Approach to the diagnosis of hereditary autoinflammatory syndromes

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'Genetic testing in the hereditary autoinflammatory syndromes is often a useful tool, but should only be used as an adjunct to clinical diagnosis.'

The name 'hereditary autoinflammatory syndromes' is used for a growing group of monogenetic disorders, formerly known as hereditary periodic fever syndromes (**Table 1**). These disorders share a common phenotype of recurring symptoms of (systemic) inflammation, which usually includes fever, although in some newer members of the group fever is not a prominent feature. The individual syndromes each have specific characteristics offering diagnostic clues for the experienced clinician, such as the type of skin rash or duration of inflammatory episodes. Insight into prognosis, complications and treatment of the specific disorders within this group has grown dramatically over the past few years, which makes it increasingly important to reach the correct diagnosis in an individual patient. Since the genetic basis of these syndromes has been unraveled, genetic tests may confirm clinical diagnosis of these disorders. This availability of firm diagnostic confirmation is often seen as one of the major advantages of monogenetic disorders. However, contrary to expectation, genetic testing does not always simplify matters. I will use the following hypothetical case to illustrate the challenges that arise in both selecting the appropriate genetic tests and interpreting their results.

A 22-year-old man from Armenia has a history of recurring episodes of fever and abdominal pain since the age of 14 years. The symptoms always resolve spontaneously after approximately 3 days. Two cousins and his sister have the same symptoms. He has been hospitalized repeatedly because of the severity of his symptoms, but is still without a diagnosis, despite thorough investigations that have excluded infections, malignancy or autoimmune disease.

This is a good example of a patient with a hereditary autoinflammatory syndrome. But which of them is it? If this patient had presented in early 1997, the diagnosis might have been straightforward. Certain clinical clues, such as the patient's ethnic origin and the character of the fever episodes, suggest familial mediterranean fever (FMF). A successful trial of treatment with colchicine would have clinched the diagnosis. The underlying genetic basis of this disease was unknown at the time, so genetic confirmation was out of the question. The patient would have been started on the appropriate treatment with colchicine.

In the last 10 years, however, the field has changed significantly. If our patient presented today, the diagnostic process would not be thought complete without a genetic test of the *MEFV* gene (**Table 1**). If this test is positive for two mutations, the diagnosis of FMF is confirmed. In this setting, the advantage of genetic testing is clear, offering an objective confirmation of the diagnosis for both the patient and his affected relatives. However, things are not always that clear. I will discuss three potential pitfalls associated with strict reliance on genetic testing as the basis for diagnosis.

To start with, what if the test in our patient yields only one mutation for this autosomal recessive disorder? Or what if the test comes back negative? This is not a far-fetched scenario. In a recent study, Federici and colleagues found that only 60% of patients who met the clinical criteria for FMF and had a typical ethnic background had a positive genetic test [1]. When patients were of different ethnic origin, only 11% tested positive. In another of the autoinflammatory syndromes, just 60% of children with a clinical diagnosis of neonatal onset multisystem inflammatory disease (NOMID), also known as chronic infantile neurological, cutaneous and articular syndrome (CINCA), tested positive for mutations in the *CIAS1* gene [2]. And the same is true for the other syndromes.

Does this mean that our patient with a negative genetic test does not have FMF, even though all his symptoms fit and the treatment is effective? One option, especially used in FMF (and also in NOMID/CINCA), is to keep the clinical criteria as the mainstay for diagnosis. Patients who subsequently test negative on genetic analysis are still considered to have FMF or clinical FMF. In the case of hyper-immuoglobulin D and periodic fever syndrome (HIDS), the designation 'variant-type HIDS' is sometimes used when no mutations are found [3]. This can be helpful for the

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clinician, and also brings clarity for the patient, but should be used with care, since it might also give false reassurance and hinder a potential definite diagnosis in the future. Even a patient with a typical ethnic background and periodic fever attacks might have a condition other than FMF [4]. If, over time, the disorder develops in an unexpected way, or as new insights are published, the clinician should remain aware that the diagnosis may have to be reconsidered.

A second pitfall surrounding genetic analysis is the identification of gene variants that are of uncertain status. An example of this is the E148Q variant in the *MEFV* gene, which is found in FMF patients but also in healthy controls. It is sometimes seen as a mutation associated with a mild form of FMF, but others consider it a polymorphism with, at most, some influence on inflammation in general [5]. The same is true for the variants R92Q or P46L in the tumor necrosis factor (TNF)-receptor I gene, which might or might not directly cause TNF-receptor associated periodic syndrome (TRAPS) [6]. Again, this yields a dilemma in the diagnosis. When a R92Q variant in a patient with suspected TRAPS is discovered, do you consider this a confirmation of the diagnosis, or a reason for further investigations? Opinions among experts can be divided, and will change over time. Where does that leave the patient?

Table 1. Hereditary autoinflammatory syndromes.

Abbreviation	Full name	Inheritance*	Gene (protein)
FMF	Familial Mediterranean fever	Recessive	*MEFV* (pyrin)
TRAPS	TNF-receptor associated periodic syndrome	Dominant	*TNFRSF1A* (TNF-receptor type 1)
HIDS	Hyper-IgD and periodic fever syndrome	Recessive	*MVK* (mevalonate kinase)
CAPS‡	Cryopyrin-associated periodic syndrome	Dominant	*CIAS1* (cryopyrin or NALP3)
BS/EOS	Blau syndrome/ early-onset sarcoidosis	Dominant	*NOD2/CARD15* (NOD2)
PAPA	Pyogenic arthritis, pyoderma gangrenosum and acne syndrome	Dominant	*CD2BP1/PSTPIP1* (PSTPIP1)

**All have an autosomal inheritance pattern.*

‡This includes Muckle–Wells syndrome, familial cold autoinflammatory syndrome and neonatal-onset multisystemic inflammatory disorder, also known as chronic infantile neurologic cutaneous and articular syndrome.

Ig: Immunoglobulin; TNF: Tumor necrosis factor.

'Establishing firm, evidence-based clinical criteria for the differential diagnosis should prove helpful, but remains a great challenge, especially because of the overlap in symptoms and the difficulty of collecting large numbers of patients.'

The third dilemma I wish to discuss is how far should we pursue genetic testing? If we return to our hypothetical patient, his clinical picture and treatment response all fit with FMF, so even if no pyrin mutations are detected, a clinical diagnosis of FMF seems warranted. Real-life cases are often not so clear-cut. What if he only had a partial response to colchicine? Or what if he came from Denmark instead of Armenia? In such cases, most of us would agree that further investigations are indicated. The next question would then be, what other syndromes should be considered? As mentioned before, there are a growing number of disorders, and thus a growing number of genetic tests available. It is questionable whether, in a clinical setting, these should all be tested for, one by one, in every patient with recurrent inflammation. In the first place, the chance of discovering mutations fitting with a hitherto unexpected disorder should not be overestimated [7]. Secondly, doing more tests will increase the risk of turning up results that are difficult to interpret, such as the variants mentioned above, or single mutations instead of two in a recessive disease gene. It is not uncommon to find combinations of polymorphisms or single mutations in different genes [8]. This might only increase clinical uncertainty. And, in the third place, these tests are expensive and it might take months or years to get all the results.

This last disadvantage will likely diminish in the near future, as costs for genetic analysis continue to decrease and combined diagnostic tests for multiple autoinflammatory syndromes will become available. These combined tests will have the advantage that they will pick up rare disorders that the clinician may not even have heard of previously. They will not, however, address the other problems mentioned.

In some cases, it may be advisable to settle for a tentative diagnosis, such as hereditary autoinflammatory syndrome, not otherwise specified. This has the advantage of allowing patient and doctor to move from the stage of diagnostic uncertainty to that of treatment and/or acceptance. However, just as in the case of clinical FMF

or variant HIDS, such a diagnostic epithet should only be used if it is taken to imply that a more definite diagnosis might be possible at a future date.

As a consequence of the pitfalls of genetic testing that I have discussed here, it is still of great importance to develop thorough clinical definitions and criteria for these syndromes. A clinician with experience of these rare disorders can often distinguish the relevant clues, even though this expert opinion might not be evidence-based. Clinical reviews and algorithms based on such expert opinion may help those who only infrequently encounter a patient with recurrent fevers [1,9]. Establishing firm, evidence-based clinical criteria for the differential diagnosis should prove helpful, but remains a great challenge, especially because of the overlap in symptoms and the difficulty of collecting large numbers of patients [10].

The fact that a definite diagnosis remains elusive in approximately two-thirds of patients with recurring inflammatory episodes is evidence for the involvement of other genes and proteins. This is a rich field for scientists interested in innate immunity.

In conclusion, genetic testing in the hereditary autoinflammatory syndromes is often a useful tool, but should only be used as an adjunct to clinical diagnosis [11]. As is true for many monogenetic disorders, a considerable percentage of patients with a clear phenotype do not have the expected corresponding genotype. This can present a challenge in clinical practice. In the next few years, I expect that a number of new disorders will be discerned within this group of patients. It will be interesting to see whether these discoveries will have to be classified as separate new syndromes, or alternatively as new causes for existing clinical syndromes.

Executive summary

Introduction

- Hereditary autoinflammatory syndromes are a group of rare disorders characterized by recurrent episodes of excessive inflammation.
- Increased insight into prognosis, complications and treatment of the specific disorders emphasizes the need to reach the correct diagnosis in a patient.
- Since the genetic background of these syndromes has been unraveled, genetic tests are available, but there are a number of pitfalls related to over-reliance on genetic diagnosis.

Pitfalls in the genetic diagnosis of hereditary autoinflammatory syndromes

- Up to 60% of patients with a clear clinical phenotype do not have the (complete) expected genotype.
- Certain gene variants detected behave more like polymorphisms than straight mutations.
- In the absence of a clear clinical phenotype for direction, it can be hard to choose the correct genetic test, and doing several genetic tests has its disadvantages.

Conclusion & future perspective

- Genetic testing should be used as an adjunct to the clinical diagnosing process, not as a replacement.
- In the next few years, new disorders will be discerned in this group of autoinflammatory syndromes.

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