Is it time for the International League of Associations for Rheumatology juvenile idiopathic arthritis 'class'ification to graduate?

"…in order to avoid classifying children with uniform genetic and phenotypic features into an amorphous 'undifferentiated' classification, future modifications of the classification schema should accommodate the relevance of these biomarkers."

KEYWORDS: classification ■ juvenile idiopathic arthritis ■ rheumatoid arthritis

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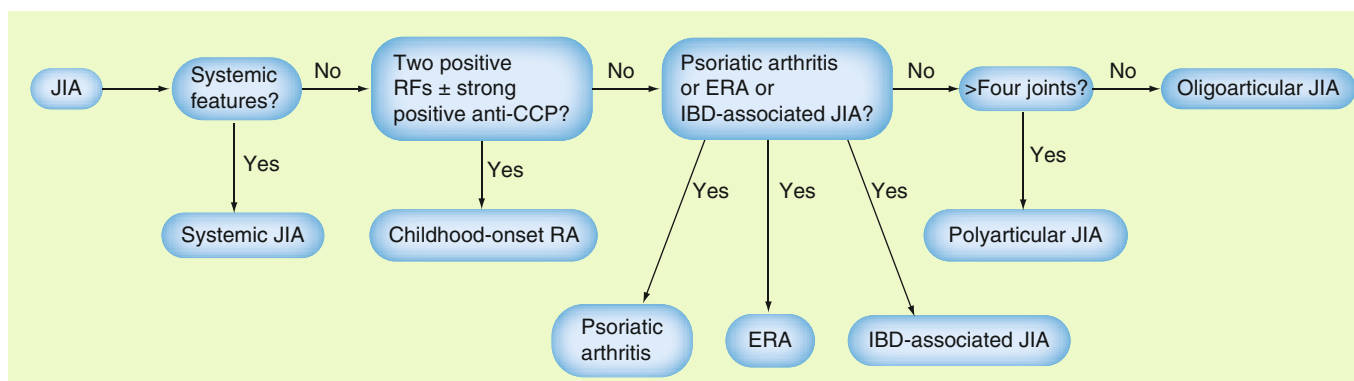Department of Human Genetics, Emory
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Under the organization of the International League of Associations for Rheumatology (ILAR), the widely applied current classification system for juvenile idiopathic arthritis (JIA) was established in 1995 [1] and revised in 1997 [2] and 2001 [3]. The main goal of this new classification of childhood arthritides was to develop criteria that would identify homogeneous groups of children with chronic arthritis to facilitate research in immunogenetics, epidemiology, outcomes and therapy. There are seven categories in this schema: systemic arthritis; oligoarthritis, persistent or extended; polyarthritis rheumatoid factor (RF)⁻; polyarthritis RF⁺; psoriatic arthritis; enthesitis-related arthritis (ERA); and undifferentiated arthritis. Although the ILAR classification has performed relatively well compared with previous classifications of JIA, the exclusion criteria designed to keep each category pristine, have been controversial and for some subgroups appear to be too rigid. As a result, many patients with otherwise homogeneous features are assigned to the 'undifferentiated arthritis' set, which becomes a mixture of chronic arthritides that lack inclusion criteria for other categories. This subset, by virtue if it's lack of homogeneity, is least likely to lend itself to research and therapeutic scrutiny.

Burgos-Vargas *et al.* [4] and Colbert [5] have pointed out in detail that the criteria for ERA are skewed toward the undifferentiated forms of spondyloarthritis, which are common presenting features of anklylosing spondylitis (AS) in childhood and away from those forms presenting with early axial disease or coexisting conditions, such as inflammatory bowel disease. By contrast, the European Spondyloarthritis Study Group [6] and the criteria of Amor *et al.* [7], which are used in adults with no lower age limit, are more inclusive of these common features. With regards to the ILAR ERA subgroup, only 56.7% of the children with HLA-B27 in a study by Cleary *et al.* [8] and 41.9% in a study by Hofer *et al.* [9] remained in the ERA category after considering exclusion criteria.

We have recently shown that the ILAR classification of JIA also excludes a large number of children with RF⁺ or positive antibodies to cyclic citrillinated peptide (CCP) from the RF⁺ polyarthritis category. We analyzed 56 children with RF⁺ or CCP⁺ JIA comparing the ILAR criteria with the 2010 ACR/European League Against Rheumatism criteria for the diagnosis of rheumatoid arthritis (RA) [10]. Only 34 (61%) met the ILAR criteria for RF⁺ polyarthritis. Those excluded were assigned to other groups: RF⁻ polyarthritis, persistent or extended oligoarthritis and undifferentiated arthritis, the latter accounting for 45% of those excluded. By contrast, 89% met ACR/European League Against Rheumatism criteria for RA. Generally, children with RF⁺ polyarthritis are thought to represent the development of RA during childhood. Our RF⁺ patients shared demographic and disease characteristics regardless of which ILAR category they were assigned. This suggests a homogenous phenotype more closely aligned with adult RA in disease severity. A meta-analysis of 86 studies found that for the diagnosis of RA, the sensitivity and specificity of anti-CCP antibodies was 67 and 95%, respectively; for RF these values were 69 and 85%, respectively [11]. Furthermore, anti-CCP antibody status is not considered in the ILAR classification of JIA. However, anti-CCP antibodies are characteristic biomarkers of seropositive RA, and given its value in the current classification schema of adult RA, we propose that anti-CCP positivity should be considered as a possible index of more aggressive and chronic disease in children warranting enhanced levels of monitoring and therapy.

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Figure 1. Proposed revision to the current International League of Associations for Rheumatology classification scheme.
It prioritizes positive serologies over family history and joint count. In our proposed classification scheme, childhood-onset RA does not require five joints as is currently stipulated in the International League of Associations for Rheumatology 2004 criteria. In our scheme, the joint count is irrelevant other than to differentiate between oligoarticular JIA and polyarticular JIA, similar to the way in which the current classification scheme does not use joint count in the diagnosis of systemic JIA, ERA and psoriatic JIA. This also takes into consideration the substantial genetic similarities between RF⁻ polyarthritis and oligoarthritis [18].
ERA: Enthesitis-related arthritis; IBD: Inflammatory bowel disease; JIA: Juvenile idiopathic arthritis; RA: Rheumatoid arthritis; RF: Rheumatoid factor.

Several of the categories of JIA represent the childhood onset of inflammatory arthropathies such as RA, AS and psoriatic arthritis that are typically seen in adults. Recent genome-wide studies and high-density genetic mapping studies in JIA, RA, AS, inflammatory bowel disease and psoriasis indicate that these clinically distinct sets of phenotypes share common susceptibility factors. For instance, *PTPN22*, *IL2* and *IL2RA*, among others, predispose to RA and JIA, while *IL23R* is associated with inflammatory bowel disease, AS and psoriasis [12–16]. The exclusivity of the ILAR JIA classification does not take into account these shared susceptibilities. We, and others, feel that in order to avoid classifying children with uniform genetic and phenotypic features into an amorphous 'undifferentiated' classification, future modifications of the classification schema should accommodate the relevance of these biomarkers [17]. A proposed classification is illustrated in FIGURE 1, and is suggested for discussion as a means of balancing the diversity and homogeneity of these categories of chronic childhood arthritis.

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