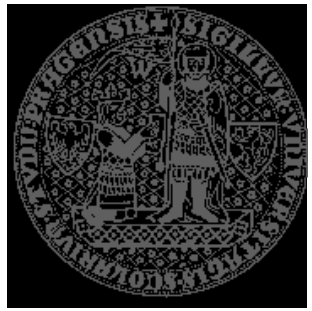
Immunological investigation in Czech patients with autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED).



A.Šedivá, [1]J.Lébl , [1]D.Čiháková

Institute of Immunology,
Second Faculty of Medicine and University Hospital Motol,

[1]Department of Pediatrics,
Third Faculty of Medicine and University Hospital Královské Vinohrady,

Charles University, Prague, Czech Republic

APECED

Autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED), also known as autoimmune polyglandular syndrome type 1 (APS1), is a rare autosomal recessively inherited disease affecting endocrine glands caused by the mutations of the gene known as autoimmune regulator – AIRE.

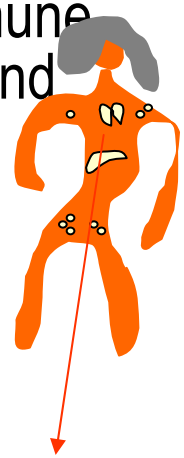
chromosome 21
q22.3

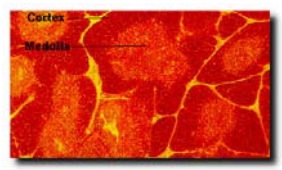
AIRE

The AIRE protein functions as a transcription factor or as a transcriptional co-activator that might have an important role in the control of immune recognition.

AIRE is expressed in the thymus, lymph node and fetal liver , tissues that have important roles in the maturation of the immune system. AIRE expression was described also in monocytes and dendritic cells.

The impaired expression of *AIRE* in the thymic medulla and antigen presenting cells may cause the breakdown of the processes of tolerance and induction of autoimmunity.

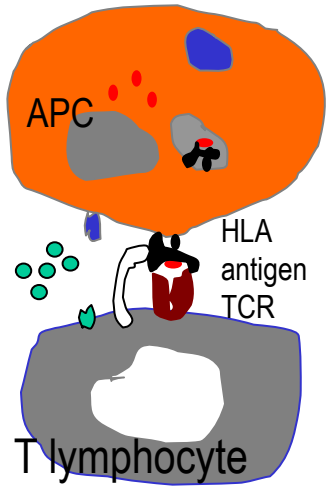




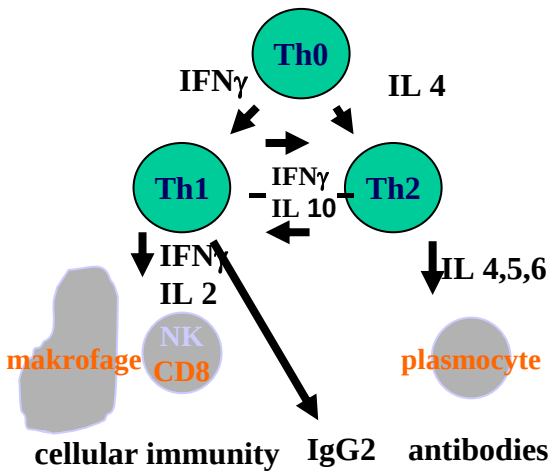
APECED and autoimmunity

The process of autoimmunity in APECED may be the result of impaired processes of both central and peripheral tolerance –

defect of expression of organ specific antigens in the thymus



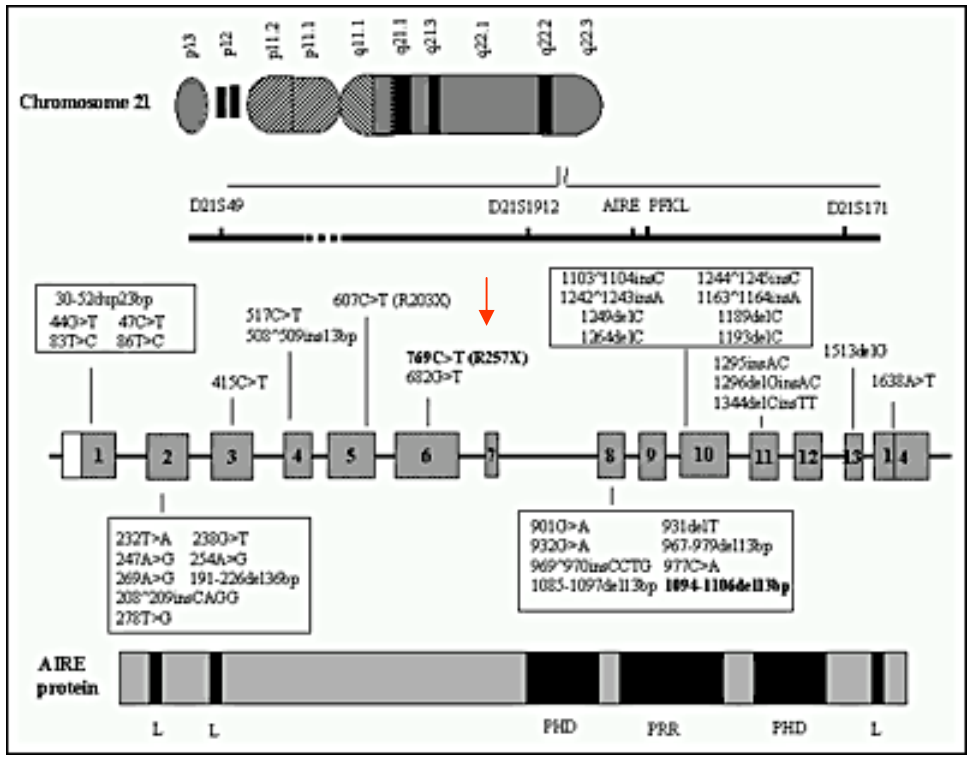
The mutations leading to APECED and defective AIRE production may contribute to the shift of immune balance towards preferential Th2 response.



genetic analysis of 24 APECED patients of Eastern and Central European origins

From 48 analysed APECED chromosomes eight mutations were detected, four (T16M, W78R, delE2-4, 156-179ins23bp) of which being novel.

The most prevalent reason for APECED in these populations was the ↓ occurrence of R257X (36 chromosomes) that has been described earlier as common and reccurent mutation in several other populations.



Analysis of autoantibodies of 24 APECED patients of Eastern and Central European origins

The analysis of humoral immunity to steroidogenic P450 cytochromes by immunoblotting of *E. coli* expressed antigens showed that 65%, 55% and 55% of the Eastern and Central European APECED patients had autoantibodies to P450c17, P450c21 and P450scc, respectively.

Czech Republic, Hungary, Slovenia, Croatia, Serbia, Russia.

Patients and methods

Four girls with APS1 diagnosed in Czech Republic, their siblings, parents and aged matched controls were included to the study of immune functions. The age of girls was 7,12, 17 and 22 years.

Patient	Age (years)	Genotype (mutations in AIRE gene)	Clinical symptoms
1	17	R257X / R257X	HP, MC, AD, CH
2	22	R257X / R257X	HP, MC, AD, AL, KC, CL
3	12	not known	HP, MC, AD, AL, CH, VI, SJ
4	7	R257X / W78R	HP, AD, AL

Age, genotype and clinical symptoms in four female patients with APECED.
HP - hypoparathyroidism; MC - mucocutaneous candidiasis; AD - Addison disease; VI - vitiligo; AL - alopecia; ED - ectodermal dystrophy; KC - keratoconjuctivitis; HT - hypothyroidism; CH - chronic active hepatitis; CL – cholelithiasis; SJ – Sjögren syndrome.

The immune parameters included immunoglobulins, panel of autoantibodies, cellular immunity and levels of cytokines IFNγ, IL-4 and IL-10 measured in the supernatants of PHA and LPS stimulated lymphocyte cultures.

Autoantibodies:

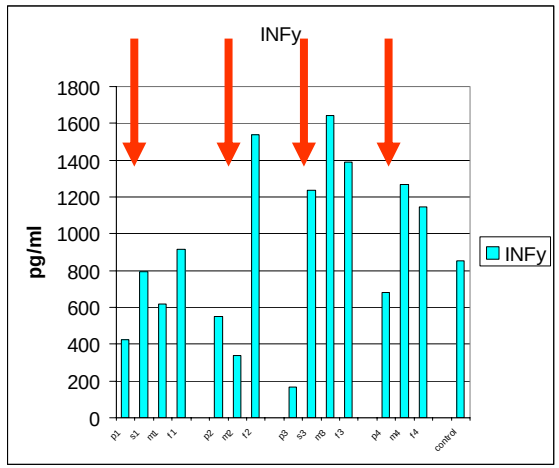
ANA, ANCA, ENA, AMA, ASMA, LKM, GPCA, EMA, anti-gliadin.

Results of immunological investigation in APECED patients

IFNγ

Low values were found in all affected girls, indicating that APECED can be connected with low production of this cytokine and possible shift to Th2 type of immune reactivity.

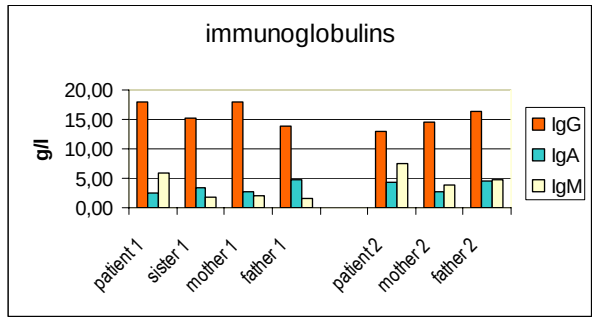
The significance of the difference between the girls with APECED and controls was tested using Man-Whitney test. The result showed clear trend, but did not reach statistical significance. The borderline p-value is surely influenced by low number of patients.

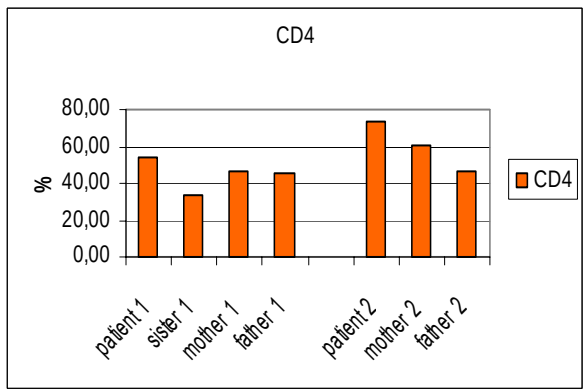


	IFNγ		Man-Whitney test
	mean (pg/ml)	standard deviation	p-value
patients (4)	455	191	0.0559
controls (14)	910	406	

Results of immunological investigation in APECED patients

IgM, CD4+ T lymphocytes

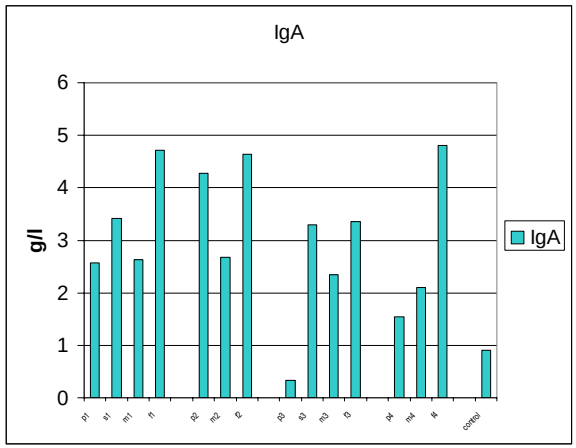


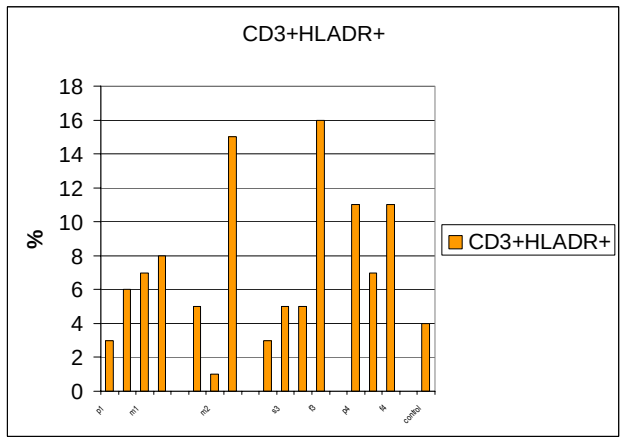


Besides low IFNγ values, the patients did not follow unified immunological pattern and present themselves with individual values. However, 2 girls with homozygous mutations R257X show very similar results with marked elevation of IgM and high numbers of CD3+CD4+ lymphocytes.

The changes in heterozygous members of the affected families

Interestingly, all fathers, but not sick girls, had elevated levels of IgA and activated T lymphocytes according to the number of CD3 HLA DR+ lymphocytes.





In 2 girls we found the positivity of autoantibodies, once against gastric parietal cells, the result shared with her mother, second time against smooth muscle.

Conclusion

- Low IFNγ production was found in all investigated APECED patients.
- The frequency of pathological immune parameters among heterozygous members of affected families is noteworthy.
- The details of the development of organ specific autoimmunity are still to be investigated.