Monogenic Autoinflammatory Diseases with Mendelian Inheritance: Genes, Mutations, and Genotype/Phenotype Correlations

Davide Martorana1*, Francesco Bonatti2, Paola Mozzoni2, Augusto Vaglio3 and Antonio Percesepe2

1 Unit of Medical Genetics, University Hospital of Parma, Parma, Italy, 2 Department of Medicine and Surgery, University Hospital of Parma, Parma, Italy, 3 Unit of Nephrology, University Hospital of Parma, Parma, Italy

Autoinflammatory diseases (AIDs) are a genetically heterogeneous group of diseases caused by mutations of genes encoding proteins, which play a pivotal role in the regulation of the inflammatory response. In the pathogenesis of AIDs, the role of the genetic background is triggered by environmental factors through the modulation of the innate immune system. Monogenic AIDs are characterized by Mendelian inheritance and are caused by highly penetrant genetic variants in single genes. During the last years, remarkable progress has been made in the identification of disease-associated genes by using new technologies, such as next-generation sequencing, which has allowed the genetic characterization in undiagnosed patients and in sporadic cases by means of targeted resequencing of a gene panel and whole exome sequencing. In this review, we delineate the genetics of the monogenic AIDs, report the role of the most common gene mutations, and describe the evidences of the most sound genotype/phenotype correlations in AID.

Keywords: autoinflammatory diseases, hereditary periodic fevers, familial Mediterranean fever, mevalonate-kinase deficiency, tumor necrosis factor receptor-associated periodic syndrome, cryopyrinopathies, inflammasome, whole exome sequencing

INTRODUCTION

The term autoinflammatory disease (AID) was proposed in 1999 to describe a group of disorders of the innate immune system characterized by recurrent episodes of inflammation without a known origin (1). AIDs are frequently caused by genetic mutations in genes encoding proteins involved in the pathways of the inflammasome, with a crucial role of proinflammatory interleukin-1 (IL-1), which is an important cytokine of the systemic inflammatory response.

Autoinflammatory diseases have in the most of cases a genetic background, with highly penetrant mutations of single genes, but in some cases are polygenic, with a strong environmental influence that can modulate the phenotype (2).

The first AID described was the familial Mediterranean fever (FMF), which is also the most prevalent AID in the world. After FMF, other two AIDs were described: TNF-receptor associated periodic syndrome (TRAPS) (1) and hyperimmunoglobulinemia D with periodic fever syndrome [hyper-IgD syndrome (HIDS)/mevalonate kinase (MVK)] (3–5). These three forms of AID were grouped in the hereditary periodic fever syndromes, because they share fever episodes. After these,
other AIDs were identified, such as familial cold autoinflammatory syndrome (FCAS), Muckle–Wells syndrome (MWS), and neonatal onset multisystem inflammatory disease (NOMID), also known as chronic infantile neurologic cutaneous and articular (CINCA) syndrome, then grouped in the cryopyrinopathies. These disorders are also known as cryopyrin-associated periodic syndromes (CAPS).

Recently, mutations in single genes involved in IL-1 processing have been demonstrated in the deficiency of IL-1 receptor antagonist (DIRA) (6). After this, evidences of drugs able to block IL-1 in the Majeed syndrome (MS), an AID bone disease with clinical similarities to DIRA, demonstrated the pivotal role of IL-1 in this disorder (7). The same drug was used for cryopyrinopathies and DIRA, further expanding its use to other monogenic AID disorders. Other granulomatous disorders are characterized by typical granulomatous formations: Blau syndrome (familial juvenile systemic granulomatosis) is characterized by granulomatous inflammation of joint, skin, and uvea.

In this review, we will focus only on monogenic AIDs, which are mostly represented by early-onset conditions and a clear pattern of autosomal dominant or recessive transmission, at least in some of the families (Table 1) and the clinical significance of exonic variants according with pathogenic criteria (Table 2). The review will analyze the evidences about the mutations in the genes involved in the pathogenesis of the disease and the genotype/phenotype correlations (8).

### TABLE 1 | Classification of monogenic autoinflammatory diseases (AIDs).

| Disorder (abbreviation) | #OMIM   | Gene (Locus) | Protein involved | Inheritance     |
|-------------------------|---------|--------------|------------------|-----------------|
| Familial Mediterranean fever | 249100  | MEFV (16p13.3) | Pyrin (marenostrin) | Autosomal recessive |
| Hyper-IgD syndrome | 260920  | MVK (12q24.11) | Mevalonate kinase | Autosomal recessive |
| Mevalonate kinase deficiency | 260920  | MVK (12q24) | Mevalonate kinase | Autosomal recessive |
| Tumor necrosis factor receptor-associated periodic syndrome | 142680  | TNFRSF1A (12p13) | Tumor necrosis factor receptor type-1 | Autosomal dominant |
| Familial cold autoinflammatory syndrome (FCAS) | 120100  | NLRP3 (1q44) | Cryopyrin | Autosomal dominant |
| Muckle–Wells syndrome | 191900  | NLRP3 (1q44) | Cryopyrin | Autosomal dominant |
| Neonatal onset multisystem inflammatory disease | 607115  | NLRP3 (1q44) | Cryopyrin | Autosomal dominant |
| Deficiency of interleukin (IL)-1 receptor antagonist | 612852  | IL1R (1q21) | IL-1 receptor antagonist | Autosomal recessive |
| Blau syndrome | 186580  | NOD2/CARD15 (16q12.1-13) | Nucleotide-binding oligomerization domain-containing protein 2 | Autosomal recessive |
| Deficiency of the IL-36 receptor antagonist | 614204  | IL36RN (2q14) | IL-36 receptor antagonist | Autosomal recessive |
| Chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature syndrome | 256040  | PSMB8 (6p21) | Inducible subunit β of the proteasome | Autosomal recessive |
| Majeed syndrome | 609628  | LIPIN2 (18p11.31) | Lipin 2 | Autosomal recessive |
| CARD14-mediated pustular psoriasis | 177900  | CARD14 (17q25.3) | Caspase recruitment domain family member 14 | Autosomal dominant |
| NLRP12-autoinflammatory disease | 609648  | NLRP12 (19q13.42) | Monarch 1 | Autosomal dominant |
| Pyogenic arthritis, pyoderma gangrenosum, and acne syndrome | 604416  | PSTPIP1 (15q24-25) | CD2 antigen-binding protein 1 | Autosomal dominant |
| Deficiency of adenosine deaminase 2 | 615688  | CEGR1 (22q11.1) | Adenosine deaminase 2 | Autosomal recessive |
| STING-associated vasculopathy | 615934  | TMEM173 (5q31.2) | Transmembrane protein 173 | Autosomal dominant |
| TNFRSF11A-associated disease | 603499  | TNFRSF11A (18q21.33) | Tumor necrosis factor receptor 11A | Autosomal dominant |
| NLRC4-associated diseases (NLRC4-MAS, SCAN4, NLRC4-FCAS) | 606831  | NLRC4 (2p22.3) | NLR family CARD domain-containing Protein 4 | Autosomal recessive |
| Sideroblastic anemia, B-cell immunodeficiency, periodic fevers, developmental delay | 616084  | TRNT1 (3p26.2) | CCA-adding enzyme | Autosomal recessive |
| Monogenic form of systemic juvenile idiopathic arthritis | 613409  | LACC1 (13q14.11) | Laccase (manganese oxidoreductase) | Autosomal recessive |

### Familial Mediterranean Fever
Familial Mediterranean fever is the most common AID, which is inherited as autosomal recessive disease, although features of autosomal dominant pattern of transmission have been demonstrated in several families (9). This different pattern might have conferred an evolutionary advantage in the resistance to an endemic pathogen; in fact, Clostridium, Yersinia, Vibrio *para
demolyticus* VopS, *Histophilus somni* IbpA, Burkhoderia, and other microbes that modify RhoGTPases are able to stimulate pyrin inflammasome. Pyrin play a role in sensing pathogen modification and inactivation of Rho GTPases (10,11). Furthermore, in some populations, as Sephardic Jews, Turks, Arabs, and Armenians, the carrier rate for a mutant *MEFV* allele is high, ranging from 1/3 to 1/6; this represents the highest carrier rates reported for an autosomal recessive disorder.

To estimate prevalence in FMF is difficult, because of the wide range of differences in areas of diffusion of the disease. In particular, the most affected patients belong to Middle Eastern living around the Mediterranean Sea areas.

The causing gene, *MEFV*, was identified in 1997 by two International Consortia, who named the encoded protein pyrin/ marenostrin (11, 12), an intracellular regulator of IL-1 production (13, 14). The disease-causing mutations spread all over the gene, even if the exon 10 carries the most typical and severe mutation; in fact, this exon encodes for the B30.2/SPRY domain at the C-terminal end of pyrin, which is demonstrated to interact...
TABLE 2 | Clinical significance of exonic variants according with the pathogenic criteria of ClinVar database (https://www.ncbi.nlm.nih.gov/clinvar/) for genes MEFV, MVK, TNFRSF1A, and NLRP3.

| Gene | Conflicting interpretation | Benign | Likely benign | Uncertain significance | Likely pathogenic | Pathogenic |
|------|---------------------------|--------|---------------|------------------------|-------------------|------------|
| MEFV | Leu110Pro                 | Glu148Gln | Ser6Arg | Gly304Arg | Glu148Gln |
|      | Glu148Gln                 | Gly202Gln | Val33Leu | Pro389Ser | Glu148Val |
|      | Gly148Val                 | Gly304Arg | Arg12G1p | Arg408Gln | Glu167Asp |
|      | Gly196Trp                 | Arg108Gln | Asn78I1e | Met680I1e | Pro180Gln |
|      | Gly304Arg                 | Asn78Ser | Gly196Trp | Lys695Arg | Thr267Ile |
|      | Pro369Ser                 | Glu84Gln | Arg408Gln | Ala744Ser | Glu276Ter |
|      | Arg408Gln                 | Glu93Gln | Gly196Trp | Leu367Val | Pro389Ser |
|      | Ile591Thr                 | Gly97Ter | Arg202Gln | His404Arg | Thr577Asn |
|      | Lys695Arg                 | Asp103His | Arg408Gln | Arg478Gln | Arg563His |
|      | Ile591Thr                 | Ser108Arg | Arg478Gln | Met680Ile | Gly687Asp |
|      | Lys695Arg                 | Thr577Asn | Gly148Val | Tyr688Ter | Ile692del |
|      | Thr577Asn                 | Ala171Thr | Arg147Ala | Met689Val | Met694del |
|      | Met694Val                 | Ala193Thr | Glu148Gln | Met694del | Lys695Arg |
|      | Ala193Thr                 | Gly196Val | Arg151Thr | Val726Ala | Ala744Ser |
|      | Thr203Met                 | Ile171Thr | Glu148Val | Arg761His | Arg761His |
|      | Ala311Val                 | Ile192Thr | Gly304Arg | Lys695Arg | Arg761His |
|      | Asp122Gly                  | Thr309Met | Thr203Met | Ile744Ser | Arg761His |
|      | Gly13Glu                   | Ala511Thr | Ala193Thr | Ala744Ser | Arg761His |
|      | Glu147Ala                  | Pro399Val | Gly320Glu | Arg761His | Arg761His |
|      | Glu147Alafs                | Ser329Glu | Arg348His | Gly687Asp | Gly687Asp |
|      | Glu148Val                  | Gly356Glu | Ile992Val | Thr726Ala | Thr726Ala |
|      | Arg151Thr                 | Pro630Alafs | Pro399Ser | Pro399Ser | Pro399Ser |
|      | Glu163Glun                 | Pro630Alafs | Arg480Gln | Arg480Gln | Arg480Gln |
|      | Ala171Thr                 | Gly446Glu | Glu446Ala | Gly446Glu | Gly446Glu |
|      | Val469Glu                  | Lys447Asn | Lys447Asn | Lys447Asn | Lys447Asn |
|      | Arg461Glu                  | Ala457Val | Ala457Val | Ala457Val | Ala457Val |
|      | Val461Val                  | Val469Glu | Val469Glu | Val469Glu | Val469Glu |
|      | Asp505Thr                  | Asp505Thr | Asp505Thr | Asp505Thr | Asp505Thr |
|      | Arg579His                  | Arg579His | Arg579His | Arg579His | Arg579His |
|      | Ala591Thr                 | Ala591Thr | Ala591Thr | Ala591Thr | Ala591Thr |
|      | Asn599Asp                  | Asn599Asp | Asn599Asp | Asn599Asp | Asn599Asp |
|      | Lys825Glun                 | Lys825Glun | Lys825Glun | Lys825Glun | Lys825Glun |
|      | Pro714Leu                  | Pro714Leu | Pro714Leu | Pro714Leu | Pro714Leu |
|      | Lys716Glu                  | Lys716Glu | Lys716Glu | Lys716Glu | Lys716Glu |
|      | Phe743Leu                  | Phe743Leu | Phe743Leu | Phe743Leu | Phe743Leu |
|      | Ile772Val                  | Ile772Val | Ile772Val | Ile772Val | Ile772Val |
|      | Pro780Thr                 | Pro780Thr | Pro780Thr | Pro780Thr | Pro780Thr |
|      | Pro111Leu                  | Pro111Leu | Pro111Leu | Pro111Leu | Pro111Leu |
|      | Ile268Val                  | Ile268Val | Ile268Val | Ile268Val | Ile268Val |
|      | Met1Thr                   | Met1Thr | Met1Thr | Met1Thr | Met1Thr |

(Continued)
TABLE 2 | Continued

| Gene | Clinical significance |
|------|-----------------------|
|      | Conflicting interpretation | Benign | Likely benign | Uncertain significance | Likely pathogenic | Pathogenic |
|      | Ser52Asn | Ser52Asn | Val15Ala | Cys21Ser | Leu27Phe | Val80Ile | Cys101Tyr | Arg106His | Ala111Thr | Pro200Ser | Pro256Leu | Gln302Ter | Arg388Gln | Leu653Gly | His209Pro | Gly257Trpfs | Leu414Pro | Tyr116His | Gly140Argfs | Ala141Glyfs | Ala148Thr | Pro165Leu | Pro167Leu | Trp188Ter | Gly202Arg | Val203Ala | Arg215Ter | Leu255Pro | Ile266Thr | Asn301Thr | Val310Met | Ala334Thr | Pro365Ser | Val377Ile | Asp388Ter | |
| TNFRSF1A | Arg121Gln | None | Pro75Leu | Val112Met | Arg121Gln | Val124Met | Asn145Ser | Glu178Lys | Ile199Thr | Pro269Arg | Pro275Ser | Pro412Ala | Ser452Arg | Asp41Glu | Phe89Leu | Asn94Lys | Arg106Gln | Cys59Arg | Cys59Ser | Cys62Gly | Cys62Ty | Thr79Met | Cys81Phe | Cys99Ser | Cys99Arg | Cys117Arg | Cys117Ty | Arg121Pro | Arg121Gln | |
| NLRP3 | Val198Met | Val72Met | Ser196Asn | Val198Met | Ser196Met | Arg193Val | Arg100Cys | Lys131Arg | Arg137His | Asn168Ser | Thr195Met | Val198Met | Asp212Asn | Ala225Val | Gln250Arg | Pro315Leu | Lys357Arg | Thr435Ala | Leu447Phe | Gly456Ser | Lys618Asn | Gln705Lys | Ser728Gly | Gln705Lys | Ser728Gly | Thr954Met | Ala1958Met | Arg206Trp | Arg303Asn | Glu304Lys | Phe309Ser | Thr348Met | Ala355Val | Leu353Pro | Thr405Pro | Ala439Val | Gly569Arg | Gly571Arg | Phe573Ser | Gly627Gly | Tyr659Cys | (Continued) |
with the protein caspase 1 (15). Although five mutations repre-
sent more than 85% of all disease-associated mutations, many
other mutations with different clinical penetrances have been
reported so far (in the Infevers website more than 300 mutations
are described) (16). Genetic test can support clinical diagnosis,
confirming the presence of two mutations in the MEFV gene,
although patients with a heterozygous mutation can show clinical
pictures of FMF, even if with an incomplete phenotype (17).

In fact, there are evidences that the mutation in the second
allele is not demonstrated in 20–25% of the patients with the
clinical picture of FMF and a positive response to colchicine
therapy (18). The reduced diagnostic accuracy of the genetic
tests in terms of mutation finding is common to most of the genes
studied for diagnostic purposes, since the diagnostic yield of the
tests is never complete, due to factors like genetic heterogeneity,
incorrect diagnosis, or phenocopies. When a heterozygous is
found, the most obvious hypothesis is that the second disease
allele lies in other genic regions not explored by the test (i.e.,
deep intronic regions); however, the second mutation has not been
found also in studies analyzing the promoter and intron regions
of the MEFV gene. In FMF, however, the evidence of autosomal
dominant transmission, segregating a heterozygous mutation
(17), or a complex allele (personal data) is consistent with a
dosage effect, which is dependent on the type of the mutation,
in analogy to models already described in other disease genes
(i.e., GJB2, in which biallelic mutations cause autosomic reces-
sive nonsyndromic deafness and dominant mutations in specific
domains of the gene cause syndromic forms of deafness with pal-
moplantar keratoderma). Another possible pathogenetic model
for the dominant forms could involve the interaction of genetic
and environmental factors in the pathogenesis of the disease, in
analogy with hemochromatosis, in which heterozygotes for the
C282Y in the HFE gene are bona fide healthy carriers unless
other factors like alcohol or viral infections induce the onset of
the clinical phenotype by contributing to the accumulation of
iron in the liver. In a genomic study of 22 Belgian individuals, 12
of whom had clinical pictures of AID, the pattern of Mendelian
inheritance was autosomal dominant. The phenotype, different
from FMF, was characterized by childhood-onset recurrent
episodes of neutrophilic dermatosis, fever, elevated acute-phase
reactants, arthralgia, and myalgia/myositis. The disease was
named pyrin-associated autoinflammation with neutrophilic
dermatosis (PAAND). Genomic analysis revealed a mutation in
the MEFV gene, S242R. This mutation causes a loss of a binding
motif in the pyrin protein different from the B30.2/SPRY domain.

Interestingly, the loss of the S242 domain was observed in bac-
terial effectors able to activate the pyrin inflammasome, such
as Clostridium difficile toxin B (TcdB). As a result, the S242R
mutation has the same effect of pathogen sensing, acting as a
trigger of the inflammasome activation and IL-1b production.
Based on this fact, the affected patients were successfully treated
with therapy targeted on IL-1b, resolving autoinflammation and
neutrophilic dermatosis (19).

Another intriguing aspect in FMF and, more in general AID,
is the different influences of certain mutations or polymorphisms
on the phenotype. For example, an E148Q mutation is sometimes
referred to as a functional polymorphism because of the high
carrier rate (more than 10%) and the lack of phenotype in some
homozygous patients. However, some patients may have severe
disease expression as well. Thus, the suggestions put forward for
the carrier state may apply to these states as well.

Environmental factors have been investigated in relation with
disease severity in FMF (19). The strongest association correlated
with amyloidosis was with the country of origin, not with the
genotype. Another interesting study showed that Turkish children
who are born and live in Turkey have a higher disease severity
score compared with Turkish children living in Germany (20);
this study demonstrated that the different patterns of infections
influence the expression of the phenotype acting as a trigger of the
weak innate immune pathway via pathogen-recognition factors.

In order to search for possible mutation in the MEFV gene,
a multiplex ligation-dependent probe amplification was setup in
216 FMF patients (21). No copy number variants were identified,
suggesting that deletion/duplication is not a mutational mecha-
nism in MEFV. The possible functional explanation relies on the
pyrin function, which is crucial in the immune surveillance, even
if with genetic variants such as point mutations and functional
polymorphisms able to modulate its function.

An interesting study aimed at investigating pyrin function
during primate evolution analyzed the domain which contains
the most MEFV mutations, named ret finger protein domain.
Amino acids involved in MEFV mutations (653, 680, 681, 726,
744, and 761 residues) in human are frequently present as wild
type in other primates. In some cases, the mutant may be consid-
ered the reappearance of an ancestral amino acid state. As a result,
an episodic positive selection was postulated. These changes in
pyrin sequence could be caused by selective pressures driven
from environmental agents (22).

Regarding the therapy, both a single mutation and two muta-
tions, supported by clinical pictures of FMF, support the use of
colchicine (23). Amyloidosis type AA is frequently correlated with the MEFV mutation M694V and the SAA1.1/SAA1.1 genotype (24).

In analogy with most of the disorders with pleiotropic expression, also for FMF, strict clinical criteria have been proposed for the diagnosis (25), taking into account the phenotypic manifestations (the recurrence of fever with serositis), the histological picture (idiopathic AA amyloidosis), and the response to therapy (in typical FMF, the colchicine test results in a favorable response). Two major criteria are necessary for a definite diagnosis of FMF. Recurrent fever without serosal involvement, cutaneous, erysipelas-like manifestations, and a positive family history for the disease in a first-degree relative are considered minor criteria for the lower specificity of the features and take part in the algorithm for diagnosis only if a major criterion is present. The presence of two mutations in MEFV gene is generally achieved in patients fulfilling the clinical criteria, but also, to a much lesser extent, also in subjects with atypical phenotypic features, whereas also heterozygous mutation carriers can suffer from an incomplete and even typical disease (17). For all these reasons, the detection of a single heterozygous mutation, in the presence of clear clinical symptoms, appears to be a sufficient prerequisite for a colchicine trial (23).

**HIDS/Mevalonate Kinase Deficiency (MKD)**

Periodic fever associated with MKD was originally identified in 1984 in patients of Dutch ancestry; they reported recurrent attacks of fever of unknown origin and a high serum IgD level (26). After this first description, the disease was named Dutch fever or HIDS. After the first report, MKD was then described in other European countries around the Mediterranean basin (27) and Asia (28).

Because of the low sensitivity and specificity of the raised IgD serum levels, the term HIDS has been replaced by periodic fever associated with MKD after the discovery of the causing mutations in the MVK gene (OMIM *251170) located on chromosome 12q24 (29).

Mevalonate kinase deficiency, also known as hyperimmunoglobulinemia D syndrome (OMIM 260920) is characterized by an autosomal recessive Mendelian inheritance pattern (5) and is allelic to another disorder, mevalonic aciduria (MA, OMIM 610377), characterized by a very low activity of the enzyme MVK.

As in other AIDs, the carrier rate of 1/350 in normal population allowed to hypothesize a selective advantage for heterozygous carriers; a possible explanation postulates that countries with a diet at high consumption of saturated animal fats rich in cholesterol could have selected heterozygous carriers of the most frequent MVK mutations (30); nevertheless, this theory has not been demonstrated and other possible explanations are possible.

So far more than 130 substitutions or deletions of the MVK gene have been reported (16), even if a small number of mutations (V377I, I268T, H20P, and P167L) represent the 71.5% of the whole mutation spectrum in MKD patients (29).

Several genotype–phenotype associations have been described. The most common mutation is the V377I variant, which is associated with a mild phenotype of MKD and some residual MVK activity. V377I is frequently found in a compound heterozygous state in most MKD patients (5, 31). At the opposite hand, some variants (i.e., V310M, A334T) are closely associated with a severe MA phenotype and severely impaired cellular MVK activity (32).

Interestingly, the H20P and I268T mutations have been described in intermediate phenotype, either with MA and MKD clinical signs, such as fever attacks associated with some neurological manifestations (mental retardation, cerebellar ataxia) of variable severity (33), leading to the hypothesis that the two diseases may represent the two extremities of the phenotypic spectrum which depends on the type (truncating vs non-truncating) of the mutations or the degree of impairment of the MVK enzyme activity. For example, mutations resulting into a MKD phenotype are exclusively missense, associated with a mild reduction of the enzymatic activity whereas in the MA phenotypes, frameshift and nonsense mutations are commonly reported (16), which completely inactivate the gene function. In fact, the MVK gene encodes the enzyme MVK, involved in the ATP-dependent phosphorylation of mevalonic acid into 5-phosphomevalonate. Mutations affecting this gene alter the MVK activity, with an overproduction of proinflammatory isoprenoids, reduced synthesis of cholesterol, and accumulation of mevalonic acid in plasma and urine. Fever rushes may be caused by high release of IL-1β as a consequence of insufficient geranylgeranyl pyrophosphate generation (32). The development of fever may be caused by a dysregulation of the MVK pathway, but the pathogenetic mechanisms leading to the autoinflammation remain to be clarified.

**Tumor Necrosis Factor Receptor-Associated Periodic Syndrome**

Tumor necrosis factor receptor-associated periodic syndrome (OMIM 142680) is the most common autosomal dominant AID in Europe; it was initially named “familial Hibernian fever” from the ancient Latin name “Hibernia” given to Ireland. In fact, in 1982, a large family from Scotland and Ireland was described with a new disorder, characterized by recurrent fevers, skin rashes, monocytic fasciitis, and abdominal pain (2). Since the first description, several cases have been identified in many other populations, such as Black Americans, Japanese, and patients of Mediterranean ancestry (34).

In 1998, the genetic basis of this condition was discovered and the name became TRAPS due to its relationship with the p551A receptor of TNF (TNFR1), encoded by the TNF super family receptor 1A (TNFRSF1A) gene (1, 2), whose mutations cause the disease. The TNFRSF1A gene is composed of 10 exons with the disease causing mutations, all missense and heterozygous, all concentrated into exons 2, 3, 4, and 6 (2). Based on the mutation position, they can be distinguished as high- or low-penetration missense mutations. The high-penetration mutations are located in cysteine-rich N-terminal domains, which are important for the assembly of the receptor’s three-dimensional structure (35, 36); furthermore, they cause an early disease onset and more severe clinical manifestations; the substitutions result in single
amino acid substitutions in the cysteine rich domains (CRDs) 1, 2, or 3 of the ectodomain of the mature TNFR protein (37). These CRDs are involved in disulfide bond formation and in the folding of the extracellular portion of the protein. On the other hand, the TNFRSF1A low-penetrance mutations, such as R92Q and P46L, are associated with lower risk of amyloidosis and adult-onset, milder and/or atypical clinical features (16, 38–40); for instance, the P46L substitution occurs in up to 20% of clinically asymptomatic West African individuals, suggesting that it represents a polymorphism rather than a disease-causing mutation, whereas the R92Q substitution, relatively common in the Caucasian population, is a low-penetrance variant, which could have a weak contribution to disease expression. Moreover, TNFRSF1A mutations affecting TNF receptor shedding from cell membranes might potentially generate a selective advantage related to an increased antibacterial capacity (41). More in general, it can be assumed that, on the contrary to other fully penetrant autosomal dominant disorders, like neurofibromatosis type I (OMIM #162200), in which the new cases of the disease are all caused by new mutations in the NFI gene, the new cases of TRAPS belong to families in which the mutation segregates through the generations without giving manifest signs of disease. For this reason, in each proband, a careful family history for the cardinal signs of recurrent fevers, fasciitis, and cutaneous rash should always be collected.

Based on the difficulties with a clinical diagnosis of AIDs, a genetic test is useful in cases of patients with clinical TRAPS phenotype, and a genetic diagnosis of TRAPS can be performed in the presence of a mutation in TNFRSF1A. Routine diagnostic analysis is limited to the exons 2, 3, 4, and 6, whereas the expansion of the analysis to the remaining coding regions of the gene is recommended only for cases with extremely suggestive phenotypes yet without a definitive diagnosis. In the absence of a family history and with borderline phenotypes, the probability of mutation finding with the extension of the genetic analysis to the whole gene remains very low and the decision should be carefully discussed with the clinician.

At pathogenic level, several mechanisms may be responsible for the disease onset, such as impaired TNF receptor shedding, defective intracellular TNF receptor trafficking to the cell surface, and subverted TNF-independent cell activation with increased production of IL-1 and IL-6, altered NF-κB pathway, increased activation of mitogen-activated protein kinases, and upregulated production of reactive oxygen species (42, 43).

The molecular link between TRAPS and IL-1 is not clear: the pathogenesis may vary with each mutation, but it is possible that IL-1 might act as a proinflammatory mediator downstream of TNF, or that aggregates of misfolded TNF receptors stimulate intracellular signals resulting in enhanced production of IL-1 and other chemokines (44).

Cryptopyrinopathies (FCAS, MWS, and NOMID)

Familial cold autoinflammatory syndrome (OMIM 120100), MWS (OMIM 191900), and CINCA syndrome (OMIM 607115), also known as neonatal onset multisystem inflammatory disease (NOMID), are autosomal dominant disorders (45–47) caused by mutations in the NLRP3 (NOD-like receptor 3, cold-induced autoinflammatory syndrome 1, also named CIAS1) gene, encoding for the cryopyrin protein, an important inflammasome protein that directly activates IL-1β (48). Until 2001, these diseases were considered as three different diseases. Since 2001, mutations in the NACHT domain of the NLRP3/CIAS1 gene were linked to FCAS and MWS (49, 50), whereas mutations in the same gene were identified in 2002 in sporadic cases with NOMID/CINCA (48, 51); after these evidences, the three disorders were grouped under the family of CAPS. FCAS and MWS are usually familial (49), while NOMID/CINCA is sporadic (52, 53).

Cryptopyrin-associated periodic syndromes are rare diseases, with an estimated prevalence of approximately 1–2 patients per 1,000,000 people in Europe and in the USA (54).

Familial cold autoinflammatory syndrome, MWS, and NOMID/CINCA share a significant symptom overlap (55), with the latter described across the world as the most severe expression of CAPS (56).

In Infevers database, 175 different nucleotide variants and more than 90 heterozygous mutations on the NLRP3 gene have been described to date (16, 57). Mutations in NLRP3 gene are described in approximately 60% of CAPS patients, causing the constitutive activation of the inflammasome and dysregulation with IL-1 overproduction; excessive IL-1 signaling appears to be a constant feature in the background of CAPS, driven by gain-of-function NLRP3 mutations, even in the absence of a second signal (58). As in all the AIDs, genetic testing is confirmatory, even if the diagnosis needs to be made on clinical symptoms.

More than 40% of NOMID/CINCA patients and a less percentage of FCAS and MWS patients do not carry germ-line mutations in NLRP3. In those patients, somatic mosaicism occurring during fetal development may explain the variation in disease onset (59); this mechanism can only be demonstrated by cell cloning and next-generation sequencing (NGS).

Genotype–phenotype correlations were demonstrated in CAPS, with some mutations associated only with a mild clinical phenotype, and others with severe clinical pictures. However, several cases were reported in which patients with the same mutations present different phenotypes (60, 61). Furthermore, some NLRP3 mutations are described in healthy subjects with no signs of CAPS, such as V198M and Q703K genetic variants, even if there is no apparent selective advantage demonstrated for CAPS (62). Nevertheless, when patients who carry these polymorphisms show CAPS symptoms, the IL-1β-inhibition response is diminished. As in the other AIDs, functional polymorphisms may be considered low penetration mutations, able to influence the activity of the gene product (58, 63).

In conclusion, CAPS onset may be influenced by environmental factors and genetic determinants, which are also able to modulate the disease phenotype.

Deficiency of Interleukin-1 Receptor Antagonist

Deficiency of IL-1 receptor antagonist is a recently described autosomal recessive disease due to mutations of IL1RN that
lead to non-expression of the encoded protein, IL-1 RA, causing unopposed IL-1 receptor activation and increased response to IL-1α and IL-1β stimulation (64).

The disease was first described in 2009 in nine patients presented with sterile multifocal osteomyelitis, periostitis, and pustulosis since the neonatal period, without fever. IL1RN gene was sequenced in those DIRA patients (6): either homozygous for mutations in IL1RN or heterozygous parents were identified. A patient was homozygous for two nucleotides deletion (c.156_157delCA) that caused a frame-shift mutation named N52KfsX25, followed by the incorporation of 24 aberrant amino acids and a termination codon. Both parents were heterozygous carriers of the same mutation. In other patients, three were homozygous for a nonsense variant affecting the amino acid residue at position 77 (c.229G>T; p.E77X). Patients from a consanguineous Lebanese family were homozygous for a nonsense mutation (c.160C>T, p.Q54X). Patient 9, from Puerto Rico, was homozygous for a deletion of approximately 175 kb on chromosome 2q that includes six genes from a cluster of IL-1-related genes: IL1RN and the genes encoding IL-1 family, members 9 (IL1F9), 6 (IL1F6), 8 (IL1F8), 5 (IL1F5), and 10 (IL1F10). The IL1RN mutations are present in founder populations in Newfoundland, the Netherlands, Puerto Rico, and possibly Lebanon and further founder mutations have since been found in other populations (65). None of these mutations were found in DNA specimens obtained from a panel of 364 controls from the New York Cancer Project.

In 2011, two unrelated Brazilian patients whose clinical phenotype was consistent with the DIRA syndrome were described (66). Both were homozygous for the same 15-bp (in-frame) deletion on IL1RN. This novel mutation of IL1RN produces a protein that does not bind the IL-1 receptor, and thus lacks functional activity. The authors hypothesize that this variant is likely to be a possible founder mutation in the Brazilian population.

In 2012, a novel nonsense mutation (p.Q119X) in IL1RN gene was identified in two Turkish patients with consanguineous parents (67).

**Blau Syndrome (BS)**

Blau syndrome is an autosomal dominant granulomatous inflammatory disease caused by mutations in the NOD2/CARD15 gene. This gene is located on chromosome 16q12 and encodes the three domain cytosolic protein of almost 1000 amino acids, the nucleotide-binding oligomerization domain containing 2 (NOD2). The protein contains two N-terminal CARDs for downstream signaling through CARD–CARD interactions, a central nucleotide binding and oligomerization domain (NACHT) with ATPase activity, and nine C-terminal LRRs for pathogen-associated molecular patterns (68).

Mutations in the NOD2/CARD15 gene cause alteration in single amino acids in the NOD2 protein, resulting in an overactive version, which may lead to abnormal inflammatory reaction.

More details on the pathogenic aspects of BS were obtained from the identification in four European families of three missense mutations in 2001. Two of these families shared the same mutation, encoding an amino acid substitution of arginine to tryptophan in position 334 (R334Q), one family had an R334W and another L469F substitution (69).

The following year, another study on the genetic analysis of NOD2 coding regions based on 10 families with BS was published (70). In five of the families, two sequence variants at position 334 of the gene product (R334W and R334Q) were identified. Affected family members from the original BS kindred, included in this study, were heterozygous for the R334W missense mutation; mutations at the same position were also observed in several unrelated BS families, some of whose phenotypes included large-vessel arteritis and cranial neuropathy. The missense mutations were segregated with the disease phenotype in the families and were not identified in 104 healthy controls.

To date, on a total amount of almost 220 patients with BS carrying CARD15/NOD2 mutations, missense substitutions of R334Q/R334W account for more than 80%, causing a genetic hot spot for mutations in codon 334. E383K has been found in almost 5% of patients, whereas other mutations have been described most rarely (71).

The number of NOD2 variants associated with BS has expanded greatly. In fact, up to 2016, the number of sequence variants of NOD2 gene is 144 (140 substitutions, 3 deletions, and 1 insertion) (16). There are no known mutations involving the untranslated and the intronic regions of the gene, even though this has not been extensively studied.

Despite the striking clinical similarities between them, for many years BS was considered a distinct entity from early onset sarcoidosis (EOS). Genetic analyses showed that many patients with EOS carry mutations in CARD15/NOD2 gene; hereafter, some authors proposed that BS and EOS are the familial and sporadic forms of the same disease (71). Moreover, CARD15/NOD2 gene mutations described in BS and EOS are mainly located in the NACHT domain of the protein. The discovery of CARD15 mutations in BS families encouraged to investigate similar CARD15 mutations in EOS patients.

Among 10 EOS cases retrospectively collected in Japan, heterozygous missense mutations were found in nine cases; four showed a c.1000C>T (p.R334W in amino acid change) that has been reported in BS, four showed novel c.1487A>T (p.H496L), c.1538T>C (p.M513T), c.1813A>G (p.R334Q), and c.2010C>A (p.N670K), and one case showed double c.1146C>G (p.D382E) and c.1834G>A (p.A612T) mutations on different alleles. The study concluded that EOS is closely related with CARD15 mutations causing constitutive NF-κB activation and shares the common genetic etiology with BS (72).

**Deficiency of the IL-36 Receptor Antagonist (DITRA)**

Deficiency of the IL-36 receptor antagonist is a recently described autosomal recessive autoinflammatory syndrome caused by mutations in the IL36RN gene, characterized clinically by recurrent episodes of generalized skin pustulation, fever, systemic inflammation, and leukocytosis. Other phenotypes of the IL36RN mutation include related pustular disorders, palmoplantar pustulosis, acrodermatitis continua of Hallopeau (ACH), and acute generalized exanthematous pustulosis. Histology shows...
spongiform pustules, acanthosis, and parakeratosis and an abundance of CD3+ and CD8+ T cells and macrophages (73).

This gene encodes IL-36 receptor antagonist (IL-36Ra), a protein belonging to the IL-1 cytokine family responsible for the tight regulation of IL-36 signaling. The IL-36 pathway is activated after binding of one of the three IL-36 agonists (IL-36α, β, and γ) to a common specific receptor IL-1Rrp2, leading to the recruitment of the co-receptor IL-1 receptor accessory protein (IL-1RaCP) and subsequent activation of intracellular NF-kB and mitogen activated protein kinase pathways (74).

Several mutations were highlighted in IL36RN gene with different effects. All IL36RN null mutations, such as c.28C>T (p.Arg10X), c.41C>A (p.Ser14X), c.80T>C (p.Leu27Pro), c.227C>T (p.Pro76Leu), c.280G>T (p.Glu94X), c.368C>G (p.Trh123Arg), c.368C>T (p.Trh123Met), and c.420_426del (p.Gly141MetfsX29) were totally unable to antagonize the IL-36 mediated activation of the NF-kB signaling pathway (75–83).

Among the most frequent genetic alterations is one Tunisian founder missense mutation: c.80C>T (p.Leu27Pro), one European recurrent missense mutation: c.338C>T (p.Ser113Leu); and one Japanese founder nonsense mutation: c.28C>T (p.Arg10X). The mutations c.95A>G (p.His32Arg), c.142C>T (p.Arg48Trp), and c.308C>T (p.Ser113Leu) only partly reduced the expression level of the corresponding IL-36Ra and consequently the capacity to repress the IL-36 mediated NF-kB signaling cascade. The detection of c.104A>G (p.Lys35Arg) and c.304C>T (p.Arg102Trp) mutations do not produce evident alterations in either protein expression and function, raising doubt about the actual pathogenic contribution of these genetic variants. They are classified as damaging by the pathogenicity prediction tools, such as SIFT and/or PolyPhen. For these mutations, additional functional studies are warranted to understand whether these variants truly have an effect on disease development or if they are polymorphisms (74).

Recently, Cordoro et al. showed a homozygous mutation within the IL36RN gene at position c.115+6T>C in a male adolescent with generalized pustular psoriasis (GPP) since infancy. This mutation has been shown to lead to a splicing defect resulting in exon skipping and a premature stop codon, leading to a truncated IL36Ra protein (81).

In summary, the c.28C>T (p.Arg10X) and c.115+6T>C (p.Arg10ArgfsX1) transitions are known to be founder mutations in cases reported in Japan (84). The c.115+6T>C transition is also recurrently found in Chinese and Malaysian patients (81, 85). The c.80C>T (p.Leu27Pro) transition is a recurrent mutation in Africa, and the c.338C>T (p.Ser113Leu) transition is a recurrent mutation in Europe (79–81). In contrast, the c.368C>T and c.368C>G transitions have been reported in one case in Japan (75, 76), the c.104A>G (p.Lys35Arg), c.142C>T (p.Arg48Trp), and c.304C>T (p.Arg102Trp) have been reported in one and two cases in Europe, respectively.

More in general, the null mutations are consistently associated with the more severe phenotypes of GPP and acute exanthematous generalized pustulosis (86, 87), whereas the hypomorph allelic alleles usually show a milder phenotypic expression featured by localized variants of palmoplantar pustular psoriasis (PPP) and ACH, although generalized pustular phenotypes can be observed as well in carriers of mild variants. The detection of the same gene variants in generalized and localized pustular phenotypes suggests the pathophysiological contribution of other factors such as disease-modifying genes, environmental factors, and epigenetic events, which may all influence disease onset, expression, and severity.

### Chronic Atypical Neutrophilic Dermatosis with Lipodystrophy and Elevated Temperature (CANDLE) Syndrome

Chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature syndrome is a rare autosomal recessive AID, with less than 100 cases described worldwide (88).

The CANDLE syndrome is caused, in the majority of cases, by homozygous mutations in PSMB8 gene, which encodes for a proteasome protein (89). There are evidences that an increase of modified and oxidated proteins occurring in fat and tissue cells, due to mutations of PSMB8 lead to an augmentation of cellular stress and apoptosis (88).

In 2012, a genome-wide analysis of nine CANDLE syndrome affected patients in eight families suggested that mutations in PSMB8 gene may cause the CANDLE syndrome. In this cohort, four patients were homozygous and two were heterozygous for a missense mutation (p.T75M), two patients were homozygous for a nonsense mutation (p.C135X), and one patient showed no mutations. None of these gene variants were observed in 750 healthy controls. Furthermore, only two of the four patients with the same mutation shared the same haplotype, indicating a possible mutational hot spot (90). Later, in 2015, a diagnosis of CANDLE syndrome was performed by targeted sequencing of one 3-year-old CANDLE syndrome Hispanic male patient, born to consanguineous healthy parents. A homozygous c.280G>C, p.A94P mutation in PSMB8 gene was not observed in any public genetic databases and was predicted to be pathogenic by several prediction tools (91).

Recently, it was demonstrated that CANDLE syndrome can also be caused by mutations in genes that encode other proteasome subunits, such as PSMB4, PSMB9, and PSMA3 (92); these mutations affect transcription, protein expression, protein folding, proteasome assembly, and, eventually, proteasome activity.

### Majeed Syndrome

Majeed syndrome is a congenital predisposition to develop early-onset multifocal osteomyelitis (CRMO), congenital dyserythropoietic anemia (CDA), congenital anemia, and inflammatory dermatosis, resulting from the infiltration of neutrophils into the dermis (93). It is transmitted with an autosomal recessive pattern of inheritance and is caused by mutations in the LPIN2 gene, which maps on chromosome 18p. The genomic sequence of LPIN2 is approximately 95 kb and comprises 20 exons, of which exon 1 and the majority of exon 20 are non-coding (5’ and 3’ untranslated regions). The mRNA is approximately 6245 bp and encodes a protein of 896 amino acids, which is expressed in almost all tissues (94). LPIN2 derives its name from its highly conserved...
N-terminal and C-terminal LIP domains. LIPIN-1, -2, and -3 are phosphatidate phosphatases (PAPs), which are important in glycerolipid biosynthesis and as transcription co-activators regulating lipid metabolism genes (95). In addition, lipid-2 regulates increased IL-1β formation in primary human and mouse macrophages by several mechanisms, including activation of the inflammasome NLRP3. In macrophages, reduced levels of lipid-2 cause a decrease of cell cholesterol levels. In conclusion, lipid-2 is able to down-regulate NLRP3 inflammasome (91).

Several mutations have been identified in LPIN2 gene. One of them, the c.540-541delAT (p.Cys181Ter), is a frameshift mutation that produces a premature stop codon producing a truncated protein that is 180 amino acids long; a second variant, the c. 2201C>T (p. Ser734Leu), is a missense mutation that replaces a highly conserved serine with a leucine (96). Al-Mosawi et al. report a third unique mutation in LPIN2 in an Arabic female with CRMO and CDA. The c. 2327+1G>C (p.Arg776SerfsTer66) nucleotide change affects a highly conserved nucleotide residue at the 5’ (donor) splice site of exon 17 and it is predicted to introduce a frameshift mutation resulting in a premature stop codon being encountered in intron 17, which would be predicted to produce a truncated message (97). A novel homozygous 2 bp deletion (c.1312_1313delCT) resulting in a premature stop codon (p.Leu438fs+16Ter) and consequently in a truncated LPIN2 protein was recently described in two Turkish brothers with MS who were treated successfully with IL-1 inhibitors (7).

LPIN2 shares homology with LPIN1, which has been shown to play a role in murine lipodystrophy (98). The role of LPIN2 mutations in producing the inflammatory phenotype of MS is not clear and does not appear to involve a disturbance in lipid metabolism. LPIN2 has an amino-terminal lipin domain, a Lipin/ Nedi1/Smp2 domain, and a putative nuclear localization signal. Lipin2 also has PAP type-1 activity and may play a role in lipid biology (99).

Although the number of individuals reported with MS is too small to study genotype–phenotype correlations, the affected individuals with a frameshift variant appear to have a more severe course and complications than individuals with other classes of pathogenic variants (100). More recent observations, however, have indicated that an affected individual with a splice site variant (97) and two affected Turkish brothers with a frameshift variant (7), who were all diagnosed and treated early, had a less complicated course. It is unclear whether their milder clinical course is attributable to the earlier detection and treatment.

**CARD14-Mediated Pustular Psoriasis (CAMPS)**

CARD14 encodes caspase recruitment domain family member 14 (CARD14). It is known to be specifically expressed in the skin and to be localized mainly to keratinocytes. CARD14 is a scaffolding protein that regulates NF-κB activation. The NF-κB family of transcription factors plays a crucial role in cell activation, survival, and proliferation and results in cancer, immunodeficiency, or autoimmune disorders (e.g., psoriasis). Hence, the presence of the CARD14 mutations may result in greater amplitude of inflammatory response upon epidermal activation. The skin disease in patients with CARD14 mutations can be limited or generalized. Autosomal dominant or sporadic gain-of-function mutations in the CARD14 gene cause GPP (101), familial pityriasis rubra pilaris (PRP) (102), psoriatic arthritis (PA) (103), PPP (104), and even pustular psoriasis suggesting a large disease severity spectrum. Fever and other systemic manifestations are generally not present but can occur with superinfections of the skin.

Three variants, c.349G>A (p.Gly117Ser), c.205C>T (p.Arg69Trp), and c.589G>A (p.Glu197Lys), affect the N-terminal region of the protein harboring its caspase recruitment domain or coiled-coil domain but with different effects. The c.589G>A (p.Glu197Lys) and c.349G>A (p.Gly117Ser) lead to upregulation of NF-κB activity, whereas the c.205C>T (p.Arg69Trp) leads to a sevenfold downregulation. In particular, the c.349G>A (p.Gly117Ser) variant described in a family of European descent altered the splicing between CARD14 exons 3 and 4. One Tunisian patient was reported with a c.1356+5G>A splice alteration which is predicted to lead to the skipping of exon 9, which encodes part of the coiled-coil domain (105). Mutations in CARD14, including p.Glu138del and p.Leu156Pro, have been associated with autosomal-dominant pityriasis rubra pilaris, which is phenotypically related to psoriasis (102).

Several gain-of-function variants/mutations in CARD14 have been reported to be a predisposing factor for psoriasis vulgaris (PV) in a large family with PV and PA. Jordan et al. identified the rare de novo CARD14 gain-of-function variant p.Glu138Ala in a child with severe early-onset GPP. They also found rare CARD14 gain-of-function variants in large PV cohorts by the NF-κB assay, which revealed that compared to the wild-type CARD14, the p.Gly117Ser, p.Glu138Ala, and p.Asp176His variants were associated with increased levels of the luciferase reporter. Additional rare variants within CARD14 are c.424G>A (p.Glu141Ala), c.511C>A (p.His171Asn), c.536G>A (p.Arg179His), and c.571G>T (p.Val191Leu) (106).

In conclusion, the above-reported data concur to reach the following conclusions: (1) differences in the genetic background among different geographic populations account for significant variances observed in psoriasis populations, both in terms of frequency and of severity (localized palmoplantar versus generalized forms) of pustular psoriasis (107, 108), (2) despite the dramatic in vitro effects of some CARD14 variants on the keratinocytes, there is a wide range of phenotypes, even among individuals who carry the same substitution, suggesting that in many instances, the variable phenotypes are likely to multiple other factors besides the genetic background.

**NLRP12-AID**

NLRP12 is an NLR encoded by NLRP12 (also known as NALP12, Monarch-1, or PYPAF7) and functions as a negative regulator of NF-κB activation (109). NLRP12 interacts via its pyrin domain with the pyrin domain of apoptosis-associated speck-like (ASC) protein (110) leading to the formation of an intracellular aggregate called speck to active IL-1β (111). Sequencing of NLRP12 revealed a heterozygous nonsense mutation c.850C>T (p.Arg284X) in
identical twin brothers presenting with symptoms overlapping FCAS and MWS. A second NLRP12 mutation (c.2072+3insT) was identified in a patient presenting with a periodic fever syndrome, including clinical manifestation of FCAS. This mutation, affecting the donor splice site of intron 3, activates a cryptic splice site located upstream in exon 3 and results in a frameshift, followed by a premature stop codon (112). These two mutations were demonstrated to be functionally associated with high levels of NF-kB activity, thus accounting for the autoinflammatory phenotype. Jérú et al. identified a missense mutation c.1054C>T (p.Arg352Cys) within the NBS domain of the protein in two unrelated patients. This missense mutation is associated with a gain of function of caspase 1 processing (110). The c.882C>G (p.Asp294Glu) mutation was found to mostly segregate with a particular sensitivity to cold exposure (especially arthralgias and myalgias), even in the absence of urticarial rash, fever, or elevation in the levels of acute-phase reactants. In any case, the clinical manifestations presented by the carriers were generally mild, although quality of life was affected, especially during the winter season (112–114). Several reports identified the NLRP12 variant F402L (c.1206 C>G) (115–117).

Pyogenic Arthritis, Pyoderma Gangrenosum, and Acne (PAPA) Syndrome

Pyogenic sterile arthritis, pyoderma gangrenosum, and acne syndrome is an autosomal dominant AID caused by mutations in the PSTPIP1 gene, which is located in chromosomal position 15q24–q25.1. Pyrin protein is a cytosolic receptor for PSTPIP1. Ligation between pyrin and PSTPIP1 induces pyrin to interact with ASC protein, inducing the creation of an active ASC pyr不错tosome. A possible explanation of PAPA syndrome is a constitutive ligation and consequent activation of pyrin with the mutated PSTPIP1 proteins (112). The disease is extremely rare, with less than 10 families described worldwide. The first case of PAPA syndrome was reported in 1975 (118) and in 1997, in the same family, PAPA syndrome was described as a heritable disease (119).

In 2000, 93 genomic loci were investigated in patients with a pleiotropic inflammatory syndrome characterized by pyoderma gangrenosum, cystic acne, and erosive arthritis, demonstrating PAPA syndrome maps in chromosomal position 15q (120).

There are two hot-spots mutations, c.688G>A (p.A230T) and c.748G>C (p.E250Q), which occur in exons 10 and 11 and have been found in many familial (121–126) and sporadic cases (127, 128). Mutations are thought to disrupt the binding of PSTPIP-1 with protein tyrosine phosphatase–PEST, a regulatory phosphatase, increasing its avidity for pyrin in the cytosol, thereby causing dysregulation of IL-1β production (129).

Until 2016, a total of 27 genetic variants were reported for PSTPIP1 gene (23 substitutions, 1 insertion, 2 deletions, and 1 duplication), 17 of which are PAPA phenotype associated (16).

Deficiency of Adenosine Deaminase 2

Searching for mutations in systemic inflammation and vasculopathy and/or necrotizing vasculitis polyarteritis nodosa patients, CECRI (cat eye syndrome chromosome region, candidate 1) gene mutations were discovered by two independent groups. Pattern of inheritance was autosomal recessive. Subsequent studies described another case with a fatal vasculopathy (130). Common clinical signs are early onset recurrent stroke, neurologic manifestations, and fever. Being the CECRI gene highly polymorphic, as other AID causative genes, the correlation between clinical signs and familial ancestry is important. The CECRI gene encodes the adenosine deaminase 2 (ADA2) protein, which has partial homology with ADA1 protein. Both ADA1 and ADA2 act as intracellular enzymes that regulate the purinergic signaling pathway. Mutations in ADA1 are known to cause severe combined immunodeficiency disease, characterized by a defect in T- and B-lymphocytes. ADA2 mutations, conversely, cause only mild hypogammaglobulinemia due to a defect in terminal differentiation of B-cells (131).

NLRC4-Associated Inflammatory Diseases (SCAN4, NLRC4-MAS, and NLRC4-FCAS)

Patients with macrophage activation syndrome or a milder phenotype like FCAS may carry gain of function mutations in the NLRC4 (IPAF; CARD12) gene (132–134). Two novel causal mutations, p.T337S and p.V341A, have been diagnosed by whole exome sequencing (WES) in two sporadic patients (trios): the reported clinical symptoms were early onset fever, failure to thrive, rash, joint pain, and elevated inflammatory markers, including hyperferritinemina (133). The two mutations map in a highly conserved HD1 region of the NLRC4 nucleotide-binding domain and may decrease the function of NLRC4 to maintain itself in an auto-inhibited state. A third mutation, p.H443P, was identified in a Japanese family with milder symptoms including cold induced rash, fever, and arthralgia, even if the patient has a different phenotype from those other two previously patients reported. Mutations are supposed to regulate the mutant proteins into a constitutively active state, with the influence of environmental factors such as cold and stress which act as trigger, causing inflammasome activation. Further studies are necessary to explore full spectrum of monogenic inflammasome-related diseases. Interestingly, the NLRC4 gene (IPAF; CARD12) is supposed to initiate inflammation in response to bacterial ligands, such as flagellin (135, 136).

Stimulator of Interferon Genes (STING)-Associated Vasculopathy with Onset in Infancy

In a trio with a patient affected by early onset symptoms of systemic inflammation, cutaneous rash, and pulmonary manifestations, and his unaffected parents, WES was performed, identifying a de novo mutation, p.N154S, in the TMEM173 gene; this gene encodes for a STING (138). Extending the analysis to other five sporadic cases of different ancestries but with similar phenotype led to the identification of missense mutations in the TMEM173 gene. Functional studies showed that a particular missense mutation, p.V155M, has been previously associated with a phenotypically different disease like systemic lupus erythematosus (139). Most of the mutations are located in the exon 5 of TMEM173 gene, which encodes for a domain important for the STING dimerization site.
The second study highlights that in families with dominantly inherited traits, the possibility of reduced penetrance should not be ignored. Sting knockout mice are prone to viral infections, because of the lacking of the ability to upregulate IFN-beta (137). As a result, all these data support the evidence that TMEM173-associated mutations are gain of function (138, 139).

**TNFRSF11A-Associated Hereditary Fever Disease**

Patients with this disease have a phenotype similar to those affected by TRAPS. In a single patient with complex phenotype including neonatal onset of systemic inflammation and congenital abnormalities, a de novo genomic duplication containing the TNFRSF11A gene was identified (140). The TNFRSF11A gene is one of the 30 genes in the 10-Mb genomic duplication. Another study, using a different approach based on candidate gene screening, identified two other patients (mother and daughter) with a novel heterozygous 1-bp deletion (p.Met416Cysfs*110) in exon 9 of TNFRSF11A gene. The resulting protein lacks the C-terminal intracellular domain. As TNFRSF11A, also TNFRSF11A gene encodes for a protein member of the TNF-receptor superfamily. TNFRSF11A (RANK, PDB, ODFR) gene encodes a signaling receptor that functions in osteoclast differentiation and bone remodeling (141, 142). RANK-ligand (RANKL) mediates essential signal for osteoclastogenesis (143).

Rank-deficient mice present osteopetrosis caused from a block in osteoclast differentiation and the lack of peripheral lymph nodes (144). The pathogenesis of this disorder is unclear; in fact, the TNFRSF11A gene duplication suggests a gain of function mutation, while the heterozygous deletion is more consistent with a haploinsufficiency or a dominant negative effect.

**TRNT1 Deficiency**

Patients presenting with a variable phenotype of congenital sideroblastic anemia, B cell immunodeficiency, and developmental delay have been termed SIFD (145). SIFD is characterized by an early onset, with frequently associated neurological symptoms, and metabolic abnormalities. SIFD has been associated to AID because it is characterized with a pediatric onset with periodic fevers and gastrointestinal involvement with sideroblastic anemia. Genetic cause of SIFD has been found in the TRNT1 gene in an autosomal recessive inheritance (146, 147). The TRNT1 gene encodes the ubiquitously expressed CCA-adding enzyme, essential for template-independent maturation of nuclear and mitochondrial transfer RNAs (148). Functional studies in yeast showed deficiency of TRNT1 homolog causes partial loss of function of TRNT1 affecting variable degrees of enzyme activity (146). Knock-out yeast for TRNT1 was fully restored with human TRNT1 and partially rescued by human mutant proteins.

**Monogenic Form of Systemic Juvenile Idiopathic Arthritis**

Systemic-onset juvenile idiopathic arthritis is a polygenic inflammatory disease characterized by fever, rash, and symmetrical polyarthritis, with persistent systemic inflammation that seems to be linked to altered innate immune system (149, 150). Mendelian inheritance is autosomal recessive. Studying five consanguineous families with 13 affected patients from the Saudi Arabia with several genomic approaches, such as linkage analysis, homozygosity mapping, and WES, a homozygous missense mutation, p.C284R, located in exon 4 of the laccase domain containing 1 (LACC1) gene was identified (151). This private mutation is highly conserved during evolutionary scale and was not described in more than 2,000 Arab controls, suggesting its role in the pathogenesis.

Laccase domain containing 1 gene belongs to a family of Laccases, multi-copper oxidoreductases able to catalyze the oxidation of a variety of phenolic and non-phenolic compounds. Protein function is largely unknown, even if may regulate the innate immune responses. In a recent study, the gene product of LACC1 gene has been named FAMIN (fatty acid metabolism–immunity nexus), important for the synthesis of endogenous fatty acids and their mitochondrial oxidation, controlling the glycolytic activity and ATP regeneration (145).

Genetic variants in the LACC1 gene have been previously associated with susceptibility to leprosy (152–154). LACC1 gene belongs to a family of Laccases, multi-copper oxidoreductases able to catalyze the oxidation of a variety of phenolic and non-phenolic compounds. Protein function is largely unknown, even if may regulate the innate immune responses.

**GENETIC DIAGNOSIS WITH NEW TECHNOLOGIES**

In recent years, with the increased use of instruments for NGS, it has become feasible to analyze several genes in a single experiment. This method is of great interest for AID, because of the increasing number of genes associated with the different forms of AID. In some cases, it is difficult to differentiate the different diseases, in particular, in those patients with intermediate phenotypes or a difficult clinical diagnosis. The analysis of a panel of several candidate genes is feasible with targeted sequencing investigating causative mutations, rare variants, or regions associated with the disease.

With the large number of genetic variants found with NGS, it is extremely important to find information about their possible role in the development of a specific disease. Several softwares have been developed in recent years and most of them have been based on the assumption that protein sequences derived from living organisms have survived a natural selection. The goal is to find if a genetic variant is a causative mutation or a common polymorphism.

There is also the possibility to analyze all the 18,000 genes of the human genome. WES is a recent strategy designed to sequence only the coding regions of the genome (which represents 1% of the human genome, about 30 megabases); this is an effective method alternative to whole genome sequencing, cheaper and less complicated in the bioinformatical/statistical analysis. Exons are generally short, functional sequences of DNA which represent the portion of the genome translated in protein. The WES has
the potential to identify the coding variants responsible for both Mendelian and common diseases.

In recent years, with the use of WES, several undiagnosed Mendelian genetic conditions have been investigated in order to search the involved gene (155, 156). WES has been applied to Mendelian genetic conditions have been investigated in order to Mendelian and common diseases.

Martorana et al. Genetics of Monogenic AIDs AID patients (157).

intermediate phenotype (156); in fact, the interaction between clinical information may help diagnosis for those patients with atypical symptoms. In the next future, NGS data combined with genotype–phenotype correlation. Some genes, such as NLRP12, with those of 1,000 Genomes Project, and searching for a possible of the detected variants, allele frequencies have been compared and TNFR1A, NLRP3, NLRP12, NOD2, PSTPIP1, IL1RN, LPIN2, and PSMB8 (157). In order to better understand the possible role of the detected variants, allele frequencies have been compared with those of 1,000 Genomes Project, and searching for a possible genotype–phenotype correlation. Some genes, such as NOD2, LPIN2, and NLRP12, showed a high frequency of genetic variants, which in theory may alter the clinical phenotype with mild or atypical symptoms. In the next future, NGS data combined with clinical information may help diagnosis for those patients with intermediate phenotype (156); in fact, the interaction between geneticists and physicians will allow to improve the diagnosis of AID patients (157).

CONCLUSION

In AID, genetic and environmental factors act modulating the clinical presentation of a specific disorder. The knowledge of the biological pathways at the basis of different AIDs is very important; the elucidation of these novel factors may have clinical relevance, because it may be included in genetic-risk modeling approaches. The genetic variants previously identified as playing a role in the same pathway represent new potential therapeutic targets. The new age of the -omics has allowed the improvement of the knowledge of AID. By means of genetic fine mapping, targeted sequencing, transcriptomics, proteomics, and metabolomics, physicians may improve treatment and therapy tailored on the single patient.

AUTHOR CONTRIBUTIONS

DM contributed in conception or design of the work, drafting the article, and final approval of the version to be published. FB and PM contributed in drafting the article and final approval of the version to be published. AV contributed in conception or design of the work, drafting the article, critical revision of the article, and final approval of the version to be published.

FUNDING

Supported in part by the grant “A tailored approach to the immune-monitoring and clinical characterization of viral and autoimmune diseases” funded by the Regione Emilia-Romagna within the Programma di Ricerca Regione Università 2010–2012, in part by “Tailoring Rituximab treatment in ANCA-associated vasculitis; a genetic and an immunological approach” funded by the Regione Emilia-Romagna within the Programma di ricerca Regione-Università Giovani Ricercatori ‘Alessandro Liberati’ 2013 and by the “Fondazione Emma ed Ernesto Rulfo per la Genetica Medica” (Italy).

REFERENCES

1. McDermott MF, Aksentijevich I, Galon J, McDermott EM, Ogunkolade BW, Centola M, et al. Germline mutations in the extracellular domains of the 55 kDa TNF receptor, TNFR1, define a family of dominantly inherited autoinflammatory syndromes. Cell (1999) 97(1):133–44. doi:10.1016/S0092-8674(00)08072-7
2. Aksentijevich I, Galon J, Soares M, Mansfield E, Hull K, Oh HH, et al. The tumor necrosis-factor receptor-associated periodic syndrome: new mutations in TNFRSF1A, ancestral origins, genotype-phenotype studies and evidence for further heterogeneity of periodic fevers. Am J Hum Genet (2001) 69:301–14. doi:10.1086/321976
3. Drenth JP, Cuisset L, Graeule G, Vasseur C, van de Velde-Visser SD, de Jong JG, et al. Mutations in the gene encoding mevalonate kinase cause hyper-IgD and periodic fever syndrome. International Hyper-IgD Study Group. Nat Genet (1999) 22:178–81. doi:10.1038/9696
4. Frenkel J, Houten SM, Waterham HR, Wanders RJ, Rijikers GT, Kimpen JL, et al. Mevalonate kinase deficiency and Dutch type periodic fever. Clin Exp Rheumatol (2000) 18:525–32.
5. Houten SM, Kuis W, Duran M, de Koning TJ, van Royen-Kerkhof A, Romeijn GJ, et al. Mutations in MVK, encoding mevalonate kinase, cause hyperimmunoglobulinemia D and periodic fever syndrome. Nat Genet (1999) 22:175–7. doi:10.1038/9691
6. Aksentijevich I, Masters SL, Ferguson PJ, Dancey P, Frenkel J, van Royen-Kerkhof A, et al. An autoinflammatory disease with deficiency of the 55 kDa TNF receptor. N Engl J Med (2009) 360(23):2426–37. doi:10.1056/NEJMoa0807865
7. Herlin T, Fiirgaard B, Bjerre M, Kerndrup G, Hasle H, Bing X, et al. Efficacy of anti-IL-1 treatment in Majeed syndrome. Ann Rheum Dis (2013) 72(3):410–3. doi:10.1136/annrheumdis-2012-201818
8. Federici S, Caorsi R, Gattorno M. The autoinflammatory diseases. Swiss Med Wkly (2012) 142:w13602. doi:10.4414/smw.2012.13602
9. Booth DR, Gillmore JD, Lachmann HJ, Booth SE, Bybee A, Soyturk M, et al. The genetic basis of autosomal dominant familial Mediterranean fever. QJM (2009) 102(4):217–21. doi:10.1093/qjmed/93.4.217
10. Cattan D. Familial Mediterranean fever: is low mortality from tuberculosis a specific advantage for MEFV mutations carriers? Mortality from tuberculosis among Muslims, Jewish, French, Italian and Maltese patients in Tunis...
Genetics of Monogenic AIDs

Martorana et al.

64. Henderson C, Goldbach-Mansky R. Monogenic IL-1 mediated autoinflammatory disease. *Arthritis Rheum* (2002) 46(12):3340–8. doi:10.1002/art.10688

65. Jesus AA, Osman M, Silva CA, Kim PW, Pham TH, Gadina M, et al. A novel mutation of IL1RN in the deficiency of interleukin-1 receptor antagonist syndrome: description of two unrelated cases from Brazil. *Arthritis Rheum* (2011) 63(12):4007–7. doi:10.1002/art.30588

66. Altok E, Aksoy F, Perk Y, Taylan F, Kim PW, Ilkkkan B, et al. A novel mutation in the interleukin-1 receptor antagonist associated with intraducron disease onset. *Clin Immunol* (2012) 145(1):77–81. doi:10.1016/j.clim.2012.08.003

67. Tromp G, Kuivaniemi H, Raphael S, Alla-Kokko L, Christiano A, Considine E, et al. Genetic linkage of familial granulomatous inflammatory arthritis, skin rash, and juvenile rheumatoid arthritis. *Am J Hum Genet* (1996) 59(5):1097–107.

68. Miceli-Richard C, Lesage S, Bytojaj M, Prieur AM, Manouvel-Hau S, Häfner R, et al. CARD15 mutations in Blau syndrome. *Nat Genet* (2001) 29(1):19–20. doi:10.1038/ng270

69. Wang X, Kuivaniemi H, Bonavita G, Mutkus L, Mau U, Blau E, et al. CARD15 mutations in familial granulomatosis syndromes: a study of the original Blau syndrome kindred and other families with large-vessel arteritis and cranial neuropathy. *Arthritis Rheum* (2002) 46(11):3041–5. doi:10.1002/art.10618

70. Kanazawa N, Okafuji I, Kambe N, Nishikomori R, Nakata-Hizume M, Nagai S, et al. Early-onset sarcoidosis and CARD15 mutations with constitutive nuclear factor kappaB activation: common genetic etiology with Blau syndrome. *Blood* (2005) 105:1195–7. doi:10.1182/blood-2004-07-2972

71. Renert-Yuval Y, Hoeve L, Babay S, Tams S, Ramot Y, Zlotogorski A, et al. IL36RN mutation causing generalized pustular psoriasis in a Palestinian patient. *Int J Dermatol* (2014) 53(7):866–8. doi:10.1111/jid.12525

72. Tauber M, Bal E, Pei XY, Madravage M, Khelil A, Sahel H, et al. IL36RN mutations affect protein expression and function: a basis for genotype-phenotype correlation in pustular diseases. *J Invest Dermatol* (2016) 136(9):1811–9. doi:10.1016/j.jid.2016.04.038

73. Farooq M, Nakai H, Fujimoto A, Fujikawa H, Matsuyama A, Kariya N, et al. Mutation analysis of the IL36RN gene in 14 Japanese patients with generalized pustular psoriasis. *Hum Mutat* (2013) 34(1):176–83. doi:10.1002/humu.22203

74. Kanazawa N, Nakamura T, Mikita N, Furukawa F. Novel IL36RN mutation in a Japanese case of early onset generalized pustular psoriasis. *J Dermatol* (2013) 40(9):749–51. doi:10.1111/1346-8133.12227

75. Körber A, Mössner R, Renner R, Stich H, Wilsmann-Theis D, Schulz P, et al. Mutations in IL36RN in patients with generalized pustular psoriasis. *J Invest Dermatol* (2013) 133(11):2634–7. doi:10.1038/jid.2013.214

76. Marrachi S, Gugue P, Renshaw BR, Puel A, Pei XY, Fraitag S, et al. Interleukin-36-receptor antagonist deficiency and generalized pustular psoriasis. *N Engl J Med* (2011) 365(7):620–8. doi:10.1056/NEJMoa1103068

77. Navarini AA, Valely-Allanore L, Setta-Kaffetzi N, Barker IN, Capon F, Creamer D, et al. Rare variations in IL36RN in severe adverse drug reactions manifesting as acute generalized exanthematous pustulosis. *J Invest Dermatol* (2013) 133(7):1904–7. doi:10.1038/jid.2013.44

78. Onoufriadis A, Simpson MA, Pink AE, Di Meglio P, Smith CH, Pullabhatla V, et al. Mutations in IL36RN/IL1F5 are associated with the severe episodic inflammatory skin disease known as generalized pustular psoriasis. *Am J Hum Genet* (2011) 89(3):432–7. doi:10.1016/j.ajhg.2011.07.022

79. Setta-Kaffetzi N, Navarini AA, Puel AM, Pullabhatla V, Pink AE, Choon J, et al. Rare pathogenic variants in IL36RN underlie a spectrum of pсорia-sis-associated pustular phenotypes. *J Invest Dermatol* (2013) 133(5):1366–9. doi:10.1038/jid.2013.490

80. Sugiuira K, Takemoto A, Yamaguchi M, Takahashi H, Shoda Y, Mitsuama T, et al. The majority of generalized pustular psoriasis without psoriasis vulgaris is caused by deficiency of interleukin-36 receptor antagonist. *J Invest Dermatol* (2013) 133(11):2514–21. doi:10.1038/jid.2013.230

81. Cordero KM, Ucmak D, Hitraya-Low M, Rosenblum MD, Liao W. Response to interleukin (IL)-17 inhibition in an adolescent with severe manifestations of IL-36 receptor antagonist deficiency (DITRA). *JAMA Dermatol* (2016) 153(1):106–9. doi:10.1001/jamadermatol.2016.3490

82. Sugiuira K, Takeichi T, Kono M, Ogawa Y, Shimoyma Y, Muro Y, et al. A novel IL36RN/IL1F5 homzygous nonsense mutation, p.Arg10X, in a Japanese patient with adult-onset generalized pustular psoriasis. *Br J Dermatol* (2012) 167(3):699–701. doi:10.1111/j.1365-2133.2012.10953.x

83. Li M, Han J, Lu Z, Li H, Zhu K, Cheng R, et al. Prevalent and rare mutations of IL-36 receptor antagonist deficiency (DITRA). *J Invest Dermatol* (2013) 133(11):2637–9. doi:10.1038/jid.2013.267

84. Baker H, Ryan TJ. Generalized pustular psoriasis. A clinical and epidemiological study of 104 cases. *Br J Dermatol* (1968) 80(12):771–93. doi:10.1111/j.1365-2133.1968.tb11947.x

85. Lee HY, Chou D, Pang SM, Thirumoorthy T. Acute generalized exanthema-tous pustulosis: analysis of cases managed in a tertiary hospital in Singapore. *Int J Dermatol* (2010) 49(5):507–12. doi:10.1111/j.1365-4632.2010.04313.x
104. Chen J, Zheng H, Bei JX, Sun L, Jia WH, Li T, et al. Genetic structure of the Han Chinese population revealed by genome-wide SNP variation. *Am J Hum Genet* (2015) 97(3):895–907. doi:10.1016/j.ajhg.2015.06.006

105. Parisi R, Symmons DP, Griffiths CE, Ashcroft DM. Identification and Management of Psoriasis and Associated Comorbidity (IMPACT) project team. Global epidemiology of psoriasis: a systematic review of incidence and prevalence. *J Invest Dermatol* (2013) 133:377–85. doi:10.1038/jid.2012.339

106. Liu F, Ying JP, Monarch J-P, YVPPAF7 and other CATERPILLER (CLR, NOD, NLPR) genes with negative regulatory functions. *Microbes Infect* (2007) 9:672–6. doi:10.1016/j.micinf.2007.01.018

107. Masumoto J, Taniguchi S, Ayukawa K, Sarovtham H, Kishino T, Niikawa N, et al. ASC, a novel 22-kDa protein, aggregates during apoptosis of human promyelocytic leukemia HL-60 cells. *J Biol Chem* (1999) 274:33383–5. doi:10.1074/jbc.274.48.33385

108. Wang L, Manji GA, Grenier JM, Al-Garawi A, Merriam S, Lora JM, et al. YVPPAF7, a novel PYRIN-containing Apaf-1-like protein that regulates activation of NF-kB and caspase-1-dependent cytokine processing. *J Biol Chem* (2002) 277:29874–80. doi:10.1074/jbc.M203915200

109. Jérô M, Duquesnoy P, Fernandes-Alnemri T, Cochet E, Yu JW, Lackmy-Port-Lis M, et al. Mutations in NALP12 cause hereditary periodic fever syndromes. *Proc Natl Acad Sci U S A* (2008) 105(5):1649–40. *doi* 10.1073/pnas.0708616105

110. Jérô M, Le Borgne G, Cochet E, Hayrapetyan H, Duquesnoy P, Greave T, et al. Identification and functional consequences of a recurrent NLRP12 missense mutation in periodic fever syndromes. *Arthritis Rheum* (2011) 63(5):1459–64. doi:10.1002/art.30241

111. Bortolami P, Tassi S, Chiesa S, Caroli F, Carta S, Caorsi R, et al. Clinical presentation and pathogenesis of cold-induced autoinflammatory disease in a family with recurrence of an NLRP2 mutatiion. *Arthritis Rheum* (2011) 63(3):839–90. doi:10.1002/art.30170

112. Yu JW, Fernandes-Alnemri T, Datta P, Wu J, Juliana C, Sorolzano L, et al. Pyrin activates the ASC pyroptosome in response to engagement by autoinflammatory PSTPIP1 mutants. *Mol Cell* (2007) 28(2):214–27. *doi* 10.1016/j.molcel.2007.08.029

113. Vitale A, Rigante D, Lucherin OM, Caso F, Cantarlini L. The role of the F402L allele in the NLRP2-associated autoinflammatory disorder. Reply to: F402L variant in NLRP2 in subjects with undiagnosed periodic fevers and in healthy controls, De Pietri et al. *Clin Exp Rheumatol* (2014) 32(6):994.

114. Cortis E, De Benedetti F, Infascio S, Cioschi S, Muratori F, D’Urbano LE, et al. Abnormal production of the tumor necrosis factor alpha in patients with PAPA syndrome. *Rheumatology* (2011) 50(8):1684–90. doi:10.1093/rheumatology/ker149

115. Jacobs JC, Goetzl EJ. “Streaking leukocyte factor,” arthritis, and pyoderma gangrenosum. *Pediatrics* (1975) 56:570–8.

116. Lindor NM, Arsenault TM, Solomon H, Seidman CE, McEvoy MT. A new autosomal dominant disorder of pyogenic sterile arthritis, pyoderma gangrenosum, and acne: PAPA syndrome. *Mayo Clin Proc* (1997) 72:611–5. doi:10.4065/72.6.611

117. Yu JW, Fernandes-Alnemri T, Cochet E, Hayrapetyan H, Duquesnoy P, Greave T, et al. Identification and functional consequences of a recurrent NLRP12 missense mutation in periodic fever syndromes. *Arthritis Rheum* (2011) 63(5):1459–64. doi:10.1002/art.30241

118. Cortis E, De Benedetti F, Infascio S, Cioschi S, Muratori F, D’Urbano LE, et al. Abnormal production of the tumor necrosis factor alpha in patients with PAPA syndrome. *Rheumatology* (2011) 50(8):1684–90. doi:10.1093/rheumatology/ker149

119. Dierselhuis MP, Frenkel J, Wulffraat NM, Boelens JJ. Anakinra for flares of chronic recurrent multifocal osteomyelitis and congenital dyserythropoietic anaemia (Majeed syndrome). *J Med Genet* (2009) 46:165–70. doi:10.1136/jmg.2007.054386

120. Cortis E, De Benedetti F, Infascio S, Cioschi S, Muratori F, D’Urbano LE, et al. Abnormal production of the tumor necrosis factor alpha in patients with PAPA syndrome. *Rheumatology* (2011) 50(8):1684–90. doi:10.1093/rheumatology/ker149

121. Schellevis MA, Stoffels M, Hoppenreijs EP, Bodar E, Simon A, van der Meer J. Variable expression and treatment of PAPA syndrome. *Ann Rheum Dis* (2009) 68(4):1443–8. doi:10.1136/ard.2008.092868

122. Holzinger D, Fassl SK, de Jager W, Lohse P, Röhrig UF, Gattorno M, et al. CANDLE syndrome subunit 8 cause chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature with evidence of genetic and phenotype heterogeneity. *Arthritis Rheum* (2012) 64(3):895–907. doi:10.1002/art.33368

123. Demidowich AP, Freeman AF, Kuhns DB, Aksentijevich I, Gallin JI, Turner J. Multifocal osteomyelitis and congenital dyserythropoietic anaemia (Majeed syndrome) due to mutations in CARD14. *Br J Dermatol* (2016) 174(2):330–7. doi:10.1111/bjd.14871

124. Brenner M, Ruzicka T, Plewig G, Thomas P, Herzer P. Targeted treatment of pyoderma gangrenosum in PAPA (pyogenic arthritis, pyoderma
gangrenosum and acne) syndrome with the recombinant human interleukin-1 receptor antagonist anakinra. *Br J Dermatol* (2009) 161(5):1199–201. doi:10.1111/j.1365-2131.2009.09404.x

125. Tofteland ND, Shaver TS. Clinical efficacy of etanercept for treatment of PAPA syndrome. *J Clin Rheumatol* (2010) 16(5):244–5. doi:10.1097/RHU.0b013e3181e969e6

126. Kumar BS, Kumar PS, Sowgandhi N, Prajwal BM, Mohan A, Sarma KV, et al. Identification of novel mutations in CD2BP1 gene in clinically proven rheumatoid arthritis patients of south India. *Eur J Med Genet* (2016) 59(8):404–12. doi:10.1016/j.ejmg.2015.06.009

127. Garg N, Kasapcopur O, Foster J II, Barut K, Tekin A, Kızılkılıç O, et al. Novel adenosine deaminase 2 mutations in a child with a fatal vasculopathy. *J Pediatr* (2014) 173(6):827–30. doi:10.1016/j.jpeds.2014.02.030

128. Zhou Q, Yang D, Ombrello AK, Zavialov AV, Toro C, Zavialov AV, et al. Early-onset stroke and vasculopathy associated with mutations in AD2A. *N Engl J Med* (2014) 370(10):911–20. doi:10.1056/NEJMoa1307361

129. Canna SW, de Jesus AA, Gouni S, Brooks SR, Marrero B, Liu Y, et al. Identification of novel mutations in CD2BP1 gene in clinically proven RHU. *0b013e3181e969b9 of PAPA syndrome.* (2010) 16(5):244–5. doi:10.1097/JClinRheumatol

130. Romberg N, Al Moussawi K, Nelson-Williams C, Stiegler AL, Loring E, Choi M, et al. Mutation of NLRC4 causes a syndrome of enterocolitis and autoinflammation. *Nat Genet* (2014) 46(10):1104–6. doi:10.1038/ng.3089

131. Kitamura A, Sasaki Y, Abe T, Kano H, Yasumoto K. An inherited mutation in NLRC4 causes autoinflammation in human and mice. *J Exp Med* (2014) 211:2385–96. doi:10.1084/jem.20141091

132. Franchi L, Amer A, Body-Malapel M, Kanneganti TD, Ozören N, Jagirdar R, et al. Cytosolic flagellin requires I palp for activation of caspase-1 and interleukin Ibeta in salmonella-infected macrophages. *Nat Immunol* (2006) 7(6):576–82. doi:10.1038/nii1346

133. Vance RE. The NAIP/NLRC4 inflammasomes. *Curr Opin Immunol* (2015) 32C:84–9. doi:10.1016/j.coi.2015.01.010

134. Liu Y, Jesus AA, Marrero B, Yang D, Ramsey SE, Marrero B, Y uang D, Ramsey SE, Montealegre Sanchez GA, et al. Mutation of NLRC4 causes autoinflammation in human and mice. *J Exp Med* (2014) 211:2385–96. doi:10.1084/jem.20141091

135. Jeremiah N, Neven B, Gentili M, Callebaut I, Maschalidi S, Stolzenberg MC, et al. Inherited STING-activating mutation underlies a familial inflammatory syndrome with lupus-like manifestations. *J Clin Invest* (2014) 124(12):5516–20. doi:10.1172/JCI73100

136. Ishikawa H, Barber GN. STING is an endoplasmic reticulum adaptor-kin-1 receptor antagonist anakinra. *Br J Dermatol* (2014) 169(1):1447–8, doi:10.1111/bjd.13879

137. Jéru I, Cochet E, Duquesnoy P, Hentgen V, Copin B, Mitjavila-Garcia MT, et al. Brief Report: involvement of TNFRSF11A molecular defects in autoinflammatory disorders. *Arthritis Rheumatol* (2015) 59(11):65–74. doi:10.1002/art.38877

138. Malik S, Percin FE, Bornholdt D, Albrecht B, Percesepe A, Koch MC, et al. Mutations affecting the BHLHA9 DNA-binding domain cause MSSD, mesoauprostatic dysplasia with phalangeal reduction, Malik-Percin type. *Am J Hum Genet* (2014) 95(6):649–59. doi:10.1016/j.ajhg.2014.10.012

139. Usuki H, Iwamato T, Ohkura H, Niwa T, Ito S, Ohnishi K, et al. Genomewide association study of leprosy. *Nat Genet* (2015) 47(10):1135–9. doi:10.1038/ng.3066

140. Zhang FR, Huang W, Chen SM, Sun LD, Liu H, Li Y, et al. Genomewide association study of leprosy. *Nat Genet* (2009) 41(27):2609–18. doi:10.1038/ng.9003753

141. Sales-Marques C, Salomão H, Fava VM, Alvarado-Arnez LE, Amaral EP, Cardoso CC, et al. LOD2 and CCD122-LACCI genes are associated with leprosy susceptibility in Brazilians. *Hum Genet* (2014) 133(12):1525–32. doi:10.1007/s00431-014-1502-9

142. Ng SB, Bigham AW, Buckingham KJ, Hannibal MC, McMillin MJ, Gildersleeve HJ, et al. Exome sequencing identifies MIL2 mutations as a cause of Kabuki syndrome. *Nat Genet* (2010) 42(9):790–3. doi:10.1038/ng.646

143. Malik S, Percin FE, Bornholdt D, Albrecht B, Percesepe A, Koch MC, et al. Mutations affecting the BHLHAl9 DNA-binding domain cause MSSD, mesoauprostatic dysplasia with phalangeal reduction, Malik-Percin type. *Am J Hum Genet* (2014) 95(6):649–59. doi:10.1016/j.ajhg.2014.10.012

144. Ruzmuni S, Federici S, Caroli F, Grossi A, Baldi M, Obici L, et al. Next-generation sequencing and its initial applications for molecular diagnosis of systemic auto-inflammatory diseases. *Ann Rheum Dis* (2016) 75(8):1550–7. doi:10.1136/annrheumdis-2015-207701

145. Touitou I, Perez C, Dumont B, Federici S, Jorgensen C. Refractory auto-inflammatory syndrome associated with digenic transmission of low-pene trance tumour necrosis factor receptor-associated periodic syndrome and cryopyrin-associated periodic syndrome mutations. *Ann Rheum Dis* (2006) 65(11):1530–1. doi:10.1136/annrheumdis-20054312

146. Federici S, Sormani MP, Ozen S, Lachmann HJ, Amaryan G, Woo P, et al. Paediatric Rheumatology International Trials Organisation (PRINTO) and Eurofever Project. Evidence-based provisional clinical classification criteria for autoinflammatory periodic fevers. *Ann Rheum Dis* (2015) 74(5):799–805. doi:10.1136/annrheumdis-2014-206580

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Copyright © 2017 Martorana, Bonatti, Mozziioni, Vaglio and Percepio. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) or licensor are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.