Familial Mediterranean Fever: New Aspects and Prospects at the End of the Millenium

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Familial Mediterranean fever is a genetic disorder characterized by recurrent febrile episodes and inflammation of serous membranes [1]. It is transmitted in an autosomal recessive form of inheritance and affects mainly ethnic groups living around the Mediterranean basin: Sephardi Jews, Armenians, Turks, Arabs, Druze, and Ashkenazi Jews. The gene responsible for FMF[1] (MEFV) has been mapped to the short arm of chromosome 16 [2], and recently cloned by two consortia — the International Consortium [3] and the French Consortium [4]. MEFV encodes a protein of 781 amino acids weighing 86 kDa, with arginine and lysine constituting 13% of the residues [3]. The protein encoded by this gene was named pyrin by the International Consortium, and Marenostrin by the French Consortium. Messenger RNA studies indicate that the pyrin/Marenostrin protein should be present almost exclusively in neutrophils and their precursors [3]. The wild-type function of the protein is believed to be that of a direct down-regulator of inflammation, specifically in neutrophils.

In the present article we shall review the phenotypic clinical symptomatology of FMF patients, based mainly on the numerous reports of the Heller Institute over the past 45 years as well as on our clinical experience treating and studying the more than 5,500 patients in our Institute's FMF clinic. We will correlate the above to the frequent mutations in MEFV that were found in the majority of FMF patients.

Although it existed in early biblical times, FMF was described as a separate nosological entity by Shepard Siegal in 1945 [5]. Siegal himself had suffered from the disease and, like most of his New York patients, was of Ashkenazi Jewish extraction. In the early 1950s, French investigators Mamou and Cattan [6] described the disease in North Africa, in Jews of Sephardi extraction. They were the first to mention the entity's familial occurrence and the lethal nephropathy that may affect patients. In the same period Reimann et al. [7], describing the disease in Armenian families, suggested that it is transmitted as a dominant trait. Following the waves of immigration of Jews from North Africa, Iraq and Turkey to the newly formed state of Israel in the fifties, Heller et al. [8–10] established a detailed clinical description of the condition. This included the recessive inheritance of the disease, the arthritis of FMF, and the nature of amyloid nephropathy. It was they who suggested the name "familial Mediterranean fever," which was accepted by the international medical community.

In 1961, Ehrenfeld et al. [11] published a series of 55 FMF patients. Stressing the fact that many of these patients did not develop amyloidosis, the Jerusalem group was the first to suggest that ethnic differences account for clinical variability in the severity of symptoms of FMF patients [11].

Clinical Features

The clinical symptoms are characterized by febrile painful episodes that constitute the hallmark of the disease. The febrile episodes or attacks are accompanied by high temperatures of 38.5–40°C, and severe pain in the abdomen, chest or joints due to inflammation of the peritoneum, pleura or synovia. During these attacks the involved organs demonstrate characteristic signs of inflammation, peritonitis with clinical signs of acute abdomen, pleuritis that may be accompanied by accumulation of one-sided pleural fluid, or acute synovitis mainly of the knee, ankle or hip. The attacks are short-lived, lasting for 1–3 days, and resolve without any treatment. Between the attacks the patients feel well and regain their normal function until the next episode. Repeated attacks at irregular intervals and in an unpredicted sequence are typical of the disease. The occurrence of one episode a week may vary, with remissions of weeks or months with no apparent cause. During the lifetime illness, a patient will probably experience several forms of attacks, but the recurrence of one type over many years is not uncommon [1].

Abdominal attacks

The most frequent manifestation of FMF is the abdominal attack, experienced by 90% of patients. These are marked by the sudden onset of fever, and pain spreading over the entire abdomen from various points of onset. As the attack gains in intensity, a guarding "board-like rigidity" of the abdominal muscles, rebound tenderness and distension of the abdomen are common signs found on physical examination. Loss of peristaltic sounds and multiple low fluid levels in the small bowel on radiography combine to suggest an acute abdominal catastrophe. After 6–20 hours the signs and symptoms recede (if the patient is not operated on), and within 24–48 hours the attack is usually over, leaving the patient as well as prior to the attack [1].

[1]FMF = familial Mediterranean fever

"Organization" of the exudate, which is formed in the peritoneum during the acute inflammation and is rich in neutrophils, may result in fibrous adhesions that in rare cases may give rise to mechanical ileus [12]. This may be the cause for sub-ileus in some patients and ascites in others. It is probably the cause of sterility in some affected FMF women [13].

Pleural attacks

A pleural attack has been experienced by 45% of our patients. It assumes the picture of an acute one-sided febrile pleuritis, resembling the peritoneal attacks in their abrupt onset, unpredicted recurrence and rapid resolution, the latter distinguishing it from infectious pleuritis that usually lasts longer. Breathing is painful and breath sounds are diminished on the affected side. There may be radiological evidence of a small exudate in the costophrenic angle. This exudate, which can be aspirated, contains numerous neutrophils and resolves within 48 hours [1].

Pericarditis attacks

Pericarditis is a rare feature of FMF. We observed clinical attacks of pericarditis characterized by retrosternal pain, ST segment elevation on echocardiogram, and evidence of pericardial effusion by echocardiography or transient enlargement of the heart silhouette by a chest radiogram in 26 of our FMF patients [14]. This type of attack also resolves within 1–3 days.

Articular attacks

The articular attack of FMF is the second most common form and was experienced by 75% of the patients in our series [1,9], many of whom are Jews originating from North Africa. The frequency of arthritis was found to be lower in Jews from Iraq, in Ashkenazi Jews, and in Armenians and Turks [15].

The acute arthritis of FMF is abrupt and has three characteristic features: a) it is accompanied by very high fever in the first 24 hours; b) in most cases it affects one of the large joints of the lower extremities such as knee, ankle or hip; and c) the signs and symptoms usually peak within 24–48 hours and then gradually subside, leaving no residue. Minor trauma or effort, such as prolonged walking, can precipitate the attacks. Synovial effusion is often demonstrable. The synovial fluid is sterile, but varies in appearance from cloudy to purulent and contains large numbers of neutrophils [1,9].

About 6% of FMF patients experience protracted arthritic attacks that may persist for more than a month. Occurring usually in the hip or knee [16], other joints such as the ankle, shoulder, temporomandibular or sternoclavicular joints may also be involved. Rather than recovering after a few days, the joint remains swollen and painful, presenting a picture of chronic monoarthritis. In most cases, the pain and inflammation subside spontaneously after several weeks or months. However, in some cases of protracted arthritis — especially in the hips — damage to the joint can be severe and cause permanent deformity that may require joint replacement [16]. In a study of 22 total hip replacements performed on patients with FMF between 1971 and 1985, a relatively high percentage of aseptic loosening of the cemented hip prosthesis was noted. This finding led our orthopedic surgeons to recommend cementless hip prosthesis in FMF patients [17].

Among 160 patients with protracted arthritis, we found 11 (in whom the HLA-B27 was negative) who fulfilled the criteria for seronegative spondyloarthropathy. Some of these patients required, in addition to nonsteroidal anti-inflammatory drugs, disease-modifying antirheumatic medications [18].

Myalgia

Muscle pain occurs in about 20% of patients with FMF. Usually the pain is not severe, appears mainly in the lower extremities after physical exertion or prolonged standing, lasts a few hours to one day, and subsides with rest or NSAIDs.

In 1994 Langevitz et al. [19] described 12 patients with FMF in whom a syndrome of protracted febrile myalgia developed. The clinical picture of protracted febrile myalgia was characterized by severe debilitating myalgia, accompanied by prolonged fever up to 38.5°C, abdominal pain without peritoneal irritation, a high sedimentation rate around 100, leukocytosis, and hyperglobulinemia. Most of the patients who developed protracted febrile myalgia were children. In patients treated with NSAIDs the attacks lasted for 6–8 weeks but subsided promptly after treatment with prednisone 1 mg/kg [19]. Since that publication, we and others saw and treated additional cases with protracted febrile myalgia. Since colchicine is known to induce neuropathy, and in rare cases myopathy, it is important to differentiate colchicine-induced myopathy from protracted febrile myalgia, particularly in transplanted patients treated with cyclosporin.

Skin manifestations

Attacks of erysipelas-like erythema, reported in 3–46% of patients, are one of the most characteristic manifestations of FMF and are sometimes combined with arthritis. Rather sharply bordered red patches, which are hot, tender and swollen, appear on the skin of the lower extremities. Usually located between the knee and ankle, or on the dorsum of the foot or ankle region, the dermatitis is often accompanied by abrupt elevation of body temperature and lasts about 24–48 hours [1]. Biopsies of the affected skin show edema and hyperemia of the dermis, as well as cellular infiltration predominantly by polymorphonuclear cells [20].

Isolated febrile attacks

Isolated short-lived elevation of temperature to 40°C without pain or signs of localized inflammation occurs mainly in children and lasts a few hours. This phenomenon of FMF is often falsely attributed to viral infection pharyngitis or tonsilitis [1].

Vasculitis in FMF

FMF patients are prone to develop different vasculitides at a somewhat higher incidence than the unaffected population. Henoch-Schönlein purpura has been reported in over 100 patients in Israel [1]. Polyarteritis nodosa, also reported in FMF patients [21], tends to occur at a younger age; perirenal hematoma is a more frequent complication [22]. Although abdominal pain and fever occur in both

FMF attacks and PAN[2], the presence of hypertension and nephritis and the persistence of symptoms favor the possibility of PAN. Hematuria, sometimes only microscopic, has been observed in some patients during and between attacks of FMF.

Various types of glomerulonephritis have also been reported in FMF [23], but data are insufficient to determine whether these disorders are more common in FMF than in the general population.

Amyloidosis of FMF

Amyloidosis is a very frequent occurrence in patients with familial Mediterranean fever. It is of the AA type, the same chemical type of reactive amyloidosis that accompanies chronic infections such as tuberculosis and bronchiectasis, chronic inflammations such as rheumatoid arthritis and Crohn's disease, and certain malignant tumors (hypernephroma) and Hodgkin's disease. We noted that although of the AA type, amyloidosis in FMF patients has three features not seen in reactive amyloidosis associated with other diseases: a) It is very frequent in untreated FMF patients and occurs in over 90% of FMF patients of North African Jewish origin [24]. b) It appears at an early age; 90% of patients who died from amyloidosis were under 40 and 6% were under 10 [24]. c) When presented clinically as a nephrotic syndrome, amyloidosis was the first sign of FMF before any acute or chronic inflammation had developed. Those forms that occurred in first-degree relatives of FMF patients we called FMF phenotype II [25].

The presenting symptom of amyloidosis in FMF is persistent heavy proteinuria leading to a nephrotic syndrome. Persistent proteinuria in patients with FMF who do not suffer from any other disease has proved to be a certain indication of renal amyloidosis [1,24]. In a study of 37 FMF patients with end-stage renal disease who underwent renal transplantation, 8 patients died — 7 of them from causes unrelated to graft failure or amyloidosis. Evidence of amyloid deposition in the transplanted kidney and other organs was found in 13 patients. Twenty of the 37 patients remain free of clinical signs of amyloidosis; all had been getting regular treatment with colchicine. The quality of life in 27 of the 29 survivors is satisfactory, with all of them working and functioning fully. Seven healthy babies have been born after transplantation [26].

Before the introduction of chronic dialysis, when patients were dying of renal failure, clinical evidence of extrarenal amyloidosis was scant. With the prolongation of life by chronic dialysis and renal transplantation, amyloid deposition in other organs has become more pronounced. In recent years we have observed extrarenal amyloid deposition in the heart, adrenals, liver, thyroid and small intestine, which interferes with the normal function of the organs. The deposition of amyloid in the small bowel is a particularly grave consequence, and was the cause of death in eight of our patients during the last 10 years (unpublished data).

In another study, it was demonstrated that the severity of symptoms, including amyloidosis, in FMF patients originating from North Africa was higher than among FMF patients from Iraq [15,24] or among Ashkenazi Jewish FMF patients [27]. The incidence of amyloidosis in FMF patients of Turkish origin is much higher than in FMF patients of Armenian and Arab origin.

Treatment

Until 1973, treatment was restricted to alleviating pain. Daily prophylactic treatment with colchicine was suggested by Goldfinger [28] and assessed by double-blind studies [29]. Treatment is started with 1 mg colchicine per day, regardless of age or body weight. This dose is increased to 1.5 or 2 mg until remission is achieved. Doses higher than 1 mg must be divided and given twice a day. Omission of a daily dose may be followed promptly by an attack. We found that 65% of FMF patients enjoy complete remission of attacks if they adhere to their daily dose of colchicine. Partial remission, defined as a significant decrease in the frequency and severity of attacks, is experienced by an additional 30% of patients. In 5% of treated patients the attack rate remains unchanged [29]. These 5% of patients are maintained on 2 mg colchicine per day in order to prevent amyloidosis. Our experience showed that continuous prophylactic treatment with colchicine in FMF patients inhibits the development of nephropathic amyloidosis. None of the patients without proteinuria who began treatment developed amyloidosis during the 23 year follow-up. Side effects of colchicine are rare and mild, with diarrhea and nausea being the most common but easily controlled by diet and gastrointestinal sedatives. Whereas amyloidosis did not develop in patients taking colchicine daily, it was found in 30% of noncompliant patients [30].

Diagnosis

Until recently there was no specific laboratory test for FMF, and the diagnosis of the disease was based on clinical grounds. The Tel-Hashomer diagnostic criteria are based on the presence of short-lived febrile episodes accompanied by inflammation of one of the serous membranes, the development of nephropathic amyloidosis, and the response to colchicine treatment. The ethnic origin of the patients, as well as additional cases among close family members, may help to direct the physician to a correct diagnosis but are not crucial for establishing a diagnosis of FMF [Figure 1].

The differential diagnosis of FMF includes diseases characterized by recurrent fever. These include recessively inherited hyperimmunoglobulinemia, where patients, mostly children, present with week-long fevers, abdominal pain, lymphadenopathy, skin eruptions and oligoarthritis. Patients with HID[3] have elevated serum IgD levels > 100 IU/ml. HID patients do not respond to colchicine treatment, and families with this disease do not show linkage to chromosome 16P and mutations in the pyrin gene.

Familial Hibernian fever is a dominantly inherited periodic disease. Occurring mostly in people of Irish origin, FHF4 is characterized by recurrent febrile episodes of 1–2 week's duration, abdominal pain, myalgia, erythematous patches, conjunctivitis and periorbital edema. Amyloidosis is a rare manifestation in this disease. FHF patients do not respond to colchicine, although fever and other symp-

[2] PAN = polyarteris nodosa

[3] HID = hyperimmunoglobulinemia

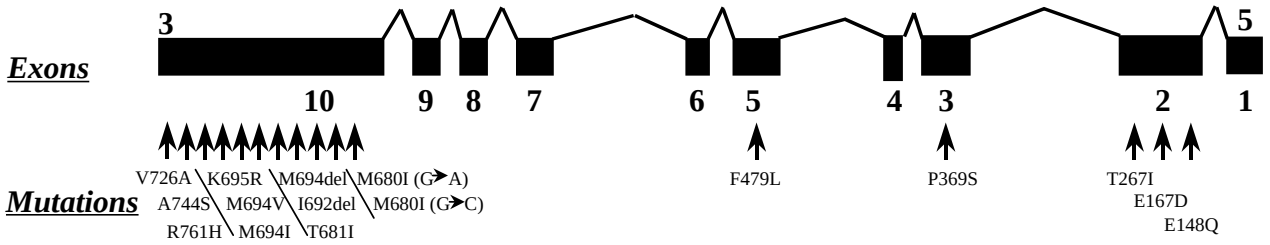

Figure 1. Schematic diagram of the MEFV. Location of the 16 various mutations found. Exons are numbered 1–10, and are drawn to scale.

toms may be alleviated by steroid treatment. A susceptibility locus to chromosome 12p13 has recently been mapped by two groups [31].

Another disease that resembles FMF is often accompanied by adenopathy, pharingitis and sometimes by aphthous stomatitis. Known as FAPA (fever, adenopathy, pharyngitis, aphthae), it has been described only in children. The recurrent febrile episodes last 4–9 days, do not respond to NSAIDs or colchicine, but do resolve with steroids [32,33].

The diagnostic criteria for FMF [Table 1] — based on the occurrence of recurrent, short-lived, febrile attacks accompanied by inflammation of one of the serous membranes, the development of AA amyloidosis, and the favorable response to colchicine treatment — do not hold for the other periodic fever syndromes. Minor criteria include recurrent febrile episodes, erysipelas-like erythema, and FMF in a close family relative. Either two of the major criteria, or one major and two minor criteria, are sufficient to establish a definite diagnosis of FMF, while one major and one minor criterion constitute a probable diagnosis. Ethnic origin (Jews, Armenians, Turks and Arabs), elevated erythrocyte sedimentation rate and acute reactive proteins cannot serve as criteria, but can add support to the diagnosis [15].

Cloning of the MEFV gene and its relation to FMF

In the last 10 years, the Heller Institute at Tel-Hashomer has collaborated with the genetic laboratory of the Arthritis and Rheumatism Branch of the National Institute of Arthritis and Musculoskeletal and Skin Disease of the National Institutes of Health, in a search for the gene responsible for FMF. After the FMF gene was mapped by positional cloning to chromosome 16 in 1992 [2], several interested laboratories from the United States, Israel and Australia joined to form the International FMF Consortium. Later, a second consortium comprising several French laboratories with international collaborators was founded. The candidate interval on chromosome 16 was reduced and defined by interfamilial recombination events in the panels of families of the two consortia. Finally, in the same month, the two consortia — the International FMF Consortium and the French FMF Consortium — after identifying four different mutations on FMF carrier chromosomes in multiple ethnic groups, isolated the gene that causes FMF. Mutations were not detected in a panel of 600 control chromosomes [3,4].

Structure and function of the pyrin protein

The gene responsible for FMF is a medium-sized gene comprising 10 exons. The International FMF Consortium has named the protein encoded by MEFV, pyrin, from the Greek word for fire and fever, while the French FMF Consortium prefers to call it Marenostrin, which is Greek for the Mediterranean Sea. MEFV encodes the pyrin/Marenostrin protein of 781 amino acids. To date, 16 mutations have been found in MEFV [Figure 1]. Most mutations are missense mutations that result in replacement of one amino acid. Two one-codon deletions, resulting in a deletion of one amino acid, were also found [3,4,34–37].

Eleven mutations occurred in exon 10, three in exon 2, and one in exon 3 and exon 5. Most mutations were found by the French [4,34] and the International Consortiums [3,36,37], and two mutations were detected by Booth et al. [35] [Figure 1]. Mutation E148Q was detected in all the ethnic groups studied, including Jews, Turks, Armenians, Arabs, Druze and Italians [34,36,37]. Among the carrier chromosomes described here, several presented double mutations in MEFV. An E148Q mutation was present, in addition to a V726A mutation, in the same chromosome [34,37]. SNP haplotype data suggest that chromosomes bearing E148Q from several ethnic groups share a common progenitor, thus implicating a founder effect [37]. In this case, the ancestor founder had lived in the early biblical or pre-biblical era.

Computational analyses of wild-type and mutant pyrin/Marenostrin molecules suggest a mechanism whereby the mutations affect the secondary structure of the molecule, which might then interfere with the normal function of the protein [3,38]. Hybridization of a probe derived from exon 2 of pyrin demonstrated expression only in neutrophil white blood cells. It was negative in all other tissues including the liver, kidneys, brain, synovium, spleen, colon, small intestine, and peripheral blood lymphocytes [3].

The exclusive expression of MEFV in neutrophil blood cells supports the clinical observations that neutrophil cells accumulate in large numbers at sites of inflammation during FMF attacks. The observation that intravenously injected colchicine accumulates rapidly in neutrophil cells suggests a relationship between the impaired function and the repair by colchicine that occurs in neutrophils of FMF patients.

It can be postulated that the function of wild-type pyrin protein is to inhibit inflammation mediated by neutrophils. Most missense mutations in MEFV resulted in a conser-

vative change of a hydrophobic amino acid. This kind of amino acid substitution often has little or no phenotypic effect but may sometimes cause dramatic effects, such as in the gene encoding transthyretin, which results in the deposition of mutant protein into amyloid fibrils found in familial amyloid polyneuropathies.

Interestingly, different mutations were found in the various population groups living around the Mediterranean. For example, in the North African Jewish population M694V accounts for more than 93% of the carrier chromosomes, while in Iraqi Jews M694V accounts for 30% of the carrier chromosomes and V726A for 30%. In Israeli Arabs M694I is the most common mutation. Considering the fact that FMF is extremely rare in other parts of the world, the prevalence of many mutations in a limited geographical area strongly suggests that the carriers of this mutation have some selective advantage. The recent cloning of MEFV and its tentative role in white blood cells support an advantage over an infectious agent prevalent in the region. We hypothesize that failure to control inflammation in heterozygotes might give them an advantage in dealing with some infections, and that this gave rise to the proliferation of the mutated gene.

Although FMF is rare in Ashkenazi Jews, astonishingly, a very high carrier rate has been detected in this population. In a study of 150 healthy Ashkenazi individuals, three mutations — E148Q, P369S and V726A — account for a carrier rate of 20% [37]. Two of the mutations — E148Q and P369S — are very subtle mutations and usually do not cause disease in the homozygous state or when they appear in combination. Only when they appear with more severe mutations such as V726A do they produce disease-associated symptoms. These facts may explain the low prevalence of clinical FMF despite the high rate of mutations in the population. Once again, the high rate of mutations points to some selective advantage offered by the mutated gene.

Genotype phenotype correlation

In order to detect minor differences in the clinical presentation and outcome of patients with FMF, we composed a key to calculate the severity index for the disease. The key is based on six clinical criteria. A higher severity score was attributed to: a) early onset, b) high frequency of attacks, c) higher daily dose of colchicine, d) presence of arthritis, e) presence of erysipelas-like erythema, and f) presence of amyloidosis [Table 2]. A severity score was calculated for each patient and was compared to the mutations that were found, namely the four frequent mutations present in over 80% of the carrier chromosomes: M694V, V726A, M680I and E148Q.

The severity index of the disease in patients who were homozygous for mutation M694V was significantly higher than the severity index in patients homozygous for mutation V726A. Furthermore, most patients who had amyloidosis were homozygous for mutation M694V [39,40]. It appears therefore that FMF patients with mutations in M694 are prone to develop amyloidosis. However, the occurrence of systemic amyloidosis in some cases of FMF bearing different mutations indicates that the development of amyloidosis in FMF is not solely dependent on the severity of the inflammatory symptoms and the M694V mutations of the pyrin protein.

Table 1. Tel-Hashomer criteria for the diagnosis of FMF

Major criteria	Minor criteria
1. Recurrent febrile episodes accompanied by peritonitis, synovitis or pleuritis	1. Recurrent febrile episodes
2. Amyloidosis of the AA-type without predisposing disease	2. Erysipelas-like erythema
3. Favorable response to continuous colchicine treatment	3. FMF in a first-degree relative
Definitive diagnosis: 2 major, or 1 major and 2 minor	
Probable diagnosis: 1 major and 1 minor	

Table 2. Tel-Hashomer key to FMF severity score

1.	**Age of onset**	
	< 5 years	3 points
	5–10 years	2 points
	10–20 years	1 point
	> 20 years	0 points
2.	**Frequency of attacks**	
	> 2 per month	3 points
	1–2 per month	2 points
	< 1 per month	1 point
3.	**Colchicine dosage to control attacks**	
	Nonresponders	4 points
	2 mg/day	3 points
	1.5 mg/day	2 points
	1 mg/day	1 point
4.	**Arthritis**	
	Protracted arthritis	3 points
	Presence of acute joints	2 points
5.	**Erysipelas-like erythema**	
	If present	2 points
6.	**Amyloidosis**	
	If present	3 points
	Phenotype II	4 points
	Mild disease	**Total of 2-5 points**
	Moderate disease	**6–10 points**
	Severe disease	**>10 points**

The discovery of MEFV as the cause of familial Mediterranean fever opens the way for important discoveries in the near future. At present, the function of the mutated pyrin/Marenostrin protein is impaired in terms of controlling inflammatory reactions that may be initiated in FMF patients by stress or by minor trauma to the joints, which in turn may ignite one of the numerous cytokines that would have been inhibited by normal pyrin/Marenostrin. The identification of pyrin mutations as the cause of FMF may substantially advance our understanding of this disorder. It represents the first step in the delineation of an important new pathway in the control of inflammation, and this knowledge might improve the treatment of certain types of inflammation, such as that seen in rheumatoid arthritis and other inflammatory joint diseases.

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Capsule

Family history of schizophrenia and environmental factors

Using data from the Civil Registration System in Denmark, a study established a population-based cohort of 1.75 million persons whose mothers were Danish women born between 1935 and 1978. The study linked this cohort to the Danish Psychiatric Central Register and identified 2,669 cases of schizophrenia among cohort members and additional cases among their parents.

The respective relative risks of schizophrenia for persons with a mother, father or sibling who had schizophrenia were 9.31, 7.20 and 6.99 respectively, as compared with persons with no affected parents or siblings. The risk of schizophrenia was associated with the degree of urbanization of the place of birth (relative risk for the capital vs. rural areas 2.40). The risk was also significantly associated with the season of birth, being highest for births in February and March and lowest for births in August and September. The population attributable risk was 5.5% for a history of schizophrenia in a parent or sibling, 34.6% for urban place of birth, and 10.5% for the season of birth.

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