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Polymorphism of innate immunity genes in juvenile arthritis

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Juvenile arthritis is one of the most common chronic diseases of childhood, with an estimated prevalence of 1 per 1,000 children. The term juvenile idiopathic arthritis (JIA) defines a heterogeneous collection of inflammatory arthritis of unknown etiology with onset prior to age 16 years and a minimum duration of 6 weeks, following the exclusion of other known causes of synovitis (ACR,2019).

Genetic studies in recent years have shown a high degree of association of autoimmune diseases with primary immunodeficiency (PID).

Schmidt RE, Grimbacher B, Nat Rev Rheumatol.(2017).

Most patients with autoimmune reactions have changes in immune genes that mask the underlying disease and affect its course.

Mazzone, R., Zwergel, C., Artico, M., Clin Epigenet 11, 34 (2019).

The analysis of the French National Register of Primary Immunodeficiency (CEREDIH) shows that individual autoimmune diseases and autoinflammatory syndromes were observed in 24.5% of 3687 patients with primary immunodeficiency during the entire life period.

Fischer A., Provot J., J Allergy Clin Immunol (2017).

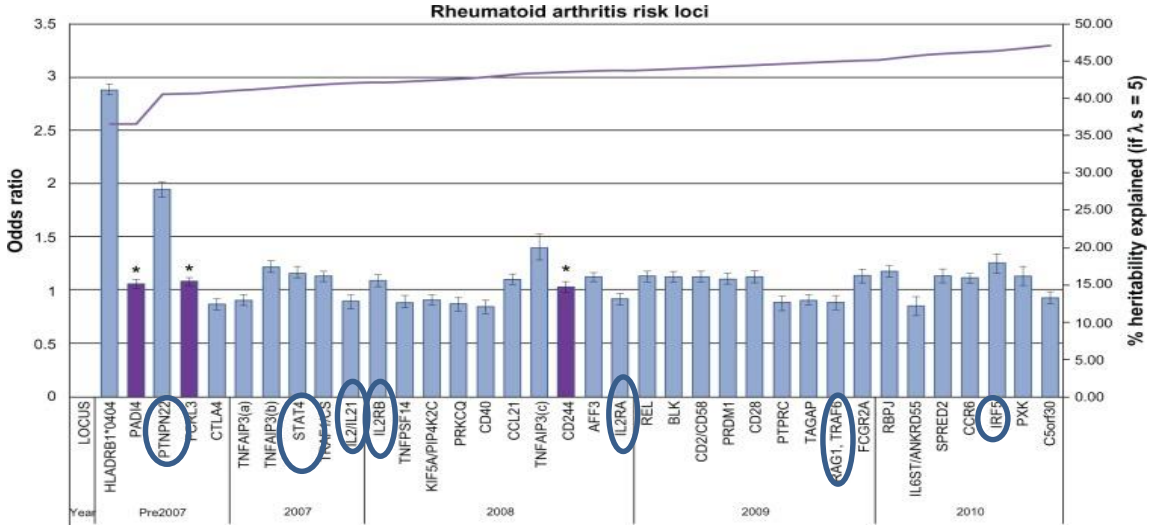
The role of heredity in the initiation of autoimmune reactions in JIA

The increase in the prevalence of familial risk to 40-50% among seropositive arthritis (especially in first degree relatives) is determined by the presence of a set of allelic genes in the HLA-DRB1 locus; the expression of these genes results in production of proteins on the membrane of immune cells containing "shared epitope".

HLA genes determine only 17% to 56% of heredity, so the search for candidate genes is constantly expanding.

J. A. Hollenbach, T. L. Bugawan. Arthritis and rheumatism, (2010)

Loci of genetic risk of rheumatoid arthritis



The most significant loci (40% of the total genetic risk): human leukocyte antigen (HLA-DRB1), PTPN22, signal transducer and activator of transcription 4 (STAT4). More than 50% of the genetic risk for RA remains unknown.

Kate McAllister, Stephen Eyre, and Gisela Orozco /Genetics of rheumatoid arthritis: GWAS and beyond Open Access Rheumatol. 2011

Institute of Pediatrics, Obstetrics and Gynecology named after acad. O.M. Lukyanova of the NAMS of Ukraine, SI, Kyiv

Aim: to study changes in nucleotide sequences in genes of innate immunity in JIA in order to improve diagnostics and develop approaches to their individualized therapy.

Methods: A high-performance panel exomic new generation sequencing (NGS), based on the decoding of fragments of the DNA molecule, using the Illumina's HiSeq device (manufactured in the USA) in the Invitae laboratory (San Francisco, USA). Sanger sequencing is used for each change in the nucleotide sequence.

Coding sequences of 207 known genes of primary immunodeficiency (30 autoinflammatory) are subjected to target enrichment.

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General characteristics of patients with JIA

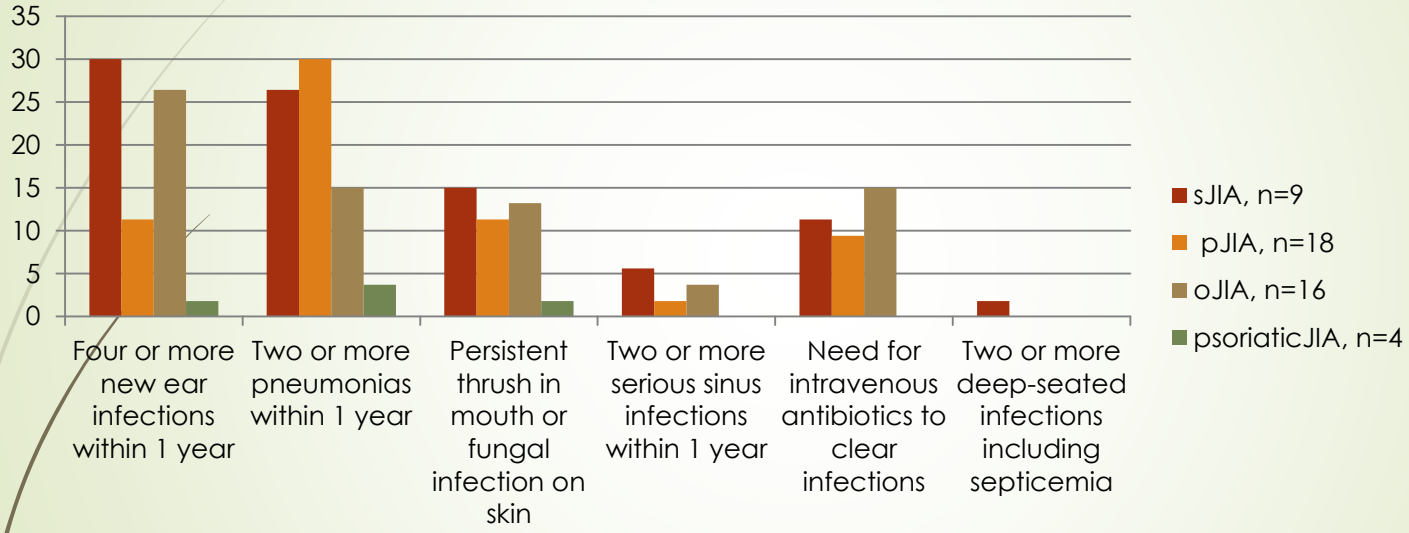
Indicator	Indicator values
Number of patients, abs.number	53
Age, years Me	9 (1-17)
Duration of illness, years	(4,3±3,3)
Gender (boys/girls), abs.number	22/31
JIA subtype, abs.number (%): Oligoarthritis JIA Polyarthritis JIA Systemic JIA Psoriatic JIA	 22 (41,5) 18 (33,9) 9 (16,9) 4 (7,54)
ANA (+), abs.n. (%)	30 (56,6)
ANA (-), abs.n. (%)	23 (43,3)
HLA-B27 (+), abs.n. (%)	16 (30,1)
HLA-B27 (-), abs. n. (%)	37 (69,8)
A-CCP (-)	53 (100)

Frequency of immunodeficiency signs in JIA

Immunodeficiency signs	sJIA, n=9	pJIA, n=18	oJIA, n=16	psoriaticJIA, n=4
Four or more new ear infections within 1 year	30	11.3	26.4	1.8
Two or more pneumonias within 1 year	26.4	30.0	15.0	3.7
Persistent thrush in mouth or fungal infection on skin	15.0	11.3	13.2	1.8
Two or more serious sinus infections within 1 year	5.6	1.8	3.7	0
Need for intravenous antibiotics to clear infections	11.3	9.4	15	0
Two or more deep-seated infections including septicemia	1.8	0	0	0

%

Frequency of immunodeficiency signs in JIA



Results

Genes of autoimmunity

Patogenic mutation:

IL7R,WFS1,SP110
RMRP,TREX1, MUTYH

Variant(s) of Uncertain Significance identified:

ATM,RTEL1, CASP10, IL21R, LPIN2, NFKB2, IRAK4,RNASEH2A, STAT3,JAK3,IL12RB1,IL21R,PTPRC, STAT5B,PRKDC, CASP8 ,IRF7,SF2RA,IL10RA,RNASEH2A, CARD14 , ACP5, RAG1 ,SLC29A3, IL7R, CARD11,CASP10, IL10RA, CD79B, TREX1,PSTPIP1.

Genes of autoinflammation

Increased Risk Allele identified:

NOD2

Variant(s) of Uncertain Significance identified:

ADA2,ELANE,MEFV,NLRP12 , PSTPIP1, LPIN2

Pathogenic mutations in PID genes were detected in 13,2 % children (IL7R, RMRP, TREX1, SP110, MUTYH, WFS1).

18,8% of patients with JIA had an increased risk in the NOD2 gene.

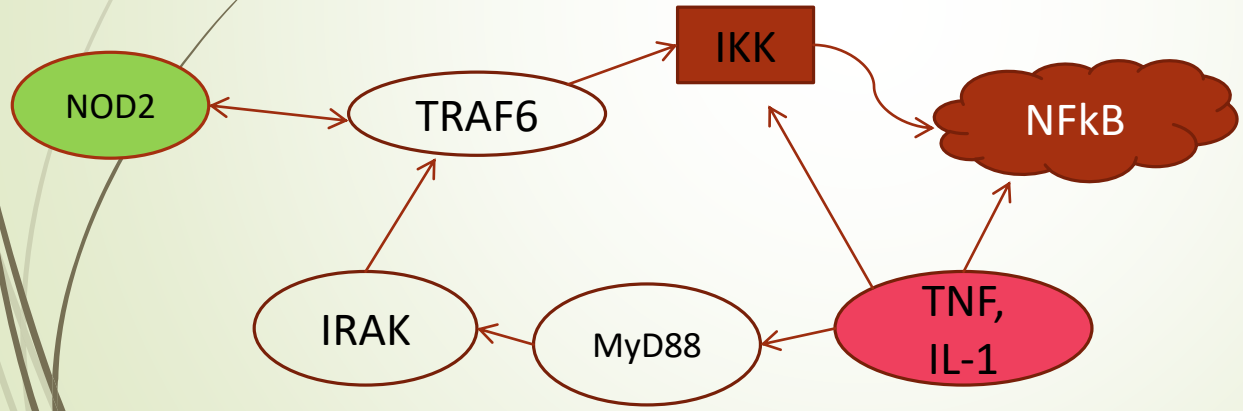
In all patients identified variants of uncertain significance in: ATM, RTEL1, CASP10, CARD11, JAK3, IL21R, IL10RA, STAT3, NFKB2, IRAK4.

14 patients (26.4%) with JIA have changes in the nucleotide sequence in the autoinflammatory genes (NOD2, ADA2, ELANE, MEFV,NLRP12, PSTPIP1, LPIN2)

NOD2 polymorphism in JIA

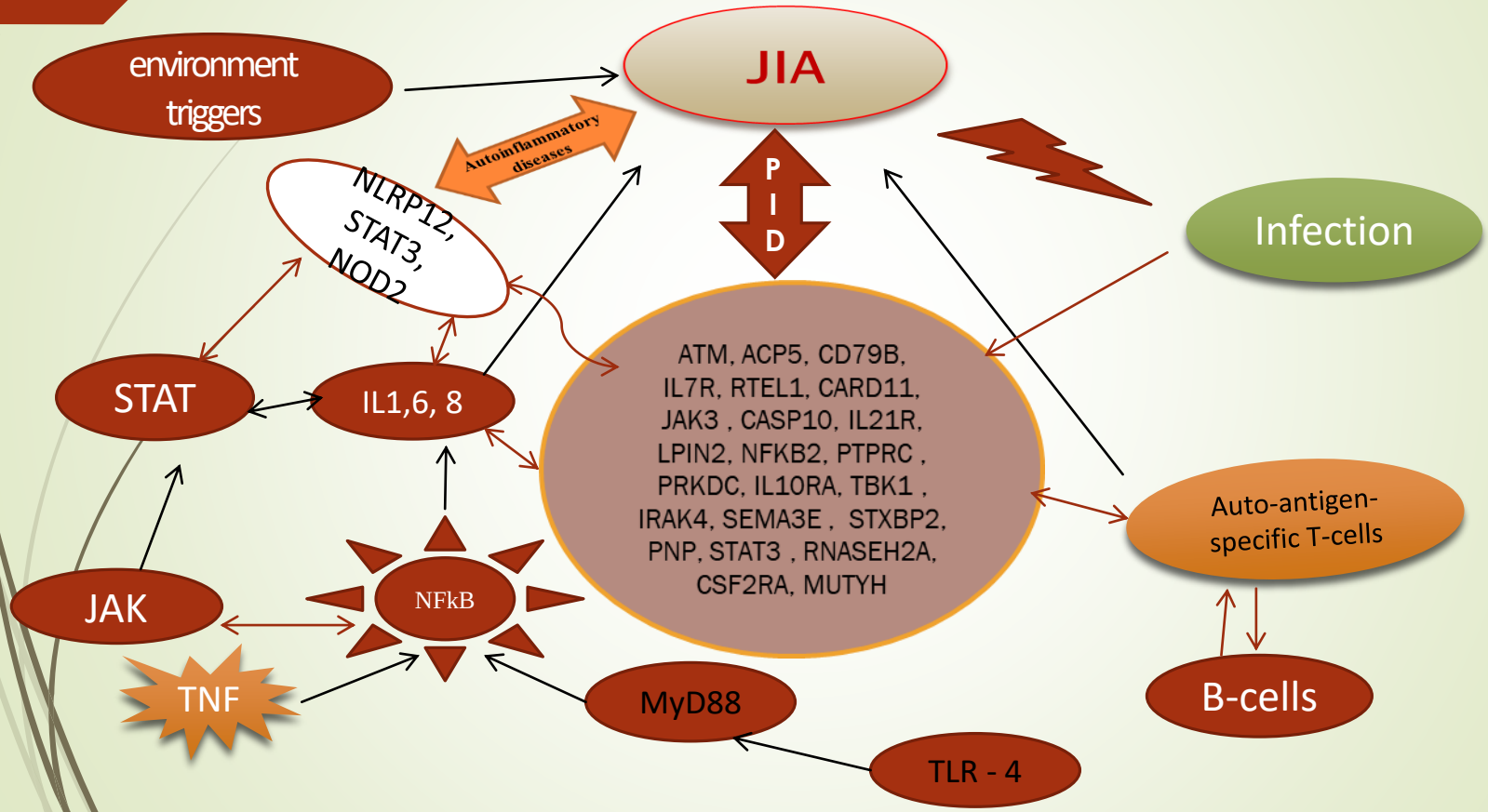
In the population, 1-3% of the population has a polymorphism of the NOD 2 gene: c.2104C> T (p.Arg702Trp), c.2722G> C (p.Gly908Arg) and c.3019dupC (p.Leu1007Profs * 2), which increases the risk of clinical manifestation in a heterozygous state by 2-4 times and in a homozygous state by 7-9 times.

Franca R, Vieira SM, Talbot J, et al. Expression and activity of NOD1 and NOD2/RIPK2 signalling in mononuclear cells from patients with rheumatoid arthritis. Scand J Rheumatol. 2016;45(1):8-12.



18,8% of patients with JIA had an increased risk in the NOD2 gene, що визначає статистично вірогідну різницю з популяційною частотою [OR=11.395, CI 2.395-54.227].

Genetic and immunological triggers of JIA



Conclusions

1. Immunodeficiency signs are more common in the anamnesis of children with systemic and polyarticular subtypes of JIA in 30%, which determines the reasonability of examining this population to exclude PID.
2. 92% of children have PID gene polymorphism, which must be taken into account in the diagnosis to choose the target therapy.
3. Pathogenic mutations in PID genes were detected in 13,2 % children (IL7R, RMRP, TREX1, SP110, MUTYH, WFS1).
4. Screening for PID before starting immunosuppressive treatment for JIA will help in establishing the diagnosis and avoiding the development of severe infectious complications