REVIEW ARTICLE

Twists and turns of the genetic story of mevalonate kinase-associated diseases: A review

Isabelle Touitou a,b

a IRMB, Univ Montpellier, INSERM, Montpellier 34090, France
b Department of Medical Genetics, Rare Diseases and Personalized Medicine, Rare and Autoinflammatory Diseases Unit, CeReMAIA, CHU, Montpellier 34000, France

Received 20 January 2021; received in revised form 19 April 2021; accepted 12 May 2021
Available online 9 June 2021

KEYWORDS
Autoinflammatory disease; Genetic disease; Mevalonate kinase deficiency; Porokeratosis; Subtypes

Abstract  Mevalonate kinase (MK)-associated diseases encompass a broad spectrum of rare auto-inflammatory conditions, all resulting from pathogenic variants in the mevalonate kinase gene (MVK). Their clinical manifestations are highly variable, ranging from more or less serious systemic disorders, such as hereditary recurrent fevers, to purely localized pathologies such as porokeratosis. The oldest condition identified as linked to this gene is a metabolic disease called mevalonic aciduria, and the most recent is disseminated superficial actinic porokeratosis, a disease limited to the skin. The modes of inheritance of MK-associated diseases also diverge among the different subtypes: recessive for the systemic subtypes and dominant with a post-zygotic somatic genetic alteration for MVK-associated porokeratosis. This review quickly retraces the historical steps that led to the description of the various MK-associated disease phenotypes and to a better understanding of their pathophysiology, then summarizes and compares the different genetic mechanisms involved in this group of disorders, and finally discusses the diverse causes that could underlie this phenotypic heterogeneity.

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Abbreviations: DSAP, Disseminated superficial actinic porokeratosis; HIDS, Hyper-IgDsyndrome with periodic fever; IL-1, Interleukin 1; MA, Mevalonic aciduria; MK, Mevalonate kinase (protein); MKD, Mevalonate kinase deficiency; MVK, Mevalonate kinase (gene); PK, Porokeratosis; RP, Retinitis pigmentosa.

E-mail address: isabelle.touitou@inserm.fr.

Peer review under responsibility of Chongqing Medical University.

https://doi.org/10.1016/j.gendis.2021.05.002
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Introduction

Mevalonate kinase (MK) is an enzyme involved in the isoprenoid pathway and cholesterol synthesis that converts mevalonate into 5-phosphomevalonate. MK is ubiquitously expressed, notably in blood leukocytes and skin keratinocytes. The gene encoding MK, MVK, is located on chromosome 12q24 and contains 10 coding exons and one non-coding exon.

Several phenotypes have been associated with pathogenic variants in MVK. They all belong to a heterogeneous group of conditions called autoinflammatory diseases, resulting from mutations in genes of the innate immune system. The first MK-associated disease described was mevalonic aciduria (MA; OMIM 610377); enzyme precursors were constantly detected in patients’ urine. Recently, dominant MVK mutations were also identified in patients with porokeratosis (PK), a phenotype localized to the skin and totally different from the systemic form.

The various clinical subtypes and modes of inheritance that have emerged and many molecular developments that have occurred over the last 28 years have led to a better knowledge of the pathophysiology of these diseases, and to improved patient care. The main clinical advances brought about by pinpointing the culprit gene was the implementation of sequencing tests for diagnosis. The advances brought about by pinpointing the culprit gene was the implementation of sequencing tests for diagnosis.10 The understanding that MK-associated diseases are caused by a recessive metabolic disorder named mevalonic aciduria (MA; OMIM 610377); enzyme precursors were constantly detected in patients’ urine.1 Recently, dominant MVK mutations were also identified in patients with porokeratosis (PK), a phenotype localized to the skin and totally different from the systemic form.

The literature provides abundant information on the clinical or mutational spectrum and/or therapeutic aspects of MK-associated hereditary recurrent fever and PK. Therefore, this review does not extensively cover these themes already well illustrated elsewhere but rather uses the MVK gene, instead of the phenotype, as the entry point for the study. Indeed, MK-associated diseases represent a fascinating example of the accumulation of patients and genetic knowledge overturning our initial belief that mutations in this single gene lead to a systemic disease only. The aim was to provide an original historical and genetic overview of MK-associated diseases, to investigate the different genetic mechanisms underlying these disorders and their respective modes of inheritance and to address questions that have been little explored until now, such as how a single gene can be the cause of so many different clinical pictures.

A long story in a nutshell

The first major step taken to result in our current understanding of MK-associated diseases was the identification of the human MVK gene, in 1992 (Fig. 1). The link between MVK mutations and serious MA disease as well as its recessive transmission was established in 1997. Two years later, MVK variants were also linked to a milder, seemingly different, inflammatory disease called at the time “hyper-IgD syndrome with periodic fever” (HIDS; OMIM 260920) because high amounts of IgD were found in the serum of most patients. It is now suggested that the term “HIDS” be dropped because elevated IgD level is neither specific nor constant and may well be a result rather than a cause of the disease. Phenotypes of intermediate severity have been described as well, revealing a continuum between the milder and severe disease, which thus represent the two extremes of the same genetic disorder.

Decreased enzyme activity has been demonstrated in all systemic forms, which therefore are strongly suggested to be grouped under the common umbrella “MK deficiency” (MKD), mild or severe. Recently, and somewhat unexpectedly, whole-exome sequencing in Chinese families with disseminated superficial actinic porokeratosis (DSAP) revealed that dominant pathogenic MVK variants were responsible for this purely dermatological disease. A second somatic hit was eventually discovered in the epidermis lesions of some DSAP patients.

The clinical and genetic landscape of MK-associated diseases

Systemic MK-associated diseases (MKDs) are recessively inherited

Although MKD was first described in the Netherlands and France, it is now recognized worldwide. The first symptoms occur early in life, generally in the first 2 years and include inflammatory symptoms such as fever and elevated acute-phase reactants. Severe MKD is characterized by a massive and constitutive urinary excretion of metabolites accumulated upstream of the defective enzyme. The activity of the defective enzyme in cultured fibroblasts or leukocytes generally decreases to about 0.5%–2% of that of controls and is sometimes undetectable below 0.5%. Complete enzyme deficiency seems incompatible with life. The inflammatory symptoms are chronic and obscured by severe neurological signs (cerebellar ataxia, seizures, and mental, motor and growth retardation). Eye manifestations such as cataract, conjunctivitis and retinitis pigmentosa (RP) are common.

In the milder form, bouts of fever last 3–7 days and are typically associated with lymphadenopathy, diarrhea, vomiting and aphthosis. Flares are often triggered by vaccination, fatigue and stress. Mild MKD also features decreased enzyme activity and abnormal urinary excretion of mevalonic acid, but to a much lesser extent, with mevalonic aciduria detectable only during febrile attacks. When patients have sufficient residual enzyme activity, about 10% of that of controls, symptoms appear as attacks and tend to improve from adolescence onward.

Patients with atypical MKD features have been documented. Ocular symptoms may occur in both MKD subtypes, although they are more frequent in MKD-MA. Non-syn- dromic RP caused by MVK pathogenic variants has been described but almost always with some systemic MKD features. Other atypical presentations that may result in delayed diagnosis include prominent liver or cardiopulmonary disease, inflammatory bowel disease or amyloid A amyloidosis.
The pathophysiology of MKD, although better understood now, has not yet revealed why certain mutations lead to one phenotype rather than another. In brief (Fig. 2), pathogenic variants impede the folding and stability of MK and therefore its enzymatic activity, which results in mevalonic acid accumulation and decreased production of downstream geranyl-geranyl-pyrophosphate, itself leading to defective prenylation. Defective prenylation in turn leads to inactivation of RhoA GTPase and subsequent defective activation of specific kinases, namely, the serine-
threonine kinases protein kinase N1 (PKN1) and PKN2.\textsuperscript{5,6} These latter bind and phosphorylate pyrin, blocking activation of the pyrin inflammasome.\textsuperscript{41} Inflammasomes are protein platforms that aggregate upon detection of a pro-inflammatory signal to activate secretion of potent pro-inflammatory cytokines such as IL-1.\textsuperscript{42} Constitutive activation of pyrin and NOD-like receptor family, pyrin domain containing 3 (NLRP3) inflammasomes has been established in two other hereditary recurrent fevers, familial Mediterranean fever (FMF) and NLRP3-associated autoinflammatory diseases, but remained unsuspected in MKD until recently. The inflammatory features of MKD are caused by excessive production of IL-1,\textsuperscript{43} but the neurological or ocular symptoms seen in MKD-MA are less understood.\textsuperscript{29,44} Elevated mevalonic acid level could be toxic, or isoprenoids could be differentially regulated in the brain and retinal tissues (Fig. 2).

Patients with systemic MKD have two recessively inherited mutations, in the homozygous or the compound heterozygous state. More than 140 pathogenic MKD-associated variants are known and are registered in an online database dedicated to autoinflammatory mutations (https://infivers.umai-montpellier.fr/web).\textsuperscript{45} Most variants (115/147; 72%) are substitutions, and others are small intragenic rearrangements, including three deletions of exons (115/147; 72%) are substitutions, and others are small intragenic rearrangements, including three deletions of exons 2, 3 or 5. The first reported, p.(Ala334Thr), was intragenic rearrangements, including three deletions of exons 2, 3 or 5. The first reported, p.(Ala334Thr), was attributed to gene conversion of the wild type to a mutated allele. This decreased expression of the normal allele was attributed to gene conversion of the wild type to a mutated allele, resulting in an enhanced proportion of the initial mutation in lesional tissues.\textsuperscript{46} The same group identified a second acquired \textit{MVK} mutation in lesions of one patient with DSAP (F38) (i.e., a post-zygotic c.1003G\textsuperscript{r}A transversion resulting from RNA-editing of the wild-type allele in addition to the c.1093T\textsuperscript{r}A germline mutation).

More recently, Kubo et al.\textsuperscript{47} detected a second hit in genes of the mevalonate pathway that occurred solely in cutaneous lesions of seven Japanese patients with DSAP. One of these patients acquired several different \textit{MVK} pathogenic variants in the wild-type allele as demonstrated by PCR-based cloning and sequencing of genomic DNA extracted from different biopsies of the lesional epidermis. The somatic events included various transitions (mainly C\textsuperscript{r}G or G\textsuperscript{r}A) as well as loss of heterozygosity due to mitotic homologous recombination. The mutations differed from the germline variant found in blood cells, differed among the cutaneous lesions in a same patient, and were absent in healthy skin. The authors concluded that each skin lesion originated from a postnatal keratinocyte clone. The proportion of cells with genetic alteration among normal cells determined the mosaicism rate in the lesional tissues.

Altogether, these results support that a second, postnatal mutation of the wild-type in the mevalonate pathway genes is required for PK to develop. The loss of the normal allele was the result of a gene conversion, RNA modification, or large deletion; a homologous chromosomal recombination; or an as yet unknown epigenetic mechanism (Fig. 3). The acquired genetic alteration transforms the native heterozygous genotype into a biallelic mutated genotype in the sick cells. Thus, the apparent dominant heredity with incomplete time-dependent penetrance observed in some patients in fact reflects a somatic recessive expression due to the late occurrence of a second post-zygotic loss-of-function mutation in keratinocytes. This concept mirrors the “two-hit” hypothesis of Knudson
for cancers and is consistent with the late onset of PK and with the fact that certain PK patients are at greatest risk for malignant transformation.51

How are MK and PK linked? Functional studies are scarce, and levels of enzymatic activity or MA have not been measured (or at least reported) to directly prove the enzyme deficiency in PK patients. However, Liu et al. reported that three mutant MK proteins were less stable than the wild-type protein and that one mutation p.(Gly335Asp) resulted in the misfolding of the ATP binding domain. Zhu et al. recently demonstrated decreased kinase activity, reduced cholesterol production, and increased apoptosis in cells transfected with two MVK pathogenic variants identified in DSAP patients. Shortage of isoprenoids could predispose patients to idiopathic inflammation of the skin because the mevalonate pathway is crucial in regulating calcium-induced keratinocyte differentiation and proliferation.22,23 Moreover, cholesterol, a product of the mevalonate pathway, is a key component of the extracellular lipid matrix that is important for the barrier function of the skin.65 Overexpression of wild-type MVK has been associated with increased differentiation and decreased type A ultraviolet radiation (UVA)-induced apoptosis of keratinocytes.66 The authors of this study hypothesized that environmental (i.e., UVA) factors precipitate cell death in patients with impaired MK function, which may account for the clinical distribution of the skin lesions in DSAP patients.

Unanswered questions and perspectives

This review quickly summarizes nearly three decades of intensive studies on MK-associated diseases, focusing on the most recent breakthroughs that have emerged from modern genetics. The understanding, at least in part, of the genetic mechanisms involved in this group of disorders has had many twists and turns, which will have a major impact on both our fundamental knowledge and genetic counseling for patients. Indeed, for the first identified phenotype (i.e., systemic MKD), the recessive mode of transmission, a feature common to most enzyme disorders, has been clear and never discussed, but the latest data on the purely cutaneous PK form have contradicted this paradigm and have revealed an unexpected genetic mechanism, which involves, at least in some patients, an initial germline mutation followed by a second somatic event. This second post-zygotic hit explains why, despite the dominant heredity of PK, its clinical expression is somatically recessive in nature. Nevertheless, several issues remain that have been little explored until now.

One issue concerns a possible genotype—phenotype correlation between the MVK variants carried by patients and the MK-associated subtypes they ultimately display. The fact that a same mutation (e.g., p.Gly202Arg) can be found in both systemic and skin forms is puzzling.45 Is there a link between the gene location or type of the mutation(s) and the clinical expression of the disease? Some general
trends have already been suggested, with p.(Val377Ile) and p.(Ala334Thr) associated with mild and severe or complicated systemic phenotypes, respectively, but exceptions exist.\textsuperscript{20,25,32} One clue has recently been provided by a multi-omic approach revealing the role of signal transducer and activator of transcription 1 (STAT1) as a modifier gene.\textsuperscript{66} STAT1 is central in the regulatory pathway of human mevalonate kinase and activator of transcription 1 (STAT1) as a modifier of AKT in tumourigenesis and immunity of cases, respectively.\textsuperscript{25} Conversely, the fact that PK patients do not have PK skin lesions.\textsuperscript{24,67} Finally, does the two-hit hypothesis account for other cases of recessive autoinflammatory diseases such as FMF, with heterozygous patients sometimes being asymptomatic?\textsuperscript{24} This hypothesis has not been formally investigated, but two cases of acquired FMF have been reported.\textsuperscript{69,70} In conclusion, the example of the genetic story of MVK-associated diseases retraces how amazing and various are the mechanisms underlying phenotypic heterogeneity. Large-scale integrated genomic technologies currently under development\textsuperscript{66} will undoubtedly provide more surprises in the near future and bring new diagnostic and therapeutic solutions to patients in the context of precision medicine.

Acknowledgements

The author is indebted to Dr Guilaine Boursier, Dr Laurence Cuisset, and Dr Guillaume Sarrabay for their valuable discussions and/or comments on the manuscript. Laura Smales (BioMedEditing, Toronto, Canada) is thanked for the English language review.
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