Guidelines for the genetic diagnosis of hereditary recurrent fevers

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ABSTRACT

Hereditary recurrent fevers (HRFs) are a group of monogenic autoinflammatory diseases characterised by recurrent bouts of fever and serosal inflammation that are caused by pathogenic variants in genes important for the regulation of innate immunity. Discovery of the molecular defects responsible for these diseases has initiated genetic diagnostics in many countries around the world, including the Middle East, Europe, USA, Japan and Australia. However, diverse testing methods and reporting practices are employed and there is a need for consensus guidelines for HRF genetic testing.

Draft guidelines were prepared based on current practice deduced from previous HRF external quality assurance schemes and data from the literature. The draft document was disseminated through the European Molecular Genetics Quality Network for broader consultation and amendment. A workshop was held in Bruges (Belgium) on 18 and 19 September 2011 to ratify the draft and obtain a final consensus document. An agreed set of best practice guidelines was proposed for genetic diagnostic testing of HRFs, for reporting the genetic results and for defining their clinical significance.

INTRODUCTION

Patients with hereditary recurrent fevers (HRFs) present with recurrent bouts of fever and inflammatory symptoms involving, in particular, the abdomen, joints and skin.1 2 The causative genes for HRFs encode proteins involved in the regulation of innate immunity, mainly by affecting proinflammatory cytokines and apoptosis pathways. While familial Mediterranean fever (FMF) is relatively common in several Mediterranean and Middle Eastern populations,3 most HRFs are rare diseases. The best-characterised HRFs are two recessively inherited diseases: FMF, gene MEFV, MIM 608107 and mevalonate kinase deficiency (MKD, gene MVK, MIM 251170) and two dominantly inherited diseases: tumour necrosis factor (TNF) receptor-associated periodic syndrome (TRAPS, gene TNFRSF1A, MIM 191190) and cryopyrin-associated periodic syndrome (CAPS, gene NLRP3, MIM 606416).

Since the discovery of these four HRF genes, almost 700 nucleotide variants have been identified and recorded in Infevers, a database dedicated to autoinflammatory sequence variants (http://www.infevers.org).6-8 Some of these variants are clearly pathogenic, but most are unconfirmed or seemingly non-pathogenic variants. A significant number of patients clinically diagnosed with recessive HRFs have been found to carry only one disease-associated mutation in the respective genes despite extensive searching for a second pathogenic mutation in the coding region,8 9 and continuing search for mutations affecting regulatory sequences or transcript splicing that would affect gene expression.10 11

Genetic testing for HRF is a logical and feasible way to corroborate clinical diagnosis.12 13 Five-year experience of external quality assessment and proficiency testing (PT) (external quality assurance/PT) conducted between 2006 and 2010 showed that although there has been an impressive improvement in the quality of HRF testing and reporting, many issues still remain to be addressed and standardised.14 Guidelines using the standard definition by Field and Lohr15 are now proposed to provide a framework for best laboratory practice and reporting on the genetic diagnosis of HRFs as agreed by an international consortium of experts in the field. They are intended to be used primarily by molecular geneticists and by other health professionals involved in the care of these patients.

METHODOLOGY

A draft report was written by the organisers and assessors of the European Molecular Genetics Quality Network for HRFs with reference to relevant literature, reviews of reports issued during the five previous international HRF meetings, web-based resources relating to the subject and examples of guidelines for other hereditary diseases (eg, haemochromatosis,16 cystic fibrosis17 and von Willebrand18 diseases). The draft was disseminated to molecular geneticists and clinicians working in the field of HRFs and discussed with them during a best practice workshop held in Bruges (Belgium) on 18 and 19 September 2011. In the light of feedback of the participants, amendments were made and a second draft was disseminated by email, after which, the final document was ratified.
INDICATIONS FOR HRF TESTING

Minimal requirements for the genetic test

We suggest that the following minimum set of requirements should be obtained: patient name, date of birth, gender, ethnicity/origin, written informed consent (depending on country-specific law), referring doctor’s name and contact details of the person who will receive the results.

Symptomatic patients

The main indication for genetic testing of HRFs is in the case of a patient with a clinical symptom pattern consistent with one or more of the syndromes. Thus, clinical data that justify the choice of one or more HRFs genetic tests are required. It is not unusual that when overlapping, partial or atypical clinical symptoms impede an accurate clinical diagnosis, screening of several HRF-responsible genes gives the correct diagnosis.

The clinical HRF referral usually includes the frequency of attacks, duration, sites affected, acute phase reactants levels, biomarkers for mevalonic aciduria or amyloidosis and a letter by an expert clinician. An example of a clinical chart is provided in online supplementary figure S1. It has been established in France by GenMIAI, the national network for genetic diagnosis of auto-inflammatory diseases, in conjunction with the clinical reference centres. Decision trees for genetic diagnosis in atypical patients and patients with sporadic disease have been proposed. In addition, a diagnostic score for children with periodic fever has been elaborated in Italy.

Presymptomatic diagnosis and carrier status

In general, presymptomatic diagnosis is not advisable, as its interpretation is inconclusive, may be complicated for mutations with incomplete penetrance and it usually does not call for medical intervention. Presymptomatic testing may be recommended after genetic counselling for asymptomatic family members when a severe genotype has been found in relatives with an overt disease, or if there is a family history of amyloidosis. Follow-up of people at risk may avoid occurrence of this life-threatening complication. However, whether such cases should be given prophylactic treatment remains controversial. Evaluation of carrier status could be recommended in healthy relatives to phase two known disease-associated or new mutations, when identified in an affected patient.

Prenatal diagnosis and preimplantation genetic diagnosis

Generally prenatal diagnosis (PND) and preimplantation genetic diagnosis (PGD) are not considered appropriate for HRF as most of these conditions are treatable and symptoms usually decrease over time. However, it may be appropriate to discuss PND or PGD in families affected by a particularly severe form of MKD or chronic infantile neurological, cutaneous and articular syndrome (CINCA) as these disorders can be associated with debilitating complications: blindness, deafness, mental retardation, ataxia and bone deformation. However, most severe CINCA-associated mutations occur de novo and this should be considered before offering PND and PGD. If PND is planned, it should be performed after genetic counselling.

INTERPRETATION

Classification and validation of HRF sequence variants

The Human Genome Variation Society (HGVS) has recommended avoiding the use of ‘mutation’ and ‘polymorphism’ as
### Table 1

<table>
<thead>
<tr>
<th>Exons</th>
<th>Disease</th>
<th>Gene</th>
<th>Reference sequence/LRG</th>
<th>Sequence variants</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-11</td>
<td>FMF</td>
<td>MEFV</td>
<td>NM_000243.2/LRG_190</td>
<td>Screening* X X X X</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>71:1599→2012;</td>
</tr>
<tr>
<td></td>
<td>MKD</td>
<td>–</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>TRAPS</td>
<td>TNFRSF1A</td>
<td>NM_001065.3/LRG_193</td>
<td>Screening* X</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Category†</td>
</tr>
<tr>
<td></td>
<td>CAPS</td>
<td>NLRP3</td>
<td>NM_001243133.1 or NM_004895.4/LRG_197</td>
<td>Screening*</td>
</tr>
</tbody>
</table>

#### Recommendation

1. **Clearly pathogenic variants.** Genetic confirmation of HRFs is more straightforward in cases of sequence variants that associate with a well-recognized HRF phenotype (e.g., p.Met694Val, NM_000243.2:c.2080A→G in MEFV), or those clearly altering the protein structure (e.g., cysteine mutations in TNFRSF1A; deletions, insertions in MVK). When evidence is sufficient, laboratories should clearly indicate when a detected variant (or combination of variants) is predicted to cause HRFs. If the variant has been associated with severe or moderate symptoms, references could be provided but with the note that this does not necessarily predict the individual's disease phenotype.

2. **Variants of uncertain significance.** These include debated frequent variants and rare or private variants.

   a. **Variants that have been initially published as pathogenic but later reassigned.** It is not unusual that some variants that have been initially described as disease-associated are now found to be common in the general population, or do not segregate with the phenotype in multiplex families, or do not have much effect on the normal function of the protein. Well-known examples are p.Glu148Cys (NM_000243.2:c.442G→C) or MEFV, p.Arg121Gln (NM_001065.3:c.362G→A) of TNFRSF1A, or p.Arg121Gln (NM_001065.3:c.362G→A) and p.Pro57Leu (NM_001065.3:c.224C→T) (usual names R92Q and P46L, respectively) of TNFRSF1A and p.Val198Met (NM_001243133.1:c.592G→A) of NLRP3 (also known as V200M).

   b. **Variants with no reliable information or new variants.** Testing unaffected parental samples for the presence of a new variant is fairly straightforward and a very informative way to assess their contribution to HRF. The frequency of rare variants in genetically matched populations could be evaluated in silico by searching various databases such as dbSNP (http://www.ncbi.nlm.nih.gov/projects/SNP/), 1000 Genomes Pilot project and PubMed. There are also other web-based tools for evaluating the degree of evolutionary conservation (e.g., Genomics Evolutionary Rate Profiling: GERP, http:// mendel.stanford.edu/sidowlab/downloads/gerp/index.html) and the functional impact on the protein (e.g., PolyPhen-2 http://genetics.bwh.harvard.edu/pph2/). For variants that are suspected to affect transcript splicing the patient’s cDNA should be analysed if available.

3. **Variants that are clearly not the genetic cause should not be reported.** Coding region SNPs frequent in the general population are often encountered. Examples are p.Arg202Gln (NM_000243.2:c.605G→A), minor allele frequency (MAF)=0.18 of MEFV which is in linkage disequilibrium with p.Met694Val, NM_000243.2:c.2080A→G.
Laboratory identifiers and contact information

Genetic Diagnosis of [Acronym HRF]

(Extended name HRF)

Name of referring health care professional:
Date of receipt of the sample:

Subject: [Family name, given name patient]
Date of birth: --/--/----
Patient ID: [internal ID]
Type of sample: [DNA/blood]

Indication for testing:

Method: Method (sequencing, kit etc…) and extent of the screening (exons ---) of the [HRF] gene (ref seq: NM_XXXX.X). This allows identification of XX% of the known mutations.

Results: Two [type of the variants] were found
Mutations and genotype to be given using HGVS nomenclature

Genotype:

p.[---];[---] if phased not allelic
p.[---;---] if phased allelic
p.[---(;)---] if not phased

Interpretation:
[To be reported here as suggested in table 2]

Recommendations: Genetic counseling is advised.

Date of report
Name of the molecular geneticist(s)

Figure 1 A proposed model for reporting the genetic diagnosis of hereditary recurrent fevers (HRFs). This is an example of a recessive disease, showing the minimal items to be reported. A report should ideally highlight the major findings and not exceed one page. HGVS, Human Genome Variation Society.

p.Ser52Asn (NM_000431.1:c.155G→A, MAF=0.09) of MVK and p.Gln703Lys (NM_001243133.1:c.2107C→A, MAF=0.02) of NLRP3.27 We believe that reporting these SNPs in the context of genetic diagnosis of HRF might mislead the report recipient.

Genetic confirmation of the clinical diagnosis

As for any Mendelian conditions, the definitive genetic diagnosis of HRFs is based on the finding of unambiguous mutations in the causative genes. Theoretically, identification of one single pathogenic variant in dominant diseases, homozygosity or compound heterozygosity (confirmed by studying the parental alleles) in recessive disorders, should be enough to confirm the diagnosis. Of note, finding a single MEFV pathogenic variant in patients of Mediterranean origin does not exclude the possibility of disease-causing mutations in other HRF genes.28 However, interpretation of a result should always take into account the sensitivity of the molecular screening strategy. Failure to identify a causal mutation in a given gene can almost never exclude the diagnosis. Indeed, the entire gene is not sequenced in most routine settings and even complete gene sequencing based on PCR technology could miss a pathogenic variant (primer variants, inversion of exons, duplication of exons…) Likewise mosaicism will be most likely missed by standard sequencing.
Table 2   Guidelines for reporting and interpreting genetic results in the four main HRFs

<table>
<thead>
<tr>
<th>Patients with symptoms</th>
<th>Report of results</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>One clearly pathogenic and one VUS</td>
<td>The patient has a compound heterozygote and one variant of uncertain significance in the (MEFV/MVK) gene. They have never been reported in cis (complex allele)</td>
<td>This genetic result could be consistent with clinical diagnosis of (FMF/MKD). If relevant add: the phenotype is generally associated with a mild phenotype.</td>
</tr>
<tr>
<td>Two clearly pathogenic variants</td>
<td>Two clearly pathogenic variants were identified in the (MEFV/MVK) gene. They have never been reported in cis (complex allele).</td>
<td>This genetic result confirms clinical diagnosis of (FMF/MKD). If relevant add: the phenotype is generally associated with a mild phenotype.</td>
</tr>
<tr>
<td></td>
<td>Two VUS</td>
<td>Diagnosis relies on clinical judgement or criteria. If relevant add: possible association with a mild phenotype.</td>
</tr>
<tr>
<td></td>
<td>One VUS or no variant</td>
<td>Rare undetected variants may exist. Diagnosis relies on clinical judgement or criteria. Refer to an expert clinician to consider other HRFs.</td>
</tr>
<tr>
<td>Asymptomatic individuals</td>
<td>Adapt from above</td>
<td>The individual is at risk of developing symptoms of HRF. If relevant add: or inaugural renal amyloidosis. It is recommended that acute phase reactants (CRP, SAA) and the kidney function (urine analysis) be regularly monitored.</td>
</tr>
<tr>
<td>Recessive diseases (FMF or MKD)</td>
<td>The individual is a carrier for a (clearly pathogenic variant/variant of uncertain significance) in the (MEFV/MVK) gene.</td>
<td>This individual is not likely to develop (MKD/FMF).</td>
</tr>
</tbody>
</table>

CRP, C reactive protein; SAA, serum amyloid A; VUS, variant of uncertain clinical significance (includes debated variants and rare and novel variants with no relevant information).

REPORTING

We recommend that genetic test results should be sent to the doctor(s) designated by the patient and not directly to the patient. The referring doctor should be invited to contact the laboratory if they have not fully understood the clinical significance of the test result. In the case of family studies, genetic results should not be communicated to other relatives without their consent. We recommend that a patient’s information on genetic testing results should be given by a doctor skilled in the field of HRFs or by an expert geneticist, if available.

We strongly suggest that the reports include all items recommended by the OECD quality assurance in genetic testing (http://www.oecd.org/dataoecd/43/6/38839788.pdf) and match the international standard ISO-15189. The laboratory report should be limited to a single page, with the genetic results and interpretation highlighted and the rest in smaller characters or presented in footnotes. A model report is proposed (figure 1).

Genetic results

1. Variants should be described at both the protein and nucleotide level and should comply with the latest version of HGVS nomenclature (http://www.hgvs.org/mutnomen/). It is preferable to use the three-letter amino acid code.

2. Wherever the sequence variant name has changed owing to renumbering of the start codon, both the standard and HGVS nomenclature should be reported, to allow the referring clinician access to the relevant literature. Examples are p.Arg121Gln (NM_001065.3:c.362G→A) (common name R92Q) of TNFRSF1A and p.Val198Met of TNFRSF1A.
A particular challenge for the genetic diagnosis of HRF will be in
from large population cohorts of patients and healthy controls.

A comment on mild disease outcome can be considered for
variants and in familial cases of HRF with a history of amyloidosis.
A comment that a diagnosis of HRF is excluded. In this situation diag-
state that a diagnosis of HRF is excluded. In this situation diag-

Additional comments in the report may refer to the presumed
effect of the sequence variant on protein function and suggest future
genetic testing or clinical management. Comments related to genotype–phenotype correlations are appropriate if
there is enough evidence in the literature to support them. They
are critical when discussing the risk of amyloidosis in patients
with FMF with mutations affecting codons 680 or 694 of the
MEFV gene, in patients with TRAPS with cysteine pathogenic
variants and in familial cases of HRF with a history of amyloidosis.
A comment on mild disease outcome can be considered for
variants with mild or low penetrance sequence variants.

It is preferable to recommend referral to genetic counselling
and/or to a clinical reference centre rather than to comment
directly on treatment options or the predicted risk for the off-
spring or other family members. The clinical reference centres
are better placed to fully discuss these pertinent issues. Testing
should be offered to other symptomatic family members and
to the parents where this can help with interpretation of the
proband's results.

The other important items suggested by the OECD are sum-
marrised below:

- More than one identifier that unequivocally links the report
to the patient (name, date of birth, internal reference labo-
  ratory number).
- The name of the referring healthcare professional and con-
tact information.
- The indication for testing and specific medical information
  where it is relevant.
- The date of receipt of the sample and of report issuing.
- The laboratory contact information and the identity of the
  individual approving the report.

CONCLUSION
A consensus set of best practice guidelines has been devel-
oped for molecular genetic testing of HRFs based on feedback
received from experts in this field. The guidelines described here
are aimed at improving the quality of HRF molecular diagnos-
tics and promoting harmonisation and standardisation of labo-
ratory test reports. Understanding the molecular pathology of
these diseases, their heterogeneity and genotype–phenotype
 correlates is steadily evolving as more data become available
from large population cohorts of patients and healthy controls.
A particular challenge for the genetic diagnosis of HRF will be in
the interpretation of clinical relevance of variants that are found
at low, but >1%, frequency in various populations. These may
function as susceptibility alleles to inflammation rather than
disease-associated mutations and as such may give rise to an
inflammatory phenotype when inherited through digenic inher-
ance (in the form of double heterozygous). In that context we
feel that these guidelines may need to be regularly updated.

Useful links
igh.cnrs.fr/ISSAID/infvers/
ISSAID: Website of the International Society of Systemic
Autoinflammatory Diseases: http://fmf.igh.cnrs.fr/ISSAID/
pronto.it/eurofever/
Orphanet: Reference portal for information on rare diseases and
orphan drugs: http://www.orpha.net/
HGVS: Reference for the nomenclature for the description of
sequence variants: http://www.hgvs.org/mutnomen/
EMQN: European Molecular Genetics Quality Network: http://
www.emqn.org/emqn/
For FMF: The Centre of Arab Genomic Studies (http://www.
cags.org.ac) and the Israeli National Genetic Database (http://
www.goldenhelix.org/server/israeli/)

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Davide Martorana, Maria Grazia Pomponi, Alison Bybee, Catherine Rydelwski

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Note added in proof While this manuscript was in press, a new article by
Verma et al demonstrated a possible functional role of pQ703K (Q705K) in the
regulation of inflammation. This variant should therefore be considered a VUS
[should be in normal letters in table 1]. The Q705K Polymorphism in NLRP3 is
a Gain-of-Function Alteration Leading to Excessive Interleukin-1β and IL-18
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Correction notice This article has been corrected since it was published Online First.

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12Pronto diagnostics, Tel Aviv, Israel
REFERENCES

**Figure 1S**

**GENETIC DIAGNOSIS OF AUTOINFLAMMATORY DISEASE**

Tick the requested tests [if >2, please justify]

<table>
<thead>
<tr>
<th>Hereditary recurrent fevers: FMF</th>
<th>MKD</th>
<th>CAPS</th>
<th>TRAPS</th>
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<tbody>
<tr>
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<td>Mevalonate kinase deficiency</td>
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<tr>
<td>Cryopyrin associated periodic syndrome</td>
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<td>5</td>
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<tr>
<td>TNF receptor associated periodic syndrome</td>
<td>5</td>
<td>6</td>
<td>7</td>
</tr>
</tbody>
</table>

Other hereditary autoinflammatory disease:  

---

**Clinical form of the patient**

Box the symptoms presented by the patient before the start of the treatment  
+++ differentiate No and ND (No determined)

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<td>Mental retardation</td>
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| Squeleton | Myalgia | Yes | No | ND | Arthritis | Yes | No | ND | Arthralgia | Yes | No | ND | Deforming | |
|-----------|---------|-----|----|----|-----------|-----|----|----|-----------|-----|----|----|----------|
| Myalgia   |         | Yes | No | ND | Arthritis | Yes | No | ND | Arthralgia | Yes | No | ND | Deforming | |
| Arthritis |         |     |    |    | Arthralgia | Yes | No | ND |               |     |    |    |          |
| Arthralgia|         |     |    |    | Deforming  |       |    |    |
| Deforming |         |     |    |    | Arthropathy | Yes | No | ND |               |     |    |    |          |

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<td>Yes</td>
<td>No</td>
<td>ND</td>
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<tr>
<th>Other</th>
<th>Splenomegaly</th>
<th>Yes</th>
<th>No</th>
<th>ND</th>
<th>Hepatomegaly</th>
<th>Yes</th>
<th>No</th>
<th>ND</th>
<th>Adenopathy</th>
<th>Yes</th>
<th>No</th>
<th>ND</th>
<th>Pharyngitis</th>
<th>Yes</th>
<th>No</th>
<th>ND</th>
<th>Growth</th>
<th>Yes</th>
<th>No</th>
<th>ND</th>
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<tbody>
<tr>
<td>Splenomegaly</td>
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<td>Yes</td>
<td>No</td>
<td>ND</td>
<td>Hepatomegaly</td>
<td>Yes</td>
<td>No</td>
<td>ND</td>
<td>Adenopathy</td>
<td>Yes</td>
<td>No</td>
<td>ND</td>
<td>Pharyngitis</td>
<td>Yes</td>
<td>No</td>
<td>ND</td>
<td>Growth</td>
<td>Yes</td>
<td>No</td>
<td>ND</td>
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<tr>
<th>Triggering factor</th>
<th>Cold</th>
<th>Heat</th>
<th>Vaccination</th>
<th>Stress</th>
<th>Fatigue</th>
<th>No</th>
<th>ND</th>
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<tbody>
<tr>
<td>Cold</td>
<td></td>
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</tr>
<tr>
<td>Heat</td>
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<td>Fatigue</td>
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<tr>
<th>Attack frequency</th>
<th>&lt; 1/month</th>
<th>1 à 2/month</th>
<th>&gt; 2/month</th>
<th>No</th>
<th>ND</th>
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<td>&lt; 1/month</td>
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<tr>
<td>1 à 2/month</td>
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<tr>
<td>&gt; 2/month</td>
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<tr>
<th>Attack duration</th>
<th>----- hours</th>
<th>----- days</th>
<th>No</th>
<th>ND</th>
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<tbody>
<tr>
<td>----- hours</td>
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<tr>
<td>----- days</td>
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**PRE-REQUISITES TO MEET**

1. **Prescribing DOCTOR**  
   Complete address

2. **Informed consent** signed by the patient or her/his guardian: to be joined

3. **Clinical form** filled in by the prescribing doctor (above-cons)

4. **Genealogic tree** (to complete next page)

5. **Number of unexplained inflammatory attacks**: ≥3 yes no  

6. **CRP value during attacks**:  

7. **Age at symptoms onset**:  

**BIOLOGY** already realised to fill if known

Mevalonate aciduria during attacks  
Mevalonate kinase activity

**TREATMENT**

<table>
<thead>
<tr>
<th>Dose</th>
<th>Age at start</th>
<th>Effect (N none, P partial, T total)</th>
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</thead>
<tbody>
<tr>
<td>Colchicine</td>
<td>....../d</td>
<td>......</td>
</tr>
<tr>
<td>Corticoïdes</td>
<td>....../d</td>
<td>......</td>
</tr>
<tr>
<td>Other</td>
<td>....../d</td>
<td>......</td>
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