Significant prevalence of severe monogenic immune defects among children with Type 1 diabetes and low T1D-genetic risk score

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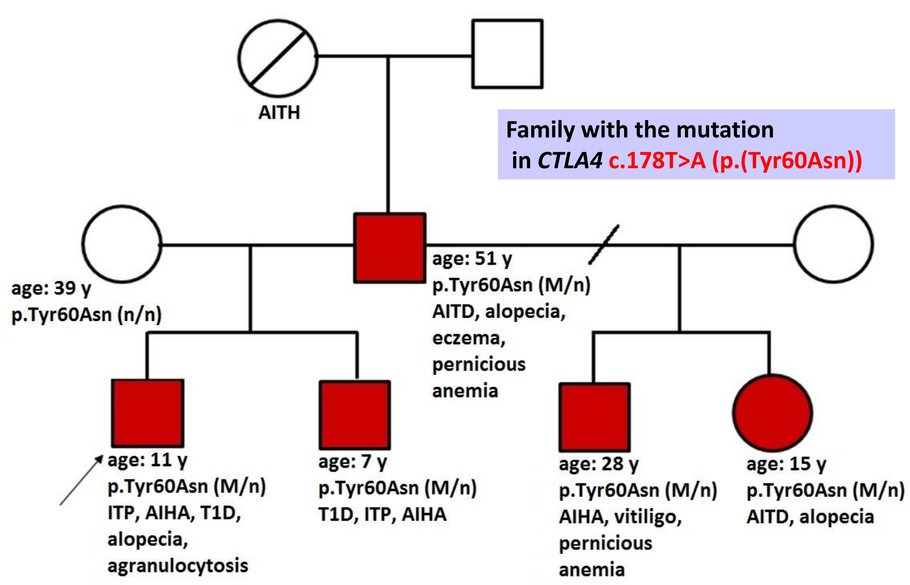
Introduction and objectives:

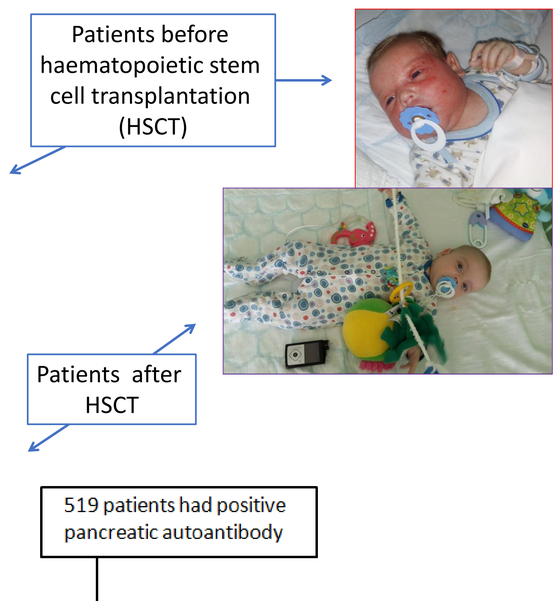
Monogenic Type 1 diabetes (T1D) is a rare disease caused by pathogenic variant in a single gene leading to dysregulation of immune system. T1D is combined with other autoimmunity like immune cytopenias, inflammatory bowel disease, rheumatoid arthritis, atopic eczema, autoimmune thyroid disease etc in these patients. Pathogenic variants in the *AIRE*, *FOXP3*, *LRBA*, *IL2RA*, *CTLA4*, *STAT3* and *STAT1* genes have been described as causal for monogenic T1D.

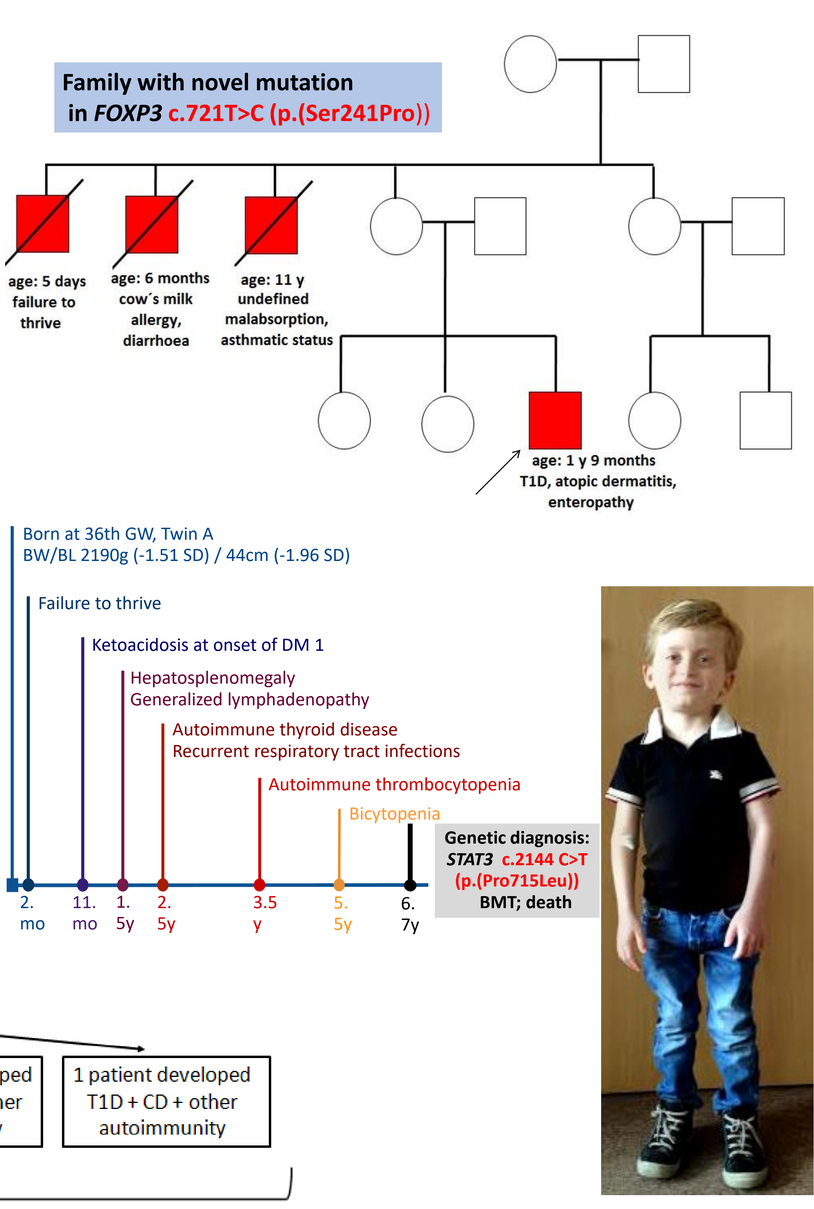
Patients and methods: Out of 519 paediatric patients with T1D from single tertiary center, 18 patients had at least two additional autoimmune conditions or a combination of T1D and autoimmune hepatitis, cytopenia or rheumatoid arthritis. In four patients with specific phenotype were analyzed by direct Sanger sequencing of the *FOXP3*, *STAT3* and *CTLA4* genes. DNA from the additional 14 patients was investigated using whole exome sequencing (WES). In addition, the T1D-genetic risk score (T1D-GRS) was used to discriminate monogenic autoimmunity from polygenic T1D.



Patient Number	Gender	Current age	Age of diabetes manifestation	Clinical features	Detected variant	T1D-GRS	T1D percentile
1	Male	1 year 9 months	6 weeks	IPEX syndrome	*FOXP3* p.(Ser241Phe)	0.568	7.9
2[a]	Male	11 years	6 years	T1D, cytopenias, alopecia, optic nerve neuritis	*CTLA4* p.(Tyr60Asn)	0.629	20.3
3[a]	Male	7 years	1 years 2 months	T1D, AITD, cytopenias	*CTLA4* p.(Tyr60Asn)	0.666	36.5
4	Male	Deceased	11 months	T1D, AITD, short stature, cytopenias	*STAT3* p.(Phe715Leu)	0.645	27.2
5	Female	7 years	1 year 10 months	T1D, CD, serious eczema	-	0.516	2.4
6	Female	14 years	10 years	T1D, AITD, CD	-	0.625	19.9
7	Male	15 years	14 years	T1D, autoimmune hepatitis	-	0.652	29.6
8	Male	18 years	3 years	T1D, AITD, immune enteropathy	-	0.653	30.3
9	Female	11 years	3 years	T1D, AITD, CD	-	0.661	34.7
10	Male	16 years	8 years	T1D, AITD, CD	-	0.668	37.2
11	Female	10 years	1 year	T1D, AITD, short stature, immune joint disease	-	0.676	41.9
12	Female	13 years	10 years	T1D, AITD, CD	-	0.684	45.4
13	Female	18 years	2 years	T1D, AITD, CD	-	0.695	51
14	Male	18 years	1 year 1 month	T1D, IBD	-	0.709	55.6
15	Male	7 years	1year 4 months	T1D, AITD, eczema, early onset IBD	-	0.716	58.9
16	Female	7 years	2 years	T1D, AITD, CD	-	0.795	94.1
17	Female	17 years	11 years	T1D, AITD, CD	-	0.816	97.8
18	Male	7 years	1 year 7 months	T1D, serious ITP	-	0.837	99

Characteristics of 18 patients examined for monogenic form of autoimmune diabetes.





Workflow of the study. T1D (Type 1 diabetes); AITD (Autoimmune thyroiditis); CD (Coeliac disease).

Results: All four clinically highly suspected patients carried the causal variants in selected genes: One patient was diagnosed with IPEX syndrome with variant in the *FOXP3* gene (p.Ser241Pro). Second patient manifested with recurrent episodes of immune thrombocytopenic purpura (ITP), autoimmune haemolytic anemia (AIHA) and T1D. He presented total alopecia and optic nerve neuritis. His younger brother manifested with T1D at age 1 year. Later on, he also developed ITP and AIHA. They carried a heterozygous variant in the *CTLA4* gene (p.Tyr60Asn). The fourth patient was diagnosed with multiple early-onset autoimmune conditions due to the activation mutation in the *STAT3* gene (p.Pro715Leu).
No other causal variant in selected genes was found in remaining 14 highly suspicious patients. These four children have the T1D-GRS below 40th centile. Twelve of all investigated patients had the T1D-GRS below the 50th centile and seven even below the 30th centile suggesting high likelyhood of a monogenic cause of diabetes in these children, with the possibility of identification of causative variants in the genes for regulation of immune system in future studies.

In conclusion, we found four of the 18 patients with genetically confirmed monogenic form of T1D representing 22% in our specific cohort with severe T1D associated multiple autoimmunity. The T1D-GRS is a novel tool that can be helpful for discrimination between monogenic and polygenic forms of diabetes and combined with analysis by WES will be useful for searching genes causing monogenic T1D.

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