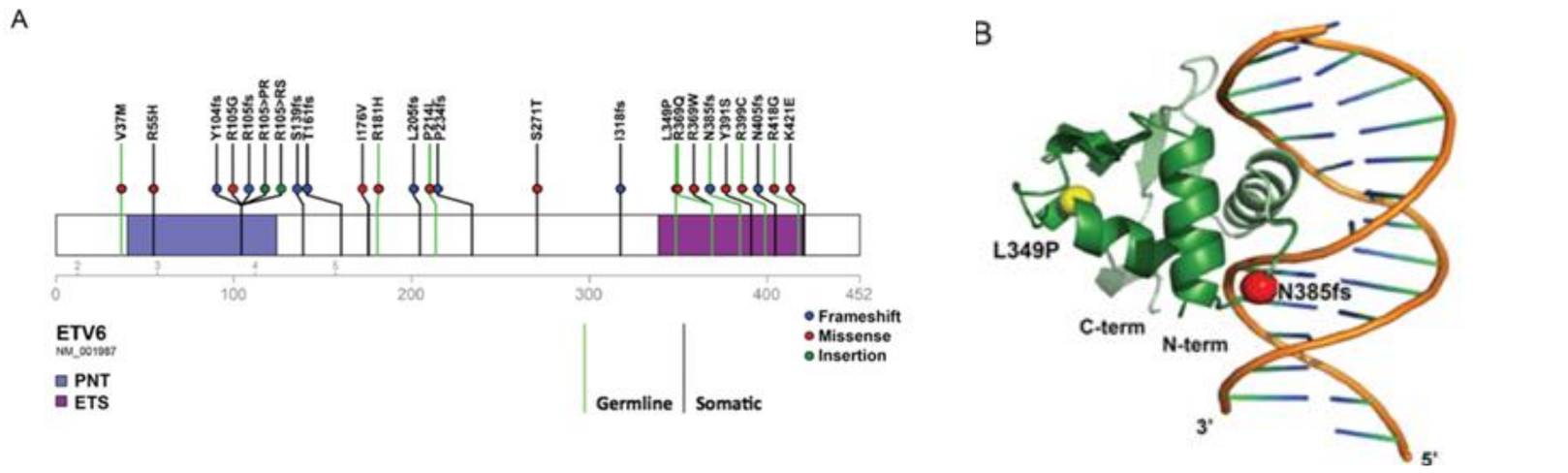
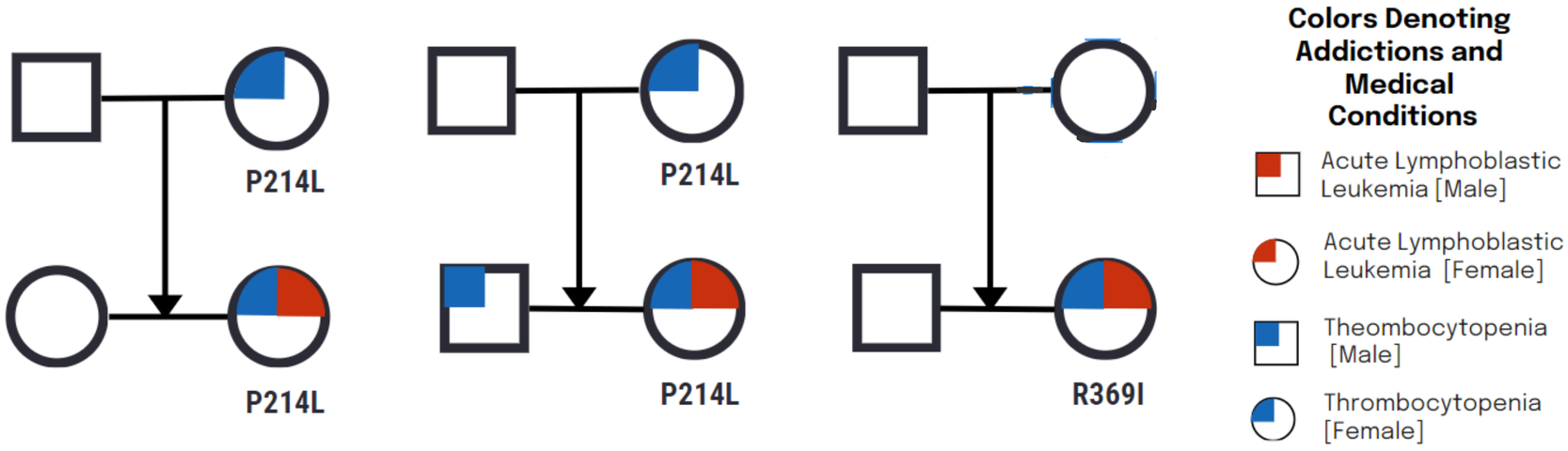


Fig. A Currently known germinal mutations of *ETV6* and their location within the transcription factor
Fig. B Visualisation of interaction of ETV6 transcription factor with target DNA sequence



Family trees of all the lineages with diagnosed germinal *ETV6* mutation in Poland

Results: So far we had known about 98 people with a germline mutation of the ETV6 gene. Vast majority of them presented with thrombocytopenia (86 subjects, app. 90%), out of which approximately one-fifth developed acute leukemia (22 patients – app. 22%). Additionally, we have diagnosed 3 families with germinal *ETV6* mutations in Poland, where 3 members were also diagnosed with acute lymphoblastic leukemia. All 3 presented with thrombocytopenia, which was further exacerbated during the treatment, to a point where due to delays they required modification of the protocol according to platelets level. We have not received many responses from authors of previosuly published *ETV6* patients, however, we have started a cooperation with professor Kim E. Nichols of St. Jude Children's Research Hospital, Cancer Predisposition Division on creating a survey to distribute globally in PHO facilities in order to gain more information about underreported cases of patients with germline *ETV6* mutations.

Conclusion: Currently we are working on developing survey to gather information about patients with germinal *ETV6* mutations from around the world. Judging by current estimates, even 1% of patients with diagnosed acute lymphoblastic leukemia may have a germinal mutation of the *ETV6* , therefore we believe that such cases are underreported . We will also continue to reach out to authors of available publications to gather follow-up data on already known patients.

Family	No. of carriers	ETV6 germline mutation protein notation	Average platelet count [G/l]	Average WBC count [G/l]	Hematological malignancies	Age at diagnosis of hematological malignancy [years]	Non-hematological disease	Non-hematological malignancies
I	3	P214L	85	5,87	preB-ALL	7	-	-
II	3	P214L	75	4,81	B-cell ALL	15	-	breast fibroadenoma, meningioma
III	2	R369W	100	5,07	-	-	-	-
IV	2	R369W	110	6,11	-	-	-	-
V	5	W380R	82	7,01	preB-ALL, polycytemia vera	7, 37	-	-
VI	3	N385Vfs	77	7,31	preB-ALL	3	-	breast fibroadenoma
VII	2	R418G+N385Vfs	101	5,01	-	-	-	breast carcinoma
VIII	4	R359X	137	7,33	preB-ALL	2 , 3 , 9	Turner syndrome, learning disability	-
IX	5	P214L	90	6,15	preB-ALL	3 , 37 (relapse CNS)	-	-
X	3	P214L	75	4,81	B-cell ALL	14	-	-
XI	2	R418G+N385Vfs	100	4,90	-	-	-	-
XII	12	L349P	32	unknown	ALL (unknown subtype), anemia, pancytopenia of unknown origin	unknown	Secondary amennorhea, ankylosing spondylitis	renal cell carcinoma, duodenal
XIII	4	N385Vfs	unknown	unknown	ALL, secondary AML	-	skeletal dysmorphism	-
XIV	9	P214L	62	4,62	refractory anemia with excess blasts type 2 (RAEB-2)	-	-	-
XV	4	A377T	72	5,30	dyserythropoesis	-	-	-
XVI	3	Y401N	106	5,23	-	-	-	-
XVII	4	I358M	85	4,73	AML	-	-	-
XVIII	3	R396G	45	unknown	-	-	-	-
XIX	1	Y401H	54	unknown	-	-	-	-
XX	4	R399C	86	4,88	preB-ALL, multiple myeloma, RAEB-1	7.5 , 45	developmental delay, seizures, GERD, myopathy, inflammatory bowel disease, GvHD	
XXI	5	R369Q	122,25	7,48	-	-	GERD, esophagal stricture	-
XXII	1	P214L	42	4,3	Mixed phenotype ALL	50	-	tacrolimus related microangiopathy
XXIII	7	t(12;14)(p13.2;q23.1)	254,86	7,9	B-cell ALL	8 , 12	Type 2 diabetes mellitus, hypertension, congestive heart failure, osteonecrosis, voncristine neuropathy, osteoporis, compression fractures	Epithelioid mesothelioma
XXIV	5	K384fsTer	127,8	unknown	B-cell ALL	3	-	-

Table 1. Currently known families with diagnosed germline ETV6 mutations, average platelet count, white blood cell count, hematological malignancies, other malignancies and disorders