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Consensus proposal for Taxonomy and Definition of the Autoinflammatory Diseases (AIDs) - A Delphi Study

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Abstract

Background: Autoinflammatory diseases (AIDs) are a relatively new family of disorders defined about 19 years ago. Some of them are hereditary and some are not.The names given to these diseases do not follow any systematic guidelines and sometimes the same disorder carries several names.

Aims: The aim of this study is to refine the definition of the autoinflammatory diseases and to provide some conventions for their naming. We have focused our attention mainly on monogenetic AIDs.

Methods: Delphi technique which enables consensus among a group of experts through Internet and mail communication and questionnaires - was employed. After achieving 100% consensus among 6 members of a steering committee, the questionnaire containing the AID definitions and the agreed-upon conventions, were sent to 26 physicians and researchers working in the field of AIDs in order to gain broader support for the committee's proposals.

Results: The committee proposed the following definition for AIDs "Autoinflammatory diseases are clinical disorders caused by defect(s) or dysregulation of the innate immune system, characterized by recurrent or continuous inflammation (elevated acute phase reactants-APR) and the lack of a *primary* pathogenic role for the adaptive immune system (autoreactive T-cells or autoantibody production)". Several rules were defined for guiding the naming of these diseases among which are: abandoning eponyms and preferring the name of the gene over its encoded protein.

Conclusions: The new definition for AIDs allows inclusion of clinical disorders mainly associated with defects in the innate immune system. The new conventions propose names with clinical meaning and in some cases even clues for treatment.

Taxonomy is the science of naming. It is relevant to all fields of biology in which we name plants, animals, objects and diseases. In medicine, naming of diseases or syndromes has a special importance since it can give some clue about the nature of the clinical condition, its clinical features, pathogenesis and sometimes even an approach to treatment. Naming is also important for accurate and effective communication among different health disciplines. However, medical disorders have not been named in a standard way [1]. Physicians, who treat patients with a particular disorder or face a new clinical condition, are often the first to propose a name for the disease. Expert working groups may later revise the names to improve their usefulness.

Names of medical disorders are often derived from one or a combination of the following sources: genetic basis or biochemical defect; geographic spread; or by eponyms. The main drawback of many names is the lack of a clinical meaning that could help the novice to understand the origin of the disease or recognize its clinical characteristics .

The autoinflammatory diseases (AIDs) are a group of medical disorders, derived from defects or dysregulation of the innate immune system [2]. This family of diseases was established in 1999 following the identification of the genes underlying two recurrent fever syndromes: familial Mediterranean fever (FMF) [3,4] and TNF-receptor-associated periodic syndrome (TRAPS) [5]. Over the last 18 years, more and more diseases have been classified amongst this group of disorders, some of which may not fit well with the classical definition of the AIDs. Moreover, many of them were given names with no systematic guidelines or rules. In some cases, the same disease carries several names (Table 1) [6-50]. This has led to a chaotic situation in naming these clinical disorders and has called for a better standardization of this field. This need is accentuated by recent progress in next generation sequencing techniques (NGS), which have led to an increasing capability to identify new genes and new syndromes, expanding the spectrum of AIDs.

Indeed, following the International Society for Systemic Autoinflammatory Diseases (ISSAID) meeting in Lausanne, in 2013, a mandate was given to one of us (E B-C) to undertake a preliminary consensus based exercise for the following aims: a. to refine the definition of the "autoinflammatory diseases". b. to provide some rules and new proposals for naming this current group of clinical conditions and those that will be identified in the future.

Methods

In order to find the different definitions proposed for AIDs over the years, we searched the MEDLINE/PubMed Central® (PMC) from 1998 to January 2016, using the MESH search term: “autoinflammatory diseases” (supplementary Figure S1). In order to find the names used for each AID, we took one of their current names as depicted in Table 1 and searched for papers where they were first reported. Then, we searched for reviews on these items to find additional synonymous names Table 1 is based on a list of AIDs published by one of the authors (IT) [51], properly integrated and updated during the consensus process and finally approved by all the steering committee members. It focused - mainly - on monogenic disorders.

For choosing the best definition for AIDs and the most appropriate name for each AID, we have used the Delphi technique, which enables consensus among a group of experts through mail communication [52]. The Delphi method is essentially a series of questionnaires involving several steps, each of which is based on the results of the previous step. The process stops when consensus of at least 80% of the participants on each item is reached. [53]

An *ad hoc* steering committee of 6 clinicians and researchers from 6 different countries who are working in the field of autoinflammation was established.

The first Delphi questionnaire was built through sending broad and open-ended questions in order to elicit different opinions from the panelists about the current definitions and names of AIDs.

Once received, the replies from the panelists were analyzed to generate a series of statements that were employed as the basis for follow up questionnaires that were sent back to the individual participants. In each subsequent questionnaire, the panelists were also provided with the overall results (responses) of the previous questionnaire from all the members. After achieving 100% consensus among the steering committee members, the questionnaire containing the AID definitions and the agreed-upon names of AIDs were sent to 26 physicians and researchers working in the field of AIDs around the world. They were identified in the Paediatric Rheumatology International Trials Organization (PRINTO) mailing list through their high active participation in the Eurofever registry [54, 55]. The aim of this step was to gain broader support for the committee's proposals and to consider changes once a name was rejected by or was not acceptable to more than 80% of the participants of the large group of AIDs experts. Delphi survey implementation was conducted by PRINTO [56].

Results

AIDs proposed definition

The literature review disclosed 536 papers of which only 7 specifically dealt with the definitions of AIDs [5, 57- 62] (supplementary Figure S1). The first definition for AIDs was proposed by the NIH group in 1999 [5]. This definition was as follows: "The autoinflammatory syndromes are systemic disorders characterized by apparently unprovoked inflammation in the absence of high-titer autoantibodies or antigen-specific T lymphocytes". This definition was based mainly upon the two diseases whose related genes had then been identified: FMF and TRAPS [3- 5]. Since in both diseases the flares appeared mostly spontaneous, the definition included the word "unprovoked". The definition stresses the lack of involvement of the adaptive immune system in these disorders, since no autoantibodies or autoreactive T-cells were involved.

Seven years later McGonagle and McDermott suggested another definition: "AIDs are characterized by self-directed inflammation, whereby local factors at sites predisposed to disease lead to activation of innate immune cells, including macrophages and neutrophils, with resultant target tissue damage. For example, disturbed homeostasis of canonical cytokine cascades (as in the periodic fevers), aberrant bacterial sensing (as in Crohn's disease), and tissue micro-damage predispose one to site-specific inflammation that is independent of adaptive immune responses" [57]. The authors proposed that immunological diseases ought to be conceived as a continuum with “pure monogenic autoinflammatory diseases” at one end and “pure monogenic autoimmune diseases” at the other. This definition is relatively complex, but explicitly invokes innate immunity and widens the spectrum of AIDs.

Later, several other definition or refinement were proposed [58-61]. In a recent study, de Jesus et al. provide an outstanding classification of AIDs strictly based on their pathophysiology [62]. However, the authors do not propose a new definition for the AIDs.

Given the proliferation of AID definitions, with sometimes conflicting concepts, the steering committee agreed to adopt the first and original definition with minor modifications: "Autoinflammatory diseases are clinical disorders caused by defect(s) or dysregulation of the innate immune system, characterized by recurrent or

continuous inflammation (elevated - APR) and the lack of a *primary* pathogenic role for the adaptive immune system (autoreactive T-cells or autoantibody production)."

This definition emphasizes the essential fact that the disorders are caused by defects in the innate immune system and are continuous or recurrent. The word "unprovoked" has been deleted since in many cases there is a trigger for the acute flares.

The steering committee is aware that diseases such as PLCG2-associated antibody deficiency and immune dysregulation (PLAID) or Heme - oxidised IRP2 ubiquitin ligase1 (HOIL-1) deficiency, traditionally included among the AIDs, will not be part of this group, because they may contain components of the adaptive immune system such as autoantibodies [63]. The "Interferonopathies" include some disorders also manifesting autoantibodies. However, the consensus seemed to be that for disorders like Aicardi-Goutières Syndrome (AGS) in which nucleic acid sensing is primarily intracellular, autoantibodies usually play a minor role in disease pathogenesis, and thus the autoinflammatory designation may still be appropriate. In their recent review Rodero and Crow propose that "type I interferonopathies can reasonably be considered as autoinflammatory in origin, with 'spill-over' into autoimmunity in some cases" [64]. The group of "typical" **autoimmune diseases** includes disorders affecting primarily or only the adaptive system such as systemic lupus erythematosus (SLE), Hashimoto thyroiditis, DNAse deficiencies and autoimmune lymphoproliferative syndrome (ALPS).

AIDs proposed nomenclature

The current names for AIDs bring several problems and issues, which called for a new approach and nomenclature modification; many AIDs possess more than a single name (FMF - 7 different names, TRAPS - 3, etc) (Table 1 and Supplementary Table S1); different clinical presentations are associated with similar sequence alterations in the same gene eg. Muckle-Wells syndrome(MWS), familial cold autoinflammatory syndrome (FCAS) and Neonatal onset multisystem inflammatory disease (NOMID) are associated with *NLRP3* gene whereas FMF and pyrin-associated autoinflammation with neutrophilic dermatosis (PAAND) are associated with *MEFV gene*. In addition discussion arose about several topics briefly summarized herein: In naming AIDs should we use the name of the gene or that of the encoded protein (*MEFV* or pyrin)? Should we include typical clinical features or just genetic attributes? Should historical names be retained?

Following more than 6 cycles of Delphi questionnaires and oral discussions among the 6 members of the steering committee with further involvement of the 26 AIDs experts around the world - a consensus of at least 80% was reached for the nomenclature of the diseases shown in Tables 1 and 2.

General conventions (Table 3)

The proposed names for AIDs have been established according to the rules and suggestions outlined in Table 3.

In many diseases the course of the disease is episodic with frequent attacks and attack-free intervals. When the frequency of the attacks is relatively regular (as is the case with Periodic fever, aphthous stomatitis, pharyngitis and adenitis (PFAPA) and sometimes with mevalonate kinase deficiency (MKD) we preferred the term "periodic". When the attacks do not have a regular pattern, we suggested the word "recurrent".

In the past, both terms, “periodic” and “recurrent”, have been used interchangeably but now the term "periodic” remained in the names of 3 conditions only; Cryopyrin-associated periodic fever syndrome (CAPS),TRAPS and PFAPA. In TRAPS, we decided to keep the original name "periodic", although its flares are recurrent rather than periodic. In CAPS, we propose a new name (NLRP3-AID) which does not contain the word “periodic since the attacks are not periodic”. Thus, we strongly suggest using the more appropriate terms in naming disorders in the future.

As a general rule, we tried to use names containing etio-pathological (genetic) features of the disease and where appropriate or possible, to add a significant clinical characteristic of the syndrome. Thus, we left the name TRAPS without change, since it consists of its genetic etiology (mutations in *TNFRSF1A* gene) and characteristic clinical features [periodic (recurrent) fever]. On the other hand, the name hyper IgD syndrome (HIDS) was abandoned since it is an absolutely inaccurate name: serum IgD is not always elevated in these patients while it may be elevated in other AIDs. Therefore, this name was replaced by MKD based upon our knowledge of the gene involved, mevalonate kinase (*MVK*). In this way, a physician or researcher who approaches these names for the first time may have immediately a basic understanding of the disorder and sometimes even a clue to the potential treatment.

In cases where the choice was between using the name of the gene associated with the disease or the protein encoded by the gene, we preferred the name of the gene

over that of the protein unless the former was meaningless. A typical example is the choice of *NLRP3* gene over cryopyrin despite the tendency of some clinicians to stay with the former term CAPS. Fortunately, in many cases the name of the gene and the encoded protein are the same (MK, NOD2) making the choice easier. However, this was not the case with the *MEFV* gene and pyrin where the name of the protein was chosen, as will be discussed later.

In our proposals for new taxonomy of AIDs, we tried to avoid the use of names of persons (such as Nakajo Nishimura syndrome) or geographical distribution of the disease (such as Guadeloupe fever) or names with unusual meaning (such as "Cherubism").

Specific names (Table 1 and Supplementary Table S1)

In the case of CAPS – which encompasses three clinical entities (FCAS, MWS, NOMID/CINCA), the committee has proposed using a single name; *NLRP3*-associated autoinflammatory disease (*NLRP3*-AID). Since the various disorders reflect different levels of phenotypic severity of the same disease, it was suggested to add the adjectives: mild, moderate, and severe phenotypes, instead of using the historical names FCAS, MWS and CINCA/NOMID, respectively.

In familial cold autoinflammatory syndrome 2 (FCAS2) (Guadeloupe fever), different families present with different phenotypes [36]. Since the gene associated with the disease (*NLRP12*) is known, the committee decided to name this syndrome *NLRP12*-associated autoinflammatory disease (*NLRP12*-AID).

In the case of *MEFV*-associated diseases, the question raised was as follows: should we use the old name FMF or "atypical FMF" for all syndromes associated with mutations in the *MEFV* gene even if they have totally different clinical manifestations? Alternatively, should we find a different way to classify these disorders? The committee chose to use a general name (as a "roof ") "pyrin-associated autoinflammatory diseases" (PAAD) which includes all diseases associated with pyrin defects or *MEFV* mutations. Under this general term, there are subtypes of disorders with different names, according to their clinical presentation or genetic features, such as: PAAND, FMF, etc. [65] (Figure 1). Although it is preferred using the name of the gene over the name of the encoded protein, in the case of FMF, the protein pyrin was chosen rather than the *MEFV* gene. One of the reasons was that the name *MEFV,* which was coined to denote its association with familial **Me**diterranean **fev**er, is no longer accurate, since it may lead to totally different AIDs,

such as PAAND and CRMO-like disorder. In addition, we did not change the name of familial Mediterranean fever (FMF), although sometimes it is neither familial nor restricted to the Mediterranean basin and in rare cases, it may even be without a documented fever. Most members of the steering committee thought that FMF is a well-known and defined entity and that changing the name would cause discomfort and confusion among the AID clinical community. The name FMF remained under the "roof" of "pyrin-associated autoinflammatory diseases" (PAAD) as a clinical entity which is restricted mainly to Middle Eastern patients or to patients elsewhere, whose disease is associated with exon 10 mutations [66].

Regarding Mevalonate kinase disorders the committee suggested leaving MKD as a general name with the option of adding "mild" for those with hyper IgD syndrome and "severe" for those with mevalonic aciduria (67). In rare cases, where the patient with MKD has also retinitis pigmentosa or porokeratosis, it is suggested to mention these manifestations in addition to MKD (Table 1, and Supplementary Table S1).

The name *NOD2*-associated granulomatous disease was chosen by the committee for the three phenotypes: Blau syndrome, familial sarcoidosis and familial Crohn's disease. Since all these syndromes are characterized by granulomas, this feature was included in the name. Nevertheless, an option was offered to add IBD in cases where the intestines are the main site of involvement eg. *NOD2*-associated granulomatous IBD (formerly called familial Crohn's disease).

The name for CRMO was replaced by the name chronic non-bacterial osteomyelitis CNO. The reason for that was the presence of many cases where the disease was neither recurrent nor multifocal. Furthermore, the new name emphasizes the main feature of the disease, non-bacterial osteomyelitis. Since this clinical entity may be associated with mutations in various genes, it is optional to add the name of the gene when it is known. For example in case the gene involved is *LPIN2* it can be marked as *LPIN2*-CNO (previously known as Majeed's syndrome). In adults, patients with sporadic CNO are usually diagnosed with SAPHO, a symptom complex of Synovitis, Acne, Pustulosis, Hyperostosis, and Osteitis [68].

Chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature syndrome (CANDLE syndrome) gained a new name: *PSMB8*-PRAAS - where *PSMB8* stands for Proteasome Subunit Beta 8 and PRAAS for PRoteasome-Associated Autoinflammatory Syndrome. This name replaces also the eponym Nakajo Nishimura syndrome, and JMP which stands for Joint contractures, Muscle atrophy, microcytic anemia and Panniculitis-induced lipodystrophy. The name

PSMB8-PRAAS consists of the genetic etio-pathology of the disorder but does not include any clinical feature of the disease.

CARD14-associated disease is usually characterized by psoriasis with or without pustulosis. Therefore, the name was refined to be *CARD14*-associated psoriasis.

Since the 3 variants of IL-10 deficiency are always associated with inflammatory bowel disease, the committee proposed a single name as IL-10 deficiency-associated IBD.

The names; deficiency of the interleukin 1 receptor antagonist (DIRA), deficiency of the interleukin 36 receptor antagonist (DITRA), pyogenic arthritis, pyoderma gangrenosum, and acne (PAPA) and PFAPA remained unchanged since they already conform to our naming conventions. However, the letter P in the abbreviation "PAPA" now stands for the name of the gene *PSTPIP1* rather than “Pyogenic” and, therefore, the new name is "*PSTPIP1*-associated arthritis, pyoderma gangrenosum and acne" (PAPA).

The name "Cherubism" was derived from the Biblical "cherub" (plural cherubim) who has four faces of different species and several pairs of wings,. For most physicians this name does not mean much and therefore, the committee proposed the name *SH3BP2* deficiency with multilocular cystic disease of the mandibles (SDCM). This name gives the etio-pathologic basis of the syndrome with the main clinical feature of fibrous dysplasia of the mandibles.

Finally, the name “Schnitzler syndrome” also remained as an historical one, since its pathogenesis is still obscure and its relationship with *NLRP3* mutations has not been established [69]. A proposal to convert the name of the syndrome to a clinical description: "late onset gammopathy with recurrent urticaria and fever" (LOGRUF) did not gain support from most of the committee members.

Discussion

The definition of autoinflammatory diseases has changed over the years in order to accommodate the new diseases discovered since 1999 – the year the term was first proposed [2, 5, 57-61]. Widening the scope and spectrum of definition of AIDs resulted in the inclusion of disorders with additional defects in the adaptive immune system such as PLAID or HOIL-1 deficiency. Most defects in the immune system may affect primarily either the innate or the adaptive arm. However, it is becoming increasingly obvious that the innate immune system almost always has an effect on

the adaptive system. This leads to the situation that there are disorders that do not fit neatly into the "pure" autoinflammatory or autoimmune categories, and reside actually in a "grey zone" between these two groups. In order to include these disorders with the typical AIDs under the same "rafter", Peckham et al. offered the term "Auto-inflammatory-immune diseases" [70]. We believe that this new name may lead to confusion since all the disorders caused or related to defects in the immune system can be classified under this wide term with no clear categorization. The interferonopathies are clinical disorders caused by defects in the innate response, leading to inflammation after DNA sensing. The activation of cells of the adaptive immunity is a secondary effect of this condition and seems to play a minor role in their pathogenesis. Therefore, they may create the bridge which fits the concept that the autoinflammatory diseases, and the autoimmune diseases are actually in the same spectrum of immune disorders. This continuum model is further supported by the recent discovery of the innate lymphoid cells (ILCs). These cells are defined by differential expression of cell-surface markers and are activated by neuropeptides, cytokines and other alarmins [71]. Their specialized distribution in lymphoid and non-lymphoid tissues, coupled with their functional heterogeneity, has provoked a fundamental reassessment of how they integrate innate and adaptive immune responses.

As already mentioned - many of the current names of AIDs were not appropriate, inaccurate or lack any clinical meaning. Therefore, an attempt to establish new conventions for naming them was really needed.

The conventions (Table 3), and the ensuing proposals (Table 1, and Supplementary Table S1), call for using the name of the gene associated with the disease when it is known rather than the encoded protein. In these cases, demonstration of functional significance of the identified sequence alteration is mandatory.The main advantage of using the name of the gene is that such a name gives the physician a clue about the pathogenesis of the disease and sometimes even about a potential treatment. Moreover, it may allow definite diagnosis using genetic testing. However, it should be borne in mind that including the gene in the name of the disease may pose a problem in cases where the clinical features of the patient are compatible with a certain diagnosis while no expected sequence alteration is found. Thus, the main drawback of using the name of the gene is that **definite** diagnosis can be made only by genetic testing.

In cases where the clinical features and the genetic testing results are in accord, the name is appropriate and the diagnosis is correct and definite. When there is a clearly pathogenic mutation but the clinical features are completely incompatible with the expected diagnosis, one should consider a different disease with a different name. This situation is illustrated by the case of the *MEFV* mutation S242R, which causes neutrophilic dermatosis. The name of this disease is not "FMF" or "atypical FMF" despite the fact that there are *MEFV* mutations - but "pyrin-associated autoinflammation with neutrophilic dermatosis (PAAND)". Similar approach may be applied in the case of *PSTPIP1* with the new mutation and different clinical presentation [72]. We suggest here a "roof" name : *PSTPIP1*-associated autoinflammatory diseases with two subtypes: PAPA and PAMI (*PSTPIP1*-associated myeloid-related proteinemia inflammatory syndrome). However, we cannot add this approach to Table 1 since it was not discussed in the Delphi questionnaires among the large group of participants

When the clinical features are typical for a certain disease (for example FMF) and yet no genetic support for this diagnosis is found, one can denote this medical condition as an FMF-like disease. However, a better choice would be to leave the case as an undefined AID until mutations in other genes are found or additional explanations for the disease are given. The reason is that clinical features typical for one AID may be associated with mutations in different genes. For example, in arecent report, Karacan et al. described two Turkish families in whom 4 patients presented with typical clinical features of FMF [73]. Genetic analysis performed in these patients failed to show *MEFV* mutations. However, total exon sequencing revealed that two patients were homozygous for mutations in *MVK* and the two other patients carried mutations in the *TNFRSF1A* gene. These cases illustrate the difficulties in making a diagnosis of AID based upon clinical features only and justify the proposal to use the gene in naming AIDs wherever it is known.

The way we proposed naming CAPS and FCAS 2 namely NLRP3-associated autoinflammatory disease (NLRP3-AID) and *NLRP12*-AID respectively may pave the way for naming future disorders to be discovered or identified among the other members of the large family of NOD–like receptors (NLRs).. Similarly, *PSMB8*-PRAAS, the name which was proposed to replace CANDLE syndrome, JMP and NNS, may also serve as an example for naming additional proteasome associated diseases to be discovered, just by changing their number. In fact, Brehm et al. recently described several cases that carry mutations in *PSMA3* (encodes α7),

PSMB4 (encodes β7), *PSMB9* (encodes β1i), and proteasome maturation protein (*POMP*) [74].

Unfortunately, the current study did not include many other monogenic AIDs such as those associated with *ADA2, NLRC4, NLRP1* genes or X-linked inhibitor of apoptosis (XIAP) deficiency and (SLAM)-associated protein (SAP) deficiency (75). The reason is that we limited ourselves mainly to the basic list reported by Toiutou et al.(51). However, we hope that the conventions we propose herein may help modifying names of additional diseases - old and new – when, they do not follow the rules suggested.

For this project we used the Delphi technique which allowed discussion via an *ad hoc* web-based system developed by the PRINTO staff under the supervision of NR who has an extensive expertise in consensus formation methodologies. The PRINTO system allowed remote interaction between the participants who had the possibility to share written comments with the other participants in a transparent and traceable way. A limitation of the current work was that for lack of funding we could not conduct a formal nominal group technique (NGT) which is a guided face-to-face discussion and interaction, among small groups of experts. However, the additional discussion of the *ad hoc* steering committee consensus proposal by another group of 26 worldwide experts in the field of AIDs further strengthens these proposals.

In conclusion, the currently proposed rules for nomenclatures of AIDs are expected to allow a better organization of these groups of immune diseases. However, taxonomy is a dynamic process and some of the proposed names may be changed in the future as we gain a better knowledge about their pathogenesis. The proposed taxonomy may gain a broader consensus following an effective communication with other societies such as the International Union of Immunological Societies Expert Committee (IUIS).

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Contributorship Statement

All authors (EBC, MG, AG, DLK, HJL, IT, NR) contributed equally to the planning and conduct of the study. Their placement in the authors' list is dictated by the alphabetic order of their family names.

The first version of the present manuscript was written by EBC, MG and NR, and then revised critically by all the remaining co-authors (AG, DLK, HJL, IT).

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Competing interests

Authors:

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Additional participants to the Delphi study

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Glossary - Abbreviations

AGS - Aicardi-Goutières Syndrome

AIDs - Autoinflammatory diseases

AIMDs - Autoimmune diseases

ALPS - Autoimmune lymphoproliferative syndrome

APR - Acute phase reactant

CANDLE - Chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature syndrome

CAPS - Cryopyrin-associated periodic fever syndrome

CARD - Caspase recruitment domain family member

CINCA- Chronic infantile neurologic, cutaneous and articular syndrome

CNO - Chronic non-bacterial osteomyelitis

CRMO -Chronic recurrent multifocal osteomyelitis

ADA2 - adenosine deaminase 2

DIRA - Deficiency of the interleukin 1 receptor antagonist

DITRA - Deficiency of the interleukin 36 receptor antagonist

FCAS - Familial cold autoinflammatory syndrome

FMF - Familial Mediterranean fever

HIDS - Hyper-IgD with periodic fever syndrome

HOIL -1 - Heme - oxidised IRP2 ubiquitin ligase 1

IBD - Inflammatory bowel disease
ISSAID - International society for systemic autoinflammatory diseases

JMP - Joint contractures, muscle atrophy, microcytic anemia and panniculitis-induced lipodystrophy.

LOGRUF - Late **o**nset **g**ammopathy with **r**ecurrent **u**rticarial and **f**ever

MEFV - Mediterranean fever

MK- Mevalonate kinase

MKD - Mevalonate kinase deficiency

MVK - Mevalonate kinase

MWS - Muckle-Wells syndrome;

NALP 12- NACHT, LRR and PYD domains-containing protein 1

NGS - New generation sequencing

NLR - NOD-like receptor

NLRC4 - NOD-like receptor with CARD containing 4

NLRP - NOD-like receptor with LRR (Leucine rich repeat), and PYD domain;

NOD - Nucleotide-binding oligomerization domain;

NOMID - Neonatal onset multisystem inflammatory disease

PAAND - Pyrin-associated autoinflammation with neutrophilic dermatosis

PAMI - *PSTPIP1*-associated myeloid-related proteinemia inflammatory syndrome

PAPA - *PSTPIP1* arthritis, pyoderma gangrenosum, and acne

PFAPA: Periodic fever, aphthous stomatitis, pharyngitis and adenitis

PLD - *PLCG2* dysregulation

PLAID - *PLCG2*-associated antibody deficiency and immune dysregulation

PLCG2 - Phospholipase C γ2

POMP - proteasome maturation protein

PRINTO - Pediatric rheumatology international trials organization

PRAAS - Proteasome associated autoinflammatory syndrome

PSMB 3-4,8-9 - Proteasome Subunit, β-type, 3,4,8,9

PSTPIP1 - proline serine threonine phosphatase-interacting protein 1

-**SAPHO** - synovitis, acne, pustulosis, hyperostosis, and osteitis

SDCM - SH3BP2 deficiency with multilocular cystic disease of the mandibles.

SH3BP2 - SH3 Domain Binding Protein2

SAP - SLAM - associated protein

SLE - systemic lupus erythematosus

TNF - Tumor necrosis factor

TNFRSF1A - Tumor necrosis factor receptor super family 1A

TRAPS - TNF-receptor-associated periodic syndrome

XIAP - X-linked Inhibitor of APoptosis

Table 1. Current name of the disorder (in bold) and additional names (normal characters) derived from the literature. The last column reports the proposed nomenclature for the AIDs as results of the consensus process.

Current name of the disorder and additional names	**Proposed nomenclature**
CAPS - Cryopyrin-associated periodic fever syndrome [20]	***NLRP3*-associated autoinflammatory disease (*NLRP3*-AID)**
CINCA - Chronic infantile neurological, cutaneous and articular syndrome [17], NOMID - Neonatal onset multisystem inflammatory disease	Severe
MWS - Muckle-Wells syndrome [18]	Moderate
FCAS - Familial cold autoinflammatory syndrome [19]	Mild
***CARD14*-associated disease**	***CARD14*-associated psoriasis**
PRP - Familial Pityriasis rubrapilaris [30] CAMPS - *CARD14*-mediated pustular psoriasis [31]	
Cherubism [45]	***SH3BP2* deficiency with multi locular cystic disease of the mandibles (SDCM)**
Familial Multilocular Cystic Disease of the Jaws [46] Cherubism--familial fibrous dysplasia of the jaws [47] CGCL - Central giant cell lesion [48]	
CRMO - Chronic recurrent multifocal osteomyelitis [29]	**Chronic non-bacterial osteomyelitis (CNO) -** (when the gene is known it should be added)
Majeed syndrome [26], Congenital dyserythropoietic anemia and chronic recurrent multifocal osteomyelitis [27] LIPIN2-associated disease [28]	***LPIN2*-CNO**
DIRA – Deficiency of the IL-1 receptor antagonist [24]	**(No change)**
DITRA - Deficiency of the IL-3 6receptor antagonist [25]	**(No change)**
FCAS2 – Familial cold autoinflammatory syndrome 2 [36]	***NLRP12*-associated autoinflammatory disease (*NLRP12*-AID)**
Guadeloupe fever, NALP12 periodic fever	

Current name of the disorder and additional names	**Proposed nomenclature**
syndrome [36]	**Pyrin-associated autoinflammatory disease (PAAD)**
FMF - Familial Mediterranean fever (FMF)[7] Benign paroxysmal peritonitis [4] , Periodic disease [5], Armenian disease, Periodic disease "Maladie periodique" [6], Familial Mediterranean fever (FMF) [7], Recurrent polyserositis [8], Familial paroxysmal polyserositis [9]	**(No change)**
PAAND - Pyrin-associated autoinflammation with neutrophilic dermatosis [10]	**(No change)**
JMP **Joint contractures, Muscle atrophy, Microcytic Anemia and Panniculitis Induced Lipodystrophy [38],** Chronic Atypical Neutrophilic Dermatosis with Lipodystrophy and Elevated Temperature (CANDLE) Syndrome [37], Nakajo-Nishimura Syndrome (NNS) [39	**Proteasome-associated autoinflammatory syndrome (PRAAS)** ***PSMB8*-PRAAS, *PSMB4*/*PSMB9*-PRAAS, *PSMB4*/*PSMB9*-PRAAS, *PSMA3*/*PSMB8*-PRAAS**
HIDS - Hyper IgD syndrome [15] **Mevalonic aciduria (67)** Mevalonate kinase disease (Deficiency) [13, 14] Dutch type periodic fever [16]	**Mevalonate kinase deficiency (MKD)** **Mild** **Severe** (Add porokeratosis or retinitis pigmentosa when present)
IL-10 Deficiency IBD - IL-10R-associated very early [32] Infantile colitis [33]	**IL-10 deficiency-associated Inflammatory bowel disease**
***NOD2 CARD15*-Associated disease** Blau syndrome [21], Early onset sarcoidosis [22], Familial Crohn's disease [23]	***NOD2*-associated granulomatous disease** (Optional: add Blau syndrome or IBD according to the main clinical features**)**
PAPA / Pyogenic Arthritis, Pyoderma gangrenosum, and Acne syndrome [35]	***PSTPIP1*-associated arthritis, pyoderma gangrenosum, and acne (PAPA)**

Current name of the disorder and additional names	**Proposed nomenclature**
PFAPA - Periodic fever, aphthous stomatitis, pharyngitis and adenitis Periodic fever, aphthous stomatitis, pharyngitis and adenitis or periodic fever aphthous pharyngitis and cervical adenopathy [41] Marshall's syndrome [42]	**(No change)**
Schnitzler syndrome [40] PUPAP - Periodic fever with urticaria and paraprotein	**(No change)**
TRAPS - TNF receptor-associated periodic fever syndrome[3] Familial Hibernian fever [11] Familial autosomal dominant periodic fever [12]	**(No change)**

Table 2. Results from the Delphi questionnaires for consensus on nomenclature

Definition or Disease	Group of AIDs experts consensus (N=26)
Definition	
Autoinflammatory diseases are clinical disorders caused by defect(s) or dysregulation of the innate immune system, characterized by recurrent or continuous inflammation (elevated APR) and by the lack of a *primary* pathogenic role of the adaptive immune system (auto - reactive T-cells or autoantibody production).	87%
Final names proposed for the AIDs	
CARD14-associated psoriasis	91%
CNO: Chronic non-bacterial osteomyelitis	87%
DIRA: Deficiency of the IL-1 receptor antagonist	96%
DITRA: Deficiency of the IL-36 receptor antagonist	96%
IL-10 deficiency-associated inflammatory bowel diseases	83%
PAAD: Pyrin-associated autoinflammatory disease: FMF, PAAND	88%
MKD: Mevalonate kinase deficiency	87%
NLRP3-AID – *NLRP3*-associated autoinflammatory disease	88%
NLRP12-AID – *NLRP12*-associated autoinflammatory disease	88%
NOD2-associated granulomatous diseases	83%
PAPA: *PSTPIP1*-associated arthritis, pyoderma gangrenosum and acne	87%
PFAPA: Periodic fever, aphthous stomatitis, pharyngitis and adenitis	83%
PRAAS : Proteasome-associated autoinflammatory syndrome	84%
Schnitzler syndrome	87%
SDCM - *SH3BP2* deficiency with multilocular cystic disease of the mandibles	94%
TRAPS - TNF receptor-associated periodic fever syndrome	83%

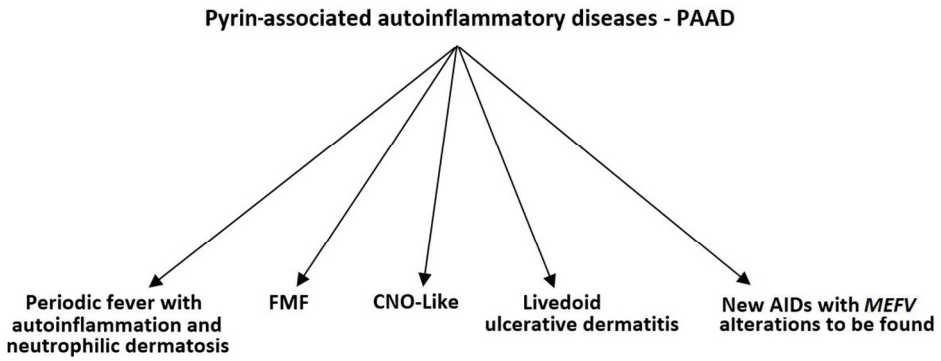
Table 3. Recommandations for naming AIDs

1. Try not to change wherever the name is appropriate.
2. Avoid names of persons or geographical spread of disease (eponyms)
3. Include the genetic basis (name of the gene) of the disease where it is known (prefer the name of the gene over the name of the encoded protein unless the name of the gene is not accurate or meaningless)
4. Include key clinical features where appropriate
5. Shorten the name as much as possible
6. Choose a name that is as clear as possible
7. In diseases where our knowledge about the pathogenesis is still limited, leave the previous name (PFAPA)
8. In diseases with different phenotypes but mutations in the same gene, use a general "roof" name with subtypes (PAAD, NOD2).
9. When the clinical features seemed to be "continuous" give a general name ("roof" name) and classify the various presentations according to their phenotypic severity (*NLRP3*-AID*, MKD*).

Legends to figure

Figure 1

The group of diseases associated with *MEFV* sequence alterations. The "roof" name is a general name whereas the subtypes are more specific and meaningful.



The group of diseases associated with MEFV sequence alterations. The "roof" name is a general name whereas the subtypes are more specific and meaningful.

106x51mm (300 x 300 DPI)

Supplementary figure S1

Literature review for the definitions of Autoinflammatory diseases using the MESH search term: "autoinflammatory diseases" and subsequently all names reported in Table 1.

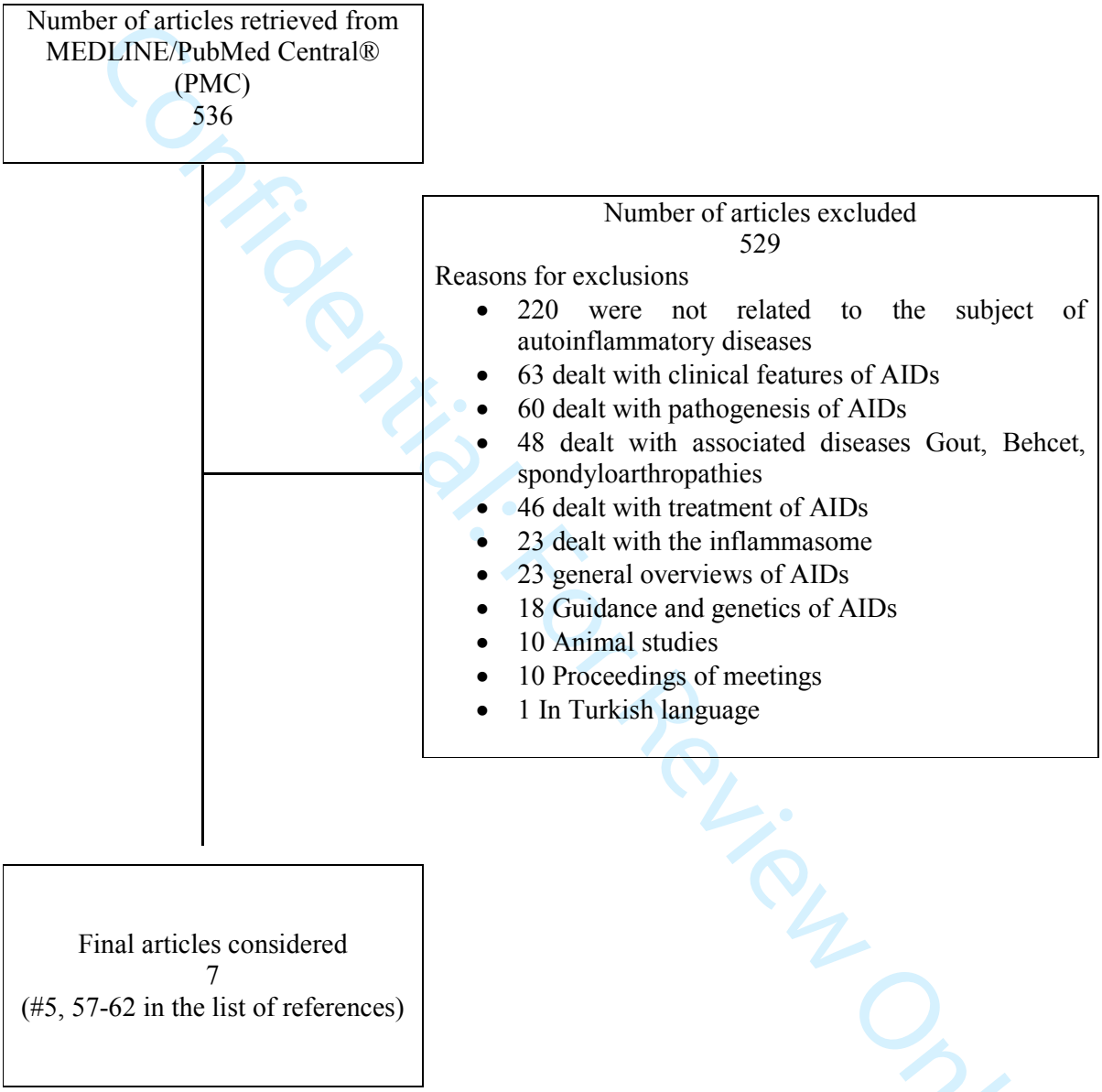


Table 1 Supplementary: Current name of the disorder and additional names derived from the literature. The last column reported the proposed nomenclature for the AIDs as results of the consensus process.

Current name of the disorder	Additional names	OMIM	Name of the gene	Name of the protein	Proposed nomenclature
CAPS Cryopyrin-associated periodic fever syndrome [20]		120100	*NLRP3/CIAS1*	Cryopyrin	**Roof name:*NLRP3*-associated autoinflammatory disease (*NLRP3*-AID)**
	Chronic infantile neurological,cutaneous and articular syndrome (CINCA)[17] Neonatal onset multisystem inflammatory disease (NOMID)	607115			Severe
	Muckle-Wells syndrome (MWS) [18]	191900			Moderate
	Familial cold autoinflammatory syndrome (FCAS) [19]				Mild
***CARD*14-associated disease**		*CARD14*	*CARD14*		***CARD*14-associated psoriasis**
	Familial Pityriasis rubrapilaris (PRP) [30]				

Current name of the disorder	Additional names	OMIM	Name of the gene	Name of the protein	Proposed nomenclature
	CAMPS - CARD14-mediated pustular psoriasis [31]				
Cherubism [45]		266270	*SH3BP2*	SH3BP2	***SH3BP2* deficiency with multi locular cystic disease of the mandibles (SDCM)**
	Familial Multilocular Cystic Disease of the Jaws [46]				
	Cherubism--familial fibrous dysplasia of the jaws [47]				
	Central giant cell lesion (CGCL) [48]				
CRMO Chronic recurrent multifocal osteomyelitis [29]					**Chronic non-bacterial osteomyelitis (CNO)** (when the gene is known it should be added)
	Majeed syndrome [26]	609628	*LPIN2*	LIPIN 2	
	Congenital dyserythropoietic anemia and chronic recurrent multifocal osteomyelitis [27]				
	LIPIN2-associated disease [28]				***LPIN2*-CNO**
DIRA Deficiency of the IL-1		612852	*IL1RN*	IL-1Ra	**(No change)**

Current name of the disorder	Additional names	OMIM	Name of the gene	Name of the protein	Proposed nomenclature
receptor antagonist [24]					
DITRA Deficiency of the IL-36R antagonist [25]		614204	*IL36RN*	IL-36Ra	**(No change)**
FCAS 2 Familial cold autoinflammatory syndrome 2 [36]		611762	*NLRP12*	NLRP12	***NLRP12*-associated autoinflammatory disease (*NLRP12*-AID)**
	Guadeloupe fever				
	NALP12 periodic fever syndrome [36]				
					Roof name: Pyrin-associated autoinflammatory disease (PAAD)
FMF Familial Mediterranean fever[7]		134610 249100	*MEFV*	Pyrin	**(No change)**
	Benign paroxysmal peritonitis [4]				
	Periodic disease [5]				
	Armenian disease				
	Periodic disease "Maladie periodique" [6]				
	Familial Mediterranean fever				

Current name of the disorder	Additional names	OMIM	Name of the gene	Name of the protein	Proposed nomenclature
	(FMF) [7]				
	Recurrent polyserositis [8]				
	Familial paroxysmal polyserositis [9]				
PAAND Pyrin-associated autoinflammation with neutrophilic dermatosis [10]					**(No change)**
					Roof name: Mevalonate kinase deficiency (MKD)
HIDS Hyper IgD syndrome [15]	Mevalonate kinase disease (Deficiency) [13, 14]	260920	*MVK*	Mevalonate kinase	Mild
	Dutch type periodic fever [16]				
Mevalonic aciduria (67)					Severe
					(Add porokeratosis or retinitis pigmentosa when present)
					Roof name: Proteasome-associated

Current name of the disorder	Additional names	OMIM	Name of the gene	Name of the protein	Proposed nomenclature
					autoinflammatory syndrome (PRAAS)
JMP Joint contractures, Muscle atrophy, Microcytic Anemia and Panniculitis Induced Lipodystrophy[38]		256040	*PSMB8*	Proteasome subunits and others	*PSMB8*-PRAAS *PSMB4/PSMB9*-PRAAS *PSMA3/PSMB8*-PRAAS
	Chronic Atypical Neutrophilic Dermatosis with Lipodystrophy and Elevated Temperature (CANDLE) Syndrome [37]				
	Nakajo-Nishimura Syndrome (NNS) [39]				
IL-10 Deficiency		612567 613148	*IL10RA or IL10RB*		**IL-10 deficiency-associated Inflammatory bowel disease**
	IL-10R-associated very early IBD [32]				
	Infantile colitis [33]				
***NOD2* (*CARD15*)-associated disease**		186580	*NOD2/CARD15*	NOD2	**Roof name: *NOD2*-associated granulomatous disease** (Optional: add Blau syndrome or IBD according to the main clinical features**)**

Current name of the disorder	Additional names	OMIM	Name of the gene	Name of the protein	Proposed nomenclature
	Blau syndrome [21]				
	Early onset sarcoidosis [22].				
	Familial Crohn's disease [23]				
PAPA PAPA syndrome (Pyogenic Arthritis, Pyoderma gangrenosum, and Acne) [35]		604416	*PSTPIP1*	CD2BP1 (CD2-binding protein1)	***PSTPIP1*-associated arthritis, pyoderma gangrenosum, and acne (PAPA)**
PFAPA					**(No change)**
Periodic fever, aphthous stomatitis, pharyngitis and adenitis	Periodic fever, aphthous stomatitis, pharyngitis and adenitis or periodic fever aphthous pharyngitis and cervical adenopathy [41]				
	Marshall's syndrome [42]				
Schnitzler syndrome [40]					**(No change)**
	Periodic fever with urticaria and paraprotein (PUPAP)				
TRAPS - TNF receptor-associated periodic fever		142680	*TNFRSF1A*	TNFR1	**(No change)**

Current name of the disorder	Additional names	OMIM	Name of the gene	Name of the protein	Proposed nomenclature
syndrome[3]					
	Familial Hibernian fever [11]				
	Familial autosomal dominant periodic fever [12]				

Consensus proposal for Taxonomy and Definition of the Autoinflammatory Diseases (AIDs) - A Delphi Study

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Key words: Taxonomy, Autoinflammatory diseases, immune system

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Abstract

Background: Autoinflammatory diseases (AIDs) are a relatively new family of disorders defined about 19 years ago. Some of them are hereditary and some are not.The names given to these diseases do not follow any systematic guidelines and sometimes the same disorder carries several names.

Aims: The aim of this study is to refine the definition of the autoinflammatory diseases and to provide some conventions for their naming. We have focused our attention mainly on monogenetic AIDs.

Methods: Delphi technique which enables consensus among a group of experts through Internet and mail communication and questionnaires - was employed. After achieving 100% consensus among 6 members of a steering committee, the questionnaire containing the AID definitions and the agreed-upon conventions, were sent to 26 physicians and researchers working in the field of AIDs in order to gain broader support for the committee's proposals.

Results: The committee proposed the following definition for AIDs "Autoinflammatory diseases are clinical disorders caused by defect(s) or dysregulation of the innate immune system, characterized by recurrent or continuous inflammation (elevated acute phase reactants-APR) and the lack of a *primary* pathogenic role for the adaptive immune system (autoreactive T-cells or autoantibody production)". Several rules were defined for guiding the naming of these diseases among which are: abandoning eponyms and preferring the name of the gene over its encoded protein.

Conclusions: The new definition for AIDs allows inclusion of clinical disorders mainly associated with defects in the innate immune system. The new conventions propose names with clinical meaning and in some cases even clues for treatment.

Taxonomy is the science of naming. It is relevant to all fields of biology in which we name plants, animals, objects and diseases. In medicine, naming of diseases or syndromes has a special importance since it can give some clue about the nature of the clinical condition, its clinical features, pathogenesis and sometimes even an approach to treatment. Naming is also important for accurate and effective communication among different health disciplines. However, medical disorders have not been named in a standard way [1]. Physicians, who treat patients with a particular disorder or face a new clinical condition, are often the first to propose a name for the disease. Expert working groups may later revise the names to improve their usefulness.

Names of medical disorders are often derived from one or a combination of the following sources: genetic basis or biochemical defect; geographic spread; or by eponyms. The main drawback of many names is the lack of a clinical meaning that could help the novice to understand the origin of the disease or recognize its clinical characteristics .

The autoinflammatory diseases (AIDs) are a group of medical disorders, derived from defects or dysregulation of the innate immune system [2]. This family of diseases was established in 1999 following the identification of the genes underlying two recurrent fever syndromes: familial Mediterranean fever (FMF) [3,4] and TNF-receptor-associated periodic syndrome (TRAPS) [5]. Over the last 18 years, more and more diseases have been classified amongst this group of disorders, some of which may not fit well with the classical definition of the AIDs. Moreover, many of them were given names with no systematic guidelines or rules. In some cases, the same disease carries several names (Table 1) [6-50]. This has led to a chaotic situation in naming these clinical disorders and has called for a better standardization of this field. This need is accentuated by recent progress in next generation sequencing techniques (NGS), which have led to an increasing capability to identify new genes and new syndromes, expanding the spectrum of AIDs.

Indeed, following the International Society for Systemic Autoinflammatory Diseases (ISSAID) meeting in Lausanne, in 2013, a mandate was given to one of us (E B-C) to undertake a preliminary consensus based exercise for the following aims: a. to refine the definition of the "autoinflammatory diseases". b. to provide some rules and new proposals for naming this current group of clinical conditions and those that will be identified in the future.

Methods

In order to find the different definitions proposed for AIDs over the years, we searched the MEDLINE/PubMed Central® (PMC) from 1998 to January 2016, using the MESH search term: “autoinflammatory diseases” (supplementary Figure S1). In order to find the names used for each AID, we took one of their current names as depicted in Table 1 and searched for papers where they were first reported. Then, we searched for reviews on these items to find additional synonymous names. Table 1 is based on a list of AIDs published by one of the authors (IT) [51], properly integrated and updated during the consensus process and finally approved by all the steering committee members. ~~Table 1 is based on a list of AIDs published by one of the authors (IT) [51] and gained consensus by all the steering committee members~~. It focused - mainly - on monogenic disorders.

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For choosing the best definition for AIDs and the most appropriate name for each AID, we have used the Delphi technique, which enables consensus among a group of experts through mail communication [52]. The Delphi method is essentially a series of questionnaires involving several steps, each of which is based on the results of the previous step. The process stops when consensus of at least 80% of the participants on each item is reached. [53]

An *ad hoc* steering committee of 6 clinicians and researchers from 6 different countries who are working in the field of autoinflammation was established.

The first Delphi questionnaire was built through sending broad and open-ended questions in order to elicit different opinions from the panelists about the current definitions and names of AIDs.

Once received, the replies from the panelists were analyzed to generate a series of statements that were employed as the basis for follow up questionnaires that were sent back to the individual participants. In each subsequent questionnaire, the panelists were also provided with the overall results (responses) of the previous questionnaire from all the members. After achieving 100% consensus among the steering committee members, the questionnaire containing the AID definitions and the agreed-upon names of AIDs were sent to 26 physicians and researchers working in the field of AIDs around the world. They were identified in the Paediatric Rheumatology International Trials Organization (PRINTO) mailing list through their high active participation in the Eurofever registry [54, 55]. The aim of this step was to gain broader support for the committee's proposals and to consider changes once a name was rejected by or was not acceptable to more than 80% of the participants of

the large group of AIDs experts. Delphi survey implementation was conducted by PRINTO [56].

Results

AIDs proposed definition

The literature review disclosed 536 papers of which only 7 specifically dealt with the definitions of AIDs [5, 57- 62] (supplementary Figure S1). The first definition for AIDs was proposed by the NIH group in 1999 [5]. This definition was as follows: "The autoinflammatory syndromes are systemic disorders characterized by apparently unprovoked inflammation in the absence of high-titer autoantibodies or antigen-specific T lymphocytes". This definition was based mainly upon the two diseases whose related genes had then been identified: FMF and TRAPS [3- 5]. Since in both diseases the flares appeared mostly spontaneous, the definition included the word "unprovoked". The definition stresses the lack of involvement of the adaptive immune system in these disorders, since no autoantibodies or autoreactive T-cells were involved.

Seven years later McGonagle and McDermott suggested another definition: "AIDs are characterized by self-directed inflammation, whereby local factors at sites predisposed to disease lead to activation of innate immune cells, including macrophages and neutrophils, with resultant target tissue damage. For example, disturbed homeostasis of canonical cytokine cascades (as in the periodic fevers), aberrant bacterial sensing (as in Crohn's disease), and tissue micro-damage predispose one to site-specific inflammation that is independent of adaptive immune responses" [57]. The authors proposed that immunological diseases ought to be conceived as a continuum with “pure monogenic autoinflammatory diseases” at one end and “pure monogenic autoimmune diseases” at the other. This definition is relatively complex, but explicitly invokes innate immunity and widens the spectrum of AIDs.

Later, several other definition or refinement were proposed [58-61]. In a recent study, de Jesus et al. provide an outstanding classification of AIDs strictly based on their pathophysiology [62]. However, the authors do not propose a new definition for the AIDs.

Given the proliferation of AID definitions, with sometimes conflicting concepts, the steering committee agreed to adopt the first and original definition with minor

modifications: "Autoinflammatory diseases are clinical disorders caused by defect(s) or dysregulation of the innate immune system, characterized by recurrent or continuous inflammation (elevated - APR) and the lack of a *primary* pathogenic role for the adaptive immune system (autoreactive T-cells or autoantibody production)."

This definition emphasizes the essential fact that the disorders are caused by defects in the innate immune system and are continuous or recurrent. The word "unprovoked" has been deleted since in many cases there is a trigger for the acute flares.

The steering committee is aware that diseases such as PLCG2-associated antibody deficiency and immune dysregulation (PLAID) or Heme - oxidised IRP2 ubiquitin ligase1 (HOIL-1) deficiency, traditionally included among the AIDs, will not be part of this group, because they may contain components of the adaptive immune system such as autoantibodies [63]. The "Interferonopathies" include some disorders also manifesting autoantibodies. However, the consensus seemed to be that for disorders like Aicardi-Goutières Syndrome (AGS) in which nucleic acid sensing is primarily intracellular, autoantibodies usually play a minor role in disease pathogenesis, and thus the autoinflammatory designation may still be appropriate. In their recent review Rodero and Crow propose that “type I interferonopathies can reasonably be considered as autoinflammatory in origin, with ‘spill-over’ into autoimmunity in some cases” [64]. The group of "typical" **autoimmune diseases** includes disorders affecting primarily or only the adaptive system such as systemic lupus erythematosus (SLE), Hashimoto thyroiditis, DNAse deficiencies and autoimmune lymphoproliferative syndrome (ALPS).

AIDs proposed nomenclature

The current names for AIDs bring several problems and issues, which called for a new approach and nomenclature modification; many AIDs possess more than a single name (FMF - 7 different names, TRAPS - 3, etc) (Table 1 and Supplementary Table S1); different clinical presentations are associated with similar sequence alterations in the same gene eg. Muckle-Wells syndrome(MWS), familial cold autoinflammatory syndrome (FCAS) and Neonatal onset multisystem inflammatory disease (NOMID) are associated with *NLRP3* gene whereas FMF and pyrin-associated autoinflammation with neutrophilic dermatosis (PAAND) are associated with *MEFV gene*. In addition discussion arose about several topics briefly summarized herein: In naming AIDs should we use the name of the gene or that of

the encoded protein (*MEFV* or pyrin)? Should we include typical clinical features or just genetic attributes? Should historical names be retained?

Following more than 6 cycles of Delphi questionnaires and oral discussions among the 6 members of the steering committee with further involvement of the 26 AIDs experts around the world - a consensus of at least 80% was reached for the nomenclature of the diseases shown in Tables 1 and 2.

General conventions (Table 3)

The proposed names for AIDs have been established according to the rules and suggestions outlined in Table 3.

In many diseases the course of the disease is episodic with frequent attacks and attack-free intervals. When the frequency of the attacks is relatively regular (as is the case with Periodic fever, aphthous stomatitis, pharyngitis and adenitis (PFAPA) and sometimes with mevalonate kinase deficiency (MKD) we preferred the term "periodic". When the attacks do not have a regular pattern, we suggested the word "recurrent".

In the past, both terms, “periodic” and “recurrent”, have been used interchangeably but now the term "periodic” remained in the names of 3 conditions only; Cryopyrin-associated periodic fever syndrome (CAPS),TRAPS and PFAPA. In TRAPS, we decided to keep the original name "periodic", although its flares are recurrent rather than periodic. In CAPS, we propose a new name (NLRP3-AID) which does not contain the word “periodic since the attacks are not periodic”. Thus, we strongly suggest using the more appropriate terms in naming disorders in the future.

As a general rule, we tried to use names containing etio-pathological (genetic) features of the disease and where appropriate or possible, to add a significant clinical characteristic of the syndrome. Thus, we left the name TRAPS without change, since it consists of its genetic etiology (mutations in *TNFRSF1A* gene) and characteristic clinical features [periodic (recurrent) fever]. On the other hand, the name hyper IgD syndrome (HIDS) was abandoned since it is an absolutely inaccurate name: serum IgD is not always elevated in these patients while it may be elevated in other AIDs. Therefore, this name was replaced by MKD based upon our knowledge of the gene involved, mevalonate kinase (*MVK*). In this way, a physician or researcher who approaches these names for the first time may have immediately a basic understanding of the disorder and sometimes even a clue to the potential treatment.

In cases where the choice was between using the name of the gene associated with the disease or the protein encoded by the gene, we preferred the name of the gene over that of the protein unless the former was meaningless. A typical example is the choice of *NLRP3* gene over cryopyrin despite the tendency of some clinicians to stay with the former term CAPS. Fortunately, in many cases the name of the gene and the encoded protein are the same (MK, NOD2) making the choice easier. However, this was not the case with the *MEFV* gene and pyrin where the name of the protein was chosen, as will be discussed later.

In our proposals for new taxonomy of AIDs, we tried to avoid the use of names of persons (such as Nakajo Nishimura syndrome) or geographical distribution of the disease (such as Guadeloupe fever) or names with unusual meaning (such as "Cherubism").

Specific names (Table 1 and Supplementary Table S1)

In the case of CAPS – which encompasses three clinical entities (FCAS, MWS, NOMID/CINCA), the committee has proposed using a single name; *NLRP3*-associated autoinflammatory disease (*NLRP3*-AID). Since the various disorders reflect different levels of phenotypic severity of the same disease, it was suggested to add the adjectives: mild, moderate, and severe phenotypes, instead of using the historical names FCAS, MWS and CINCA/NOMID, respectively.

In familial cold autoinflammatory syndrome 2 (FCAS2) (Guadeloupe fever), different families present with different phenotypes [36]. Since the gene associated with the disease (*NLRP12*) is known, the committee decided to name this syndrome *NLRP12*-associated autoinflammatory disease (*NLRP12*-AID).

In the case of *MEFV*-associated diseases, the question raised was as follows: should we use the old name FMF or "atypical FMF" for all syndromes associated with mutations in the *MEFV* gene even if they have totally different clinical manifestations? Alternatively, should we find a different way to classify these disorders? The committee chose to use a general name (as a "roof ") "pyrin-associated autoinflammatory diseases" (PAAD) which includes all diseases associated with pyrin defects or *MEFV* mutations. Under this general term, there are subtypes of disorders with different names, according to their clinical presentation or genetic features, such as: PAAND, FMF, etc. [65] (Figure 1). Although it is preferred using the name of the gene over the name of the encoded protein, in the case of FMF, the protein pyrin was chosen rather than the *MEFV* gene. One of the reasons

was that the name *MEFV,* which was coined to denote its association with familial **Me**diterranean **fev**er, is no longer accurate, since it may lead to totally different AIDs, such as PAAND and CRMO-like disorder. In addition, we did not change the name of familial Mediterranean fever (FMF), although sometimes it is neither familial nor restricted to the Mediterranean basin and in rare cases, it may even be without a documented fever. Most members of the steering committee thought that FMF is a well-known and defined entity and that changing the name would cause discomfort and confusion among the AID clinical community. The name FMF remained under the "roof" of "pyrin-associated autoinflammatory diseases" (PAAD) as a clinical entity which is restricted mainly to Middle Eastern patients or to patients elsewhere, whose disease is associated with exon 10 mutations [66].

Regarding Mevalonate kinase disorders the committee suggested leaving MKD as a general name with the option of adding "mild" for those with hyper IgD syndrome and "severe" for those with mevalonic aciduria (67). In rare cases, where the patient with MKD has also retinitis pigmentosa or porokeratosis, it is suggested to mention these manifestations in addition to MKD (Table 1, and Supplementary Table S1).

The name *NOD2*-associated granulomatous disease was chosen by the committee for the three phenotypes: Blau syndrome, familial sarcoidosis and familial Crohn's disease. Since all these syndromes are characterized by granulomas, this feature was included in the name. Nevertheless, an option was offered to add IBD in cases where the intestines are the main site of involvement eg. *NOD2*-associated granulomatous IBD (formerly called familial Crohn's disease).

The name for CRMO was replaced by the name chronic non-bacterial osteomyelitis CNO. The reason for that was the presence of many cases where the disease was neither recurrent nor multifocal. Furthermore, the new name emphasizes the main feature of the disease, non-bacterial osteomyelitis. Since this clinical entity may be associated with mutations in various genes, it is optional to add the name of the gene when it is known. For example in case the gene involved is *LPIN2* it can be marked as *LPIN2*-CNO (previously known as Majeed's syndrome). In adults, patients with sporadic CNO are usually diagnosed with SAPHO, a symptom complex of Synovitis, Acne, Pustulosis, Hyperostosis, and Osteitis [68].

Chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature syndrome (CANDLE syndrome) gained a new name: *PSMB8*-PRAAS - where *PSMB8* stands for Proteasome Subunit Beta 8 and PRAAS for PRoteasome-Associated Autoinflammatory Syndrome. This name replaces also the eponym

Nakajo Nishimura syndrome, and JMP which stands for Joint contractures, Muscle atrophy, microcytic anemia and Panniculitis-induced lipodystrophy. The name *PSMB8*-PRAAS consists of the genetic etio-pathology of the disorder but does not include any clinical feature of the disease.

CARD14-associated disease is usually characterized by psoriasis with or without pustulosis. Therefore, the name was refined to be *CARD14*-associated psoriasis.

Since the 3 variants of IL-10 deficiency are always associated with inflammatory bowel disease, the committee proposed a single name as IL-10 deficiency-associated IBD.

The names; deficiency of the interleukin 1 receptor antagonist (DIRA), deficiency of the interleukin 36 receptor antagonist (DITRA), pyogenic arthritis, pyoderma gangrenosum, and acne (PAPA) and PFAPA remained unchanged since they already conform to our naming conventions. However, the letter P in the abbreviation "PAPA" now stands for the name of the gene *PSTPIP1* rather than “Pyogenic” and, therefore, the new name is "*PSTPIP1*-associated arthritis, pyoderma gangrenosum and acne" (PAPA).

The name "Cherubism" was derived from the Biblical "cherub" (plural cherubim) who has four faces of different species and several pairs of wings,. For most physicians this name does not mean much and therefore, the committee proposed the name *SH3BP2* deficiency with multilocular cystic disease of the mandibles (SDCM). This name gives the etio-pathologic basis of the syndrome with the main clinical feature of fibrous dysplasia of the mandibles.

Finally, the name “Schnitzler syndrome” also remained as an historical one, since its pathogenesis is still obscure and its relationship with *NLRP3* mutations has not been established [69]. A proposal to convert the name of the syndrome to a clinical description: "late onset gammopathy with recurrent urticaria and fever" (LOGRUF) did not gain support from most of the committee members.

Discussion

The definition of autoinflammatory diseases has changed over the years in order to accommodate the new diseases discovered since 1999 – the year the term was first proposed [2, 5, 57-61]. Widening the scope and spectrum of definition of AIDs resulted in the inclusion of disorders with additional defects in the adaptive immune system such as PLAID or HOIL-1 deficiency. Most defects in the immune system

may affect primarily either the innate or the adaptive arm. However, it is becoming increasingly obvious that the innate immune system almost always has an effect on the adaptive system. This leads to the situation that there are disorders that do not fit neatly into the "pure" autoinflammatory or autoimmune categories, and reside actually in a "grey zone" between these two groups. In order to include these disorders with the typical AIDs under the same "rafter", Peckham et al. offered the term "Auto-inflammatory-immune diseases" [70]. We believe that this new name may lead to confusion since all the disorders caused or related to defects in the immune system can be classified under this wide term with no clear categorization. The interferonopathies are clinical disorders caused by defects in the innate response, leading to inflammation after DNA sensing. The activation of cells of the adaptive immunity is a secondary effect of this condition and seems to play a minor role in their pathogenesis. Therefore, they may create the bridge which fits the concept that the autoinflammatory diseases, and the autoimmune diseases are actually in the same spectrum of immune disorders. This continuum model is further supported by the recent discovery of the innate lymphoid cells (ILCs). These cells are defined by differential expression of cell-surface markers and are activated by neuropeptides, cytokines and other alarmins [71]. Their specialized distribution in lymphoid and non-lymphoid tissues, coupled with their functional heterogeneity, has provoked a fundamental reassessment of how they integrate innate and adaptive immune responses.

As already mentioned - many of the current names of AIDs were not appropriate, inaccurate or lack any clinical meaning. Therefore, an attempt to establish new conventions for naming them was really needed.

The conventions (Table 3), and the ensuing proposals (Table 1, and Supplementary Table S1), call for using the name of the gene associated with the disease when it is known rather than the encoded protein. In these cases, demonstration of functional significance of the identified sequence alteration is mandatory.The main advantage of using the name of the gene is that such a name gives the physician a clue about the pathogenesis of the disease and sometimes even about a potential treatment. Moreover, it may allow definite diagnosis using genetic testing. However, it should be borne in mind that including the gene in the name of the disease may pose a problem in cases where the clinical features of the patient are compatible with a certain diagnosis while no expected sequence alteration is found. Thus, the main drawback of using the name of the gene is that **definite** diagnosis can be made only by genetic testing.

In cases where the clinical features and the genetic testing results are in accord, the name is appropriate and the diagnosis is correct and definite. When there is a clearly pathogenic mutation but the clinical features are completely incompatible with the expected diagnosis, one should consider a different disease with a different name. This situation is illustrated by the case of the *MEFV* mutation S242R, which causes neutrophilic dermatosis. The name of this disease is not "FMF" or "atypical FMF" despite the fact that there are *MEFV* mutations - but "pyrin-associated autoinflammation with neutrophilic dermatosis (PAAND)". Similar approach may be applied in the case of *PSTPIP1* with the new mutation and different clinical presentation [72]. We suggest here a "roof" name : *PSTPIP1*-associated autoinflammatory diseases with two subtypes: PAPA and PAMI (*PSTPIP1*-associated myeloid-related proteinemia inflammatory syndrome). However, we cannot add this approach to Table 1 since it was not discussed in the Delphi questionnaires among the large group of participants

When the clinical features are typical for a certain disease (for example FMF) and yet no genetic support for this diagnosis is found, one can denote this medical condition as an FMF-like disease. However, a better choice would be to leave the case as an undefined AID until mutations in other genes are found or additional explanations for the disease are given. The reason is that clinical features typical for one AID may be associated with mutations in different genes. For example, in arecent report, Karacan et al. described two Turkish families in whom 4 patients presented with typical clinical features of FMF [73]. Genetic analysis performed in these patients failed to show *MEFV* mutations. However, total exon sequencing revealed that two patients were homozygous for mutations in *MVK* and the two other patients carried mutations in the *TNFRSF1A* gene. These cases illustrate the difficulties in making a diagnosis of AID based upon clinical features only and justify the proposal to use the gene in naming AIDs wherever it is known.

The way we proposed naming CAPS and FCAS 2 namely NLRP3-associated autoinflammatory disease (NLRP3-AID) and *NLRP12*-AID respectively may pave the way for naming future disorders to be discovered or identified among the other members of the large family of NOD–like receptors (NLRs).. Similarly, *PSMB8*-PRAAS, the name which was proposed to replace CANDLE syndrome, JMP and NNS, may also serve as an example for naming additional proteasome associated diseases to be discovered, just by changing their number. In fact, Brehm et al. recently described several cases that carry mutations in *PSMA3* (encodes α7),

PSMB4 (encodes β7), *PSMB9* (encodes β1i), and proteasome maturation protein (*POMP*) [74].

Unfortunately, the current study did not include many other monogenic AIDs such as those associated with *ADA2, NLRC4, NLRP1* genes or X-linked inhibitor of apoptosis (XIAP) deficiency and (SLAM)-associated protein (SAP) deficiency (75). The reason is that we limited ourselves mainly to the basic list reported by Toiutou et al.(51). However, we hope that the conventions we propose herein may help modifying names of additional diseases - old and new – when, they do not follow the rules suggested.

For this project we used the Delphi technique which allowed discussion via an *ad hoc* web-based system developed by the PRINTO staff under the supervision of NR who has an extensive expertise in consensus formation methodologies. The PRINTO system allowed remote interaction between the participants who had the possibility to share written comments with the other participants in a transparent and traceable way. A limitation of the current work was that for lack of funding we could not conduct a formal nominal group technique (NGT) which is a guided face-to-face discussion and interaction, among small groups of experts. However, the additional discussion of the *ad hoc* steering committee consensus proposal by another group of 26 worldwide experts in the field of AIDs further strengthens these proposals.

In conclusion, the currently proposed rules for nomenclatures of AIDs are expected to allow a better organization of these groups of immune diseases. However, taxonomy is a dynamic process and some of the proposed names may be changed in the future as we gain a better knowledge about their pathogenesis. The proposed taxonomy may gain a broader consensus following an effective communication with other societies such as the International Union of Immunological Societies Expert Committee (IUIS).

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Contributorship Statement

All authors (EBC, MG, AG, DLK, HJL, IT, NR) contributed equally to the planning and conduct of the study. Their placement in the authors' list is dictated by the alphabetic order of their family names.

The first version of the present manuscript was written by EBC, MG and NR, and then revised critically by all the remaining co-authors (AG, DLK, HJL, IT).

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Competing interests

Authors:

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The Gaslini Hospital, which is the public Hospital where NR works as full time public employee, has received contributions from the following industries:

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Additional participants to the Delphi study

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Glossary - Abbreviations

AGS - Aicardi-Goutières Syndrome

AIDs - Autoinflammatory diseases

AIMDs - Autoimmune diseases

ALPS - Autoimmune lymphoproliferative syndrome

APR - Acute phase reactant

CANDLE - Chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature syndrome

CAPS - Cryopyrin-associated periodic fever syndrome

CARD - Caspase recruitment domain family member

CINCA- Chronic infantile neurologic, cutaneous and articular syndrome

CNO - Chronic non-bacterial osteomyelitis

CRMO -Chronic recurrent multifocal osteomyelitis

ADA2 - adenosine deaminase 2

DIRA - Deficiency of the interleukin 1 receptor antagonist

DITRA - Deficiency of the interleukin 36 receptor antagonist

FCAS - Familial cold autoinflammatory syndrome

FMF - Familial Mediterranean fever

HIDS - Hyper-IgD with periodic fever syndrome

HOIL -1 - Heme - oxidised IRP2 ubiquitin ligase 1

IBD - Inflammatory bowel disease
ISSAID - International society for systemic autoinflammatory diseases

JMP - Joint contractures, muscle atrophy, microcytic anemia and panniculitis-induced lipodystrophy.

LOGRUF - Late **o**nset **g**ammopathy with **r**ecurrent **u**rticarial and **f**ever

MEFV - Mediterranean fever

MK- Mevalonate kinase

MKD - Mevalonate kinase deficiency

MVK - Mevalonate kinase

MWS - Muckle-Wells syndrome;

NALP 12- NACHT, LRR and PYD domains-containing protein 1

NGS - New generation sequencing

NLR - NOD-like receptor

NLRC4 - NOD-like receptor with CARD containing 4

NLRP - NOD-like receptor with LRR (Leucine rich repeat), and PYD domain;

NOD - Nucleotide-binding oligomerization domain;

NOMID - Neonatal onset multisystem inflammatory disease

PAAND - Pyrin-associated autoinflammation with neutrophilic dermatosis

PAMI - *PSTPIP1*-associated myeloid-related proteinemia inflammatory syndrome

PAPA - *PSTPIP1* arthritis, pyoderma gangrenosum, and acne

PFAPA: Periodic fever, aphthous stomatitis, pharyngitis and adenitis

PLD - *PLCG2* dysregulation

PLAID - *PLCG2*-associated antibody deficiency and immune dysregulation

PLCG2 - Phospholipase C γ2

POMP - proteasome maturation protein

PRINTO - Pediatric rheumatology international trials organization

PRAAS - Proteasome associated autoinflammatory syndrome

PSMB 3-4,8-9 - Proteasome Subunit, β-type, 3,4,8,9

PSTPIP1 - proline serine threonine phosphatase-interacting protein 1

-**SAPHO** - synovitis, acne, pustulosis, hyperostosis, and osteitis

SDCM - SH3BP2 deficiency with multilocular cystic disease of the mandibles.

SH3BP2 - SH3 Domain Binding Protein2

SAP - SLAM - associated protein

SLE - systemic lupus erythematosus

TNF - Tumor necrosis factor

TNFRSF1A - Tumor necrosis factor receptor super family 1A

TRAPS - TNF-receptor-associated periodic syndrome

XIAP - X-linked Inhibitor of APoptosis

Table 1. Current name of the disorder (in bold) and additional names (normal characters) derived from the literature. The last column reports the proposed nomenclature for the AIDs as results of the consensus process.

Current name of the disorder and additional names	**Proposed nomenclature**
CAPS - Cryopyrin-associated periodic fever syndrome [20]	***NLRP3*-associated autoinflammatory disease (*NLRP3*-AID)**
CINCA - Chronic infantile neurological, cutaneous and articular syndrome [17], NOMID - Neonatal onset multisystem inflammatory disease	Severe
MWS - Muckle-Wells syndrome [18]	Moderate
FCAS - Familial cold autoinflammatory syndrome [19]	Mild
***CARD14*-associated disease**	***CARD14*-associated psoriasis**
PRP - Familial Pityriasis rubrapilaris [30] CAMPS - *CARD14*-mediated pustular psoriasis [31]	
Cherubism [45]	***SH3BP2* deficiency with multi locular cystic disease of the mandibles (SDCM)**
Familial Multilocular Cystic Disease of the Jaws [46] Cherubism--familial fibrous dysplasia of the jaws [47] CGCL - Central giant cell lesion [48]	
CRMO - Chronic recurrent multifocal osteomyelitis [29]	**Chronic non-bacterial osteomyelitis (CNO) -** (when the gene is known it should be added)
Majeed syndrome [26], Congenital dyserythropoietic anemia and chronic recurrent multifocal osteomyelitis [27]	
LIPIN2-associated disease [28]	***LPIN2*-CNO**
DIRA – Deficiency of the IL-1 receptor antagonist [24]	**(No change)**
DITRA - Deficiency of the IL-3 6receptor antagonist [25]	**(No change)**
FCAS2 – Familial cold autoinflammatory syndrome 2 [36]	***NLRP12*-associated autoinflammatory disease (*NLRP12*-AID)**
Guadeloupe fever, NALP12 periodic fever	

Current name of the disorder and additional names	**Proposed nomenclature**
syndrome [36]	**Pyrin-associated autoinflammatory disease (PAAD)**
FMF - Familial Mediterranean fever (FMF)[7] Benign paroxysmal peritonitis [4] , Periodic disease [5], Armenian disease, Periodic disease "Maladie periodique" [6], Familial Mediterranean fever (FMF) [7], Recurrent polyserositis [8], Familial paroxysmal polyserositis [9]	**(No change)**
PAAND - Pyrin-associated autoinflammation with neutrophilic dermatosis [10]	**(No change)**
JMP **Joint contractures, Muscle atrophy, Microcytic Anemia and Panniculitis Induced Lipodystrophy [38],** Chronic Atypical Neutrophilic Dermatosis with Lipodystrophy and Elevated Temperature (CANDLE) Syndrome [37], Nakajo-Nishimura Syndrome (NNS) [39	**Proteasome-associated autoinflammatory syndrome (PRAAS)** ***PSMB8*-PRAAS, *PSMB4*/*PSMB9*-PRAAS, *PSMB4*/*PSMB9*-PRAAS, *PSMA3*/*PSMB8*-PRAAS**
HIDS - Hyper IgD syndrome [15] **Mevalonic aciduria (67)** Mevalonate kinase disease (Deficiency) [13, 14] Dutch type periodic fever [16]	**Mevalonate kinase deficiency (MKD)** **Mild** **Severe** (Add porokeratosis or retinitis pigmentosa when present)
IL-10 Deficiency IBD - IL-10R-associated very early [32] Infantile colitis [33]	**IL-10 deficiency-associated Inflammatory bowel disease**
***NOD2 CARD15*-Associated disease** Blau syndrome [21], Early onset sarcoidosis [22], Familial Crohn's disease [23]	***NOD2*-associated granulomatous disease** (Optional: add Blau syndrome or IBD according to the main clinical features**)**
PAPA / Pyogenic Arthritis, Pyoderma gangrenosum, and Acne syndrome [35]	***PSTPIP1*-associated arthritis, pyoderma gangrenosum, and acne (PAPA)**

Current name of the disorder and additional names	**Proposed nomenclature**
PFAPA - Periodic fever, aphthous stomatitis, pharyngitis and adenitis Periodic fever, aphthous stomatitis, pharyngitis and adenitis or periodic fever aphthous pharyngitis and cervical adenopathy [41] Marshall's syndrome [42]	**(No change)**
Schnitzler syndrome [40] PUPAP - Periodic fever with urticaria and paraprotein	**(No change)**
TRAPS - TNF receptor-associated periodic fever syndrome[3] Familial Hibernian fever [11] Familial autosomal dominant periodic fever [12]	**(No change)**

Table 2. Results from the Delphi questionnaires for consensus on nomenclature

Definition or Disease	Group of AIDs experts consensus (N=26)
Definition	
Autoinflammatory diseases are clinical disorders caused by defect(s) or dysregulation of the innate immune system, characterized by recurrent or continuous inflammation (elevated APR) and by the lack of a *primary* pathogenic role of the adaptive immune system (auto - reactive T-cells or autoantibody production).	87%
Final names proposed for the AIDs	
CARD14-associated psoriasis	91%
CNO: Chronic non-bacterial osteomyelitis	87%
DIRA: Deficiency of the IL-1 receptor antagonist	96%
DITRA: Deficiency of the IL-36 receptor antagonist	96%
IL-10 deficiency-associated inflammatory bowel diseases	83%
PAAD: Pyrin-associated autoinflammatory disease: FMF, PAAND	88%
MKD: Mevalonate kinase deficiency	87%
NLRP3-AID – *NLRP3*-associated autoinflammatory disease	88%
NLRP12-AID – *NLRP12*-associated autoinflammatory disease	88%
NOD2-associated granulomatous diseases	83%
PAPA: *PSTPIP1*-associated arthritis, pyoderma gangrenosum and acne	87%
PFAPA: Periodic fever, aphthous stomatitis, pharyngitis and adenitis	83%
PRAAS : Proteasome-associated autoinflammatory syndrome	84%
Schnitzler syndrome	87%
SDCM - *SH3BP2* deficiency with multilocular cystic disease of the mandibles	94%
TRAPS - TNF receptor-associated periodic fever syndrome	83%

Table 3. Recommandations for naming AIDs

1. Try not to change wherever the name is appropriate.
2. Avoid names of persons or geographical spread of disease (eponyms)
3. Include the genetic basis (name of the gene) of the disease where it is known (prefer the name of the gene over the name of the encoded protein unless the name of the gene is not accurate or meaningless)
4. Include key clinical features where appropriate
5. Shorten the name as much as possible
6. Choose a name that is as clear as possible
7. In diseases where our knowledge about the pathogenesis is still limited, leave the previous name (PFAPA)
8. In diseases with different phenotypes but mutations in the same gene, use a general "roof" name with subtypes (PAAD, NOD2).
9. When the clinical features seemed to be "continuous" give a general name ("roof" name) and classify the various presentations according to their phenotypic severity (*NLRP3*-AID*, MKD*).

Legends to figure

Figure 1

The group of diseases associated with *MEFV* sequence alterations. The "roof" name is a general name whereas the subtypes are more specific and meaningful.