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Genotype and treatment initiation in clinically unclassified children with MEFV variants: a retrospective cohort study

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Genotype and treatment initiation in clinically unclassified children with *MEFV* variants: a retrospective cohort study

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Abstract

Purpose Management of children with *MEFV* variants who do not fulfil clinical criteria for familial Mediterranean fever (FMF) at presentation is controversial. We described their clinical course and baseline factors associated with later treatment initiation.

Methods This retrospective cohort study included 116 children (<18 years) with at least one *MEFV* variant who did not fulfil the Eurofever/PRINTO criteria for FMF at first evaluation between 2015 and 2024. Children were classified as treated (n = 61) or followed without treatment (n = 55). Time to treatment initiation was analysed with the Kaplan–Meier method. Groups were compared with non-parametric, Fisher's exact and log-rank tests.

Results The median age at first visit was 8.0 [4.8–11.2] years, and the median follow-up was 2.5 [1.2–5.1] years. Treatment was started in 61 children (52.6%) at a median of 0.6 [0.3–1.1] years after the first evaluation. Among the 104 children carrying a single variant, 52 (50.0%) were treated. Their cumulative probability of treatment initiation was 37.4%, 49.1% and 57.0% at 1, 2 and 5 years. All six children with M694V/E148Q were treated (P = 0.028), compared with 5/17 (29.4%) children with isolated E148Q (P = 0.064). Baseline CRP was modestly higher in treated children (4.8 vs 3.0 mg/L, P = 0.014), whereas ESR and family history were not.

Conclusion Half of the children with a single *MEFV* variant who did not meet FMF criteria at presentation were started on treatment, mostly within the first year. These children warrant structured longitudinal follow-up. Genotype-specific findings involved small subgroups and require prospective validation.

Keywords Familial Mediterranean fever · *MEFV* · Heterozygous carrier · Colchicine · Autoinflammation · Children

What is Known:

• Many children with *MEFV* variants do not fulfil FMF classification criteria at first evaluation, and their management is uncertain.

• Isolated E148Q heterozygosity rarely causes clinically significant FMF.

What is New:

• Half of clinically unclassified children with a single *MEFV* variant were started on colchicine, mostly within the first year.

• Baseline acute-phase reactants and family history did not reliably identify children who later required treatment.

Abbreviations

CI	Confidence interval
CRP	C-reactive protein
ESR	Erythrocyte sedimentation rate
EULAR	European Alliance of Associations for Rheumatology
FMF	Familial Mediterranean fever
IL-1	Interleukin-1
INSAID	International Study Group for Systemic Autoinflammatory Diseases
IQR	Interquartile range
PReS	Paediatric Rheumatology European Society
PRINTO	Paediatric Rheumatology International Trials Organisation

Introduction

78 Familial Mediterranean fever (FMF) is the most common monogenic autoinflammatory disease.
79 It is caused by variants in the *MEFV* gene, which encodes pyrin, and is characterised by
80 recurrent, self-limiting attacks of fever with serositis or arthritis. AA amyloidosis is its most
81 serious complication [1–3]. FMF is classically an autosomal recessive disease. However, a
82 substantial proportion of symptomatic patients carry only a single detectable *MEFV* variant.
83 Incomplete penetrance, variable expressivity and an apparent dominant pattern of inheritance are
84 now well recognised [2, 4]. The pathogenicity of several common variants also remains
85 uncertain. Nearly a third are classified as variants of uncertain significance by
86 INSAID/INFEVERS, and E148Q has long been debated as either a benign polymorphism or a
87 low-penetrance disease-causing allele [5, 6]. The 2019 Eurofever/PRINTO classification criteria
88 were an important step towards standardisation [7]. In real-world practice, however, a sizeable
89 group of genetically positive patients still cannot be classified [8].
90 Widespread genetic testing has produced a growing population of children who carry an *MEFV*
91 variant but do not fulfil clinical FMF criteria at evaluation. In these children, complaints may be
92 non-specific, attacks may be infrequent or afebrile, or testing may have been prompted by family
93 history [9, 10]. The clinical significance of this finding remains uncertain. The 2024
94 EULAR/PReS recommendations aim for complete control of clinical and subclinical
95 inflammation with lifelong colchicine in established FMF [1, 11]. However, they do not address
96 asymptomatic or oligosymptomatic carriers, and there is no consensus on how these children
97 should be monitored or treated [1, 4].
98 This uncertainty has practical consequences. Over-treatment exposes children to lifelong
99 colchicine without clear benefit. Under-recognition, in contrast, may delay the control of
100 subclinical inflammation and, rarely, lead to amyloidosis [3]. We therefore reviewed a single-
101 centre paediatric cohort of children with *MEFV* variants who did not meet clinical FMF criteria at

102 presentation. We aimed to determine the proportion of children subsequently started on
103 treatment, the time to treatment initiation and the baseline features associated with this outcome.
104 We focused particularly on children carrying a single variant, the group in whom management is
105 least clear.

106 **Materials and methods**

107 ***Study population***

108 We performed a retrospective cohort study at the paediatric rheumatology clinic of Gazi
109 University Faculty of Medicine. We identified all children (<18 years at first visit) evaluated
110 between 2015 and 2024 in whom *MEFV* sequencing showed at least one variant. Children were
111 eligible if they did not fulfil the Eurofever/PRINTO classification criteria for FMF at first
112 evaluation [7]. Eurofever/PRINTO criteria were considered unmet at first evaluation when
113 complaints had not yet shown a recurrent, stereotyped episodic pattern and when joint complaints
114 consisted of arthralgia without objective arthritis. Children meeting clinical FMF criteria at
115 presentation were excluded. Children with an alternative autoinflammatory or rheumatic
116 diagnosis explaining their symptoms were also excluded. In total, 116 children were included.
117 The index date was the first paediatric rheumatology visit at which the *MEFV* result was
118 available. The reason for referral was classified as symptomatic (non-specific complaints) or
119 family screening.
120 *MEFV* analysis was performed by Sanger sequencing of exons 2, 3, 5 and 10, which contain the
121 great majority of known *MEFV* variants. Variants are described using conventional protein-level
122 abbreviations (e.g. M694V, E148Q). Variant phase (cis/trans) was not determined by parental
123 testing. Genotypes with two variants are therefore described as 'dual-variant' rather than
124 'compound heterozygous' or 'biallelic' throughout this manuscript.

125 ***Data collection and outcome***

126 From electronic and paper records, we extracted demographic data, presenting complaints, family
127 history of rheumatic or autoinflammatory disease, *MEFV* genotype and laboratory parameters at
128 presentation and at the last visit. Laboratory parameters included haemoglobin, white-cell and
129 platelet counts, ESR and CRP. Genotypes were grouped as single-variant (heterozygous) or dual-
130 variant. We also examined four overlapping groups. These were M694V carriers (heterozygous
131 or dual-variant), exon-10 variant carriers (M694V, M680I, V726A, K695R, R761H or A744S),
132 the M694V/E148Q dual-variant genotype and isolated E148Q heterozygosity.

133 The primary outcome was treatment initiation during follow-up. Treatment decisions were made
134 by the treating paediatric rheumatologist. Colchicine was initiated when a child developed
135 recurrent, stereotyped, self-limiting FMF-compatible attacks (fever, abdominal, chest or joint
136 involvement lasting 12–72 h) and/or persistent elevation of acute-phase reactants between attacks
137 after exclusion of alternative causes. Time to treatment initiation was defined as the interval, in
138 years, between the index date and the start of treatment. For treated children, we recorded the
139 clinical features at treatment initiation, the number of attacks in the preceding 6 months and the
140 attack duration. Attack duration was recorded in calendar days. An attack lasting up to 72 h may
141 therefore span four calendar days. Children were classified as treated (n = 61) or followed
142 without treatment (n = 55). Of the treated children, 60 received colchicine alone. One child also
143 received an IL-1 inhibitor because of an incomplete response to colchicine.

144 ***Statistical analysis***

145 Continuous variables were tested for normality with the Shapiro–Wilk test. As they were not
146 normally distributed, they are presented as median [IQR] and compared with the Mann–Whitney
147 U test. Categorical variables are presented as counts (%) and compared with Fisher's exact test.

148 Exact (Clopper–Pearson) 95% CIs were calculated for treatment proportions. Time to treatment
149 initiation was analysed with the Kaplan–Meier method, and untreated children were censored at
150 their last visit. One treated child with a missing treatment date was excluded from the time-to-
151 event analyses (n = 115). Treatment-free survival was compared between genotype groups with
152 the log-rank test. Two sensitivity analyses were performed. The first excluded children referred
153 for family screening, and the second excluded children followed for less than 1 year. Genotype
154 subgroup analyses were exploratory, and P-values are reported without correction for multiple
155 comparisons. A two-sided $P < 0.05$ was considered significant. Analyses were performed with
156 SPSS version 21.0 (IBM Corp., Armonk, NY, USA).

157 **Results**

158 The cohort comprised 116 children. The median age at analysis was 12.7 [9.7–17.4] years, and
159 the median age at first visit was 8.0 [4.8–11.2] years. The median follow-up was 2.5 [1.2–5.1]
160 years, with a range of 0.1 to 7.6 years (Table 1). The most frequent presenting complaints were
161 abdominal pain (56.9%), fever (36.2%), and joint complaints (20.7%); 8.6% were referred for
162 family history alone. A family history of rheumatic or autoinflammatory disease was present in
163 74 children (63.8%), most commonly FMF. Five families (4.3%) reported FMF with amyloidosis.
164 A single variant was detected in 104 children (89.7%) and two variants in 12 (10.3%). M694V/–
165 was the most frequent genotype (47.4%), followed by V726A/– (15.5%) and E148Q/– (14.7%).
166 During follow-up, treatment was initiated in 61 children (52.6%). The remaining 55 children
167 (47.4%) were followed without treatment. Their median follow-up was 2.3 [0.9–4.5] years, and
168 29 of them were followed for at least 2 years. All untreated children were asymptomatic at the
169 last visit.

170 Among treated children, the median time from the first evaluation to treatment initiation was 0.6
171 [0.3–1.1] years. Treatment was usually started after the first or second attack observed after the
172 index visit (median 1 [1–2]). Clinical features at treatment initiation are shown in Table 3. Fever
173 was present in 34 children (56.7%), abdominal pain in 35 (58.3%), joint involvement in 14
174 (23.3%) and chest pain in 4 (6.7%). Three children (5.0%) were treated for persistently elevated
175 acute-phase reactants alone. The median number of attacks was 3 [2–6] per 6 months. The
176 median attack duration was 3 [2–4] days, and attacks lasted 3 days or less in 44/60 children
177 (73.3%).
178 Treatment initiation by genotype group is shown in Figure 1. Among the 104 single-variant
179 carriers, 52 (50.0%, 95% CI 40.0–60.0%) were treated. The treatment rate was 29/55 (52.7%) in
180 children with M694V/–. Among the 12 dual-variant carriers, 9 (75.0%) were treated (P = 0.131).
181 All six children with M694V/E148Q were treated (100%, 95% CI 54.1–100%, P = 0.028).
182 Isolated E148Q heterozygosity showed a numerically lower treatment rate (5/17, 29.4%, P =
183 0.064). Treatment initiation was not associated with carriage of an exon-10 variant (54/97,
184 55.7%, P = 0.208) or of M694V (36/63, 57.1%, P = 0.351).
185 In the time-to-event analysis, the cumulative probability of treatment initiation for the whole
186 cohort was 40.8% at 1 year, 52.6% at 2 years and 59.9% at 5 years. The corresponding estimates
187 for single-variant carriers were 37.4%, 49.1% and 57.0% (Figure 2A). Treatment-free survival
188 was longer in single-variant than in dual-variant carriers (log-rank P = 0.010). In the exploratory
189 comparison, treatment-free survival was shorter in children with M694V/E148Q than in the rest
190 of the cohort (log-rank P = 0.001) (Figure 2B).
191 The results were similar in both sensitivity analyses (Online Resource 1). Of the 10 children
192 referred for family screening, 3 were treated. After their exclusion, 58/106 children (54.7%) were
193 treated. Among the 96 children followed for at least 1 year, 56 (58.3%) were treated. In this

194 group, the cumulative probability of treatment initiation was 41.1%, 52.8% and 60.1% at 1, 2 and
195 5 years.
196 Baseline CRP was higher in the treated group (4.8 [2.8–17.5] vs 3.0 [1.9–6.6] mg/L, P = 0.014).
197 Baseline ESR did not differ significantly between groups (14.0 [9.0–36.0] vs 13.0 [8.5–21.0]
198 mm/h, P = 0.123) (Table 2). At the last visit, ESR and CRP were comparable between groups and
199 within the normal range. Baseline haematological indices, age at presentation and follow-up
200 duration did not differ between groups. A positive family history was not associated with
201 treatment initiation (P = 0.334).

202 **Discussion**

203 In this cohort, half of the children who carried a single *MEFV* variant and did not meet FMF
204 criteria at presentation were subsequently started on treatment. Overall, 52.6% of the cohort was
205 treated, at a median of 0.6 years after the first evaluation. These findings indicate that a single
206 *MEFV* variant can be associated with a clinically relevant phenotype that emerges after the initial
207 assessment. This is consistent with previous reports of symptomatic heterozygous carriers [4, 5,
208 12]. In practice, these children should not be discharged after a single evaluation. Structured
209 longitudinal follow-up appears warranted, particularly when complaints recur or evolve towards
210 an FMF-compatible pattern.
211 The high treatment rate among single-variant carriers is the main finding of this study. FMF is
212 classically considered an autosomal recessive disease, and heterozygous carriers are often
213 regarded as unaffected. In our cohort, however, the treatment rate in children with M694V/–
214 (52.7%) was similar to that of the whole cohort. This is consistent with the view that
215 heterozygosity for a pathogenic exon-10 variant may contribute to a clinically relevant phenotype
216 in some children [2, 4, 5]. Most treatment decisions were made within the first year. The

217 cumulative probability curves showed that new treatment decisions continued beyond this point,
218 although at a slower rate. A single early assessment may therefore not be sufficient.
219 As expected, treatment rates were higher in dual-variant carriers. All six children with
220 M694V/E148Q were treated. M694V is associated with the most severe disease course, including
221 earlier onset, more frequent attacks and a higher risk of amyloidosis and colchicine resistance [3,
222 13]. E148Q is thought to modify the phenotype when combined with a more pathogenic variant
223 [14, 15]. In contrast, only 5 of 17 children with isolated E148Q were treated. This difference did
224 not reach statistical significance and was based on a small group. It is nevertheless consistent
225 with paediatric data indicating that E148Q alone rarely causes clinically significant FMF [14–17].
226 The genotype-specific comparisons involved small subgroups. Treating physicians were also
227 aware of each child's genotype, which may have influenced their decisions. These results should
228 therefore be regarded as exploratory.
229 Two features that are often used in clinical practice were weak predictors of treatment in this
230 cohort. Baseline CRP was only modestly higher in treated children, and ESR did not differ
231 between groups. At the last visit, both markers were similar in the two groups. Because
232 laboratory sampling was not standardised, these data do not allow firm conclusions about
233 intermittent or subclinical inflammation. More sensitive markers, such as S100A12, may be
234 useful in this population [18]. Family history was present in 63.8% of the cohort but was not
235 associated with treatment initiation. Family history remains important for identifying at-risk
236 families and the risk of amyloidosis. However, it does not appear to justify pre-emptive treatment
237 on its own. Taken together, these findings suggest that treatment decisions should be based on
238 genotype combined with clinical follow-up rather than on family history or isolated laboratory
239 markers [1, 4, 7].

240 This cohort also illustrates the diagnostic difficulty in this group. Many children presented with
241 vague or afebrile symptoms. This is consistent with the recognition that FMF does not always
242 present classically. Even useful classification criteria leave a group of genetically positive
243 children who cannot be classified [7–9, 19–21]. Colchicine is well tolerated across paediatric age
244 groups, including young children. IL-1 inhibitors are generally reserved for colchicine resistance
245 or intolerance [22–26]. The main disadvantage of pre-emptive treatment is therefore the burden
246 of unnecessary lifelong therapy rather than toxicity. Recent evidence shows that colchicine can
247 be safely withdrawn in some carriers [12]. This further underlines the need to identify
248 prospectively which children require treatment.

249 ***Limitations***

250 This study has several limitations. It was a retrospective, single-centre study without a fixed
251 schedule for laboratory testing. The sample size limited the statistical power for less common
252 genotypes and precluded multivariable modelling. Genotype subgroup comparisons were
253 exploratory and were not corrected for multiple testing. Treatment criteria were applied by the
254 treating physicians and were not prospectively standardised. Physicians were also aware of each
255 child's genotype, which may have influenced treatment decisions. Treatment initiation should
256 therefore not be regarded as a purely objective marker of disease progression. Time to treatment
257 was reconstructed from records and depended on visit frequency and documentation. Follow-up
258 was short relative to the latency of amyloidosis. Finally, as this was a referral cohort, our findings
259 may not be generalisable to other settings. Prospective multicentre studies with predefined
260 treatment criteria and longer follow-up are needed to confirm these findings.

261 **Conclusion**

Half of the children with a single *MEFV* variant who did not meet clinical FMF criteria at presentation were started on treatment during follow-up, mostly within the first year. These children therefore require structured longitudinal follow-up rather than discharge after a single assessment. In exploratory analyses, all children with M694V/E148Q were treated, whereas isolated E148Q heterozygosity showed a lower treatment rate. Family history and baseline acute-phase reactants were not consistently associated with treatment initiation. These findings require validation in prospective cohorts with predefined diagnostic and treatment criteria.

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Ethics approval The study was approved by the Ethics Committee of Gazi University (approval no. 2025-1812, decision of the 16th session dated 21 October 2025). It was conducted in accordance with the Declaration of Helsinki.

Consent to participate Individual informed consent was waived by the Ethics Committee because of the retrospective design.

Consent to publish Not applicable. The manuscript contains no identifiable individual data.

284 **Data availability** The data underlying this article will be shared on reasonable request to the
285 corresponding author.

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369 **Figure legends**

370 **Fig. 1** Treatment initiation by *MEFV* genotype group. Bars show the proportion of children in
371 each genotype group who were started on treatment during follow-up, with exact (Clopper–
372 Pearson) 95% CIs. Numbers to the right of each bar show treated/total (%) and the Fisher's exact
373 P-value for that group compared with the remainder of the cohort. Genotype groups are not
374 mutually exclusive. P-values are uncorrected

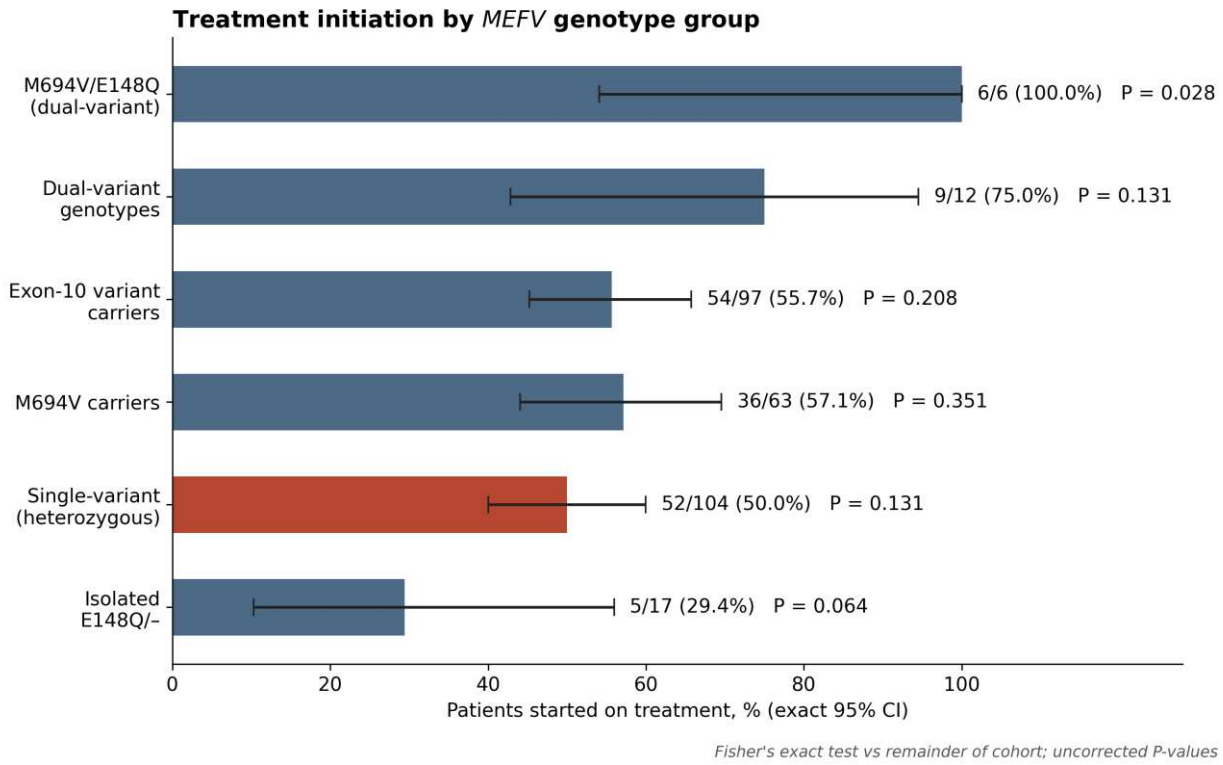
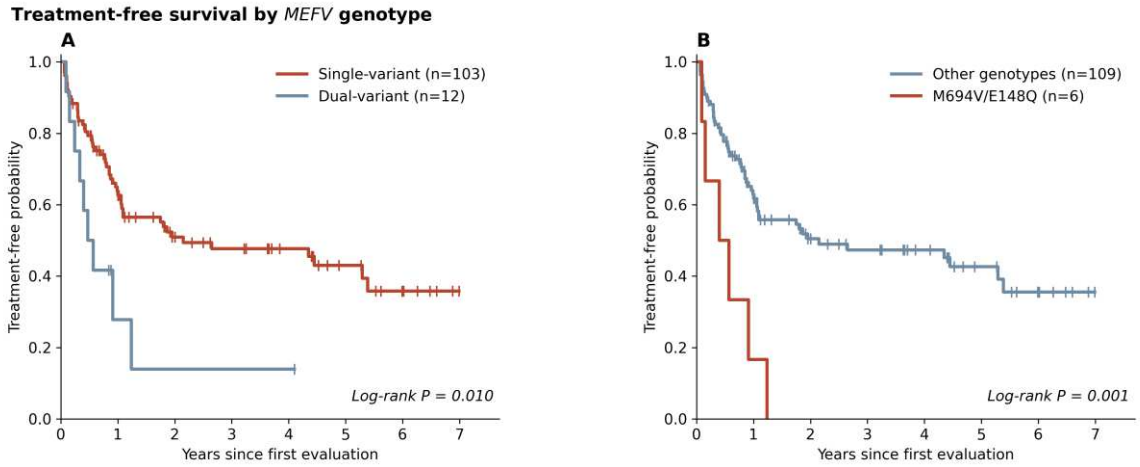


Fig. 2 Treatment-free survival by *MEFV* genotype. Kaplan–Meier estimates of the probability of remaining without treatment after the first evaluation (n = 115). (A) Single-variant (n = 103) vs dual-variant (n = 12) carriers, log-rank P = 0.010. (B) M694V/E148Q (n = 6) vs all other genotypes (n = 109), log-rank P = 0.001 (exploratory comparison). Numbers of patients at risk are shown below each panel



At risk								
Single-variant	103	55	34	28	22	13	7	0
Dual-variant	12	2	1	1	1	0	0	0

At risk								
Other genotypes	109	56	35	29	23	13	7	0
M694V/E148Q	6	1	0	0	0	0	0	0

381

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- MEFVtables23.09.2026.docx
- MEFVSupplementaryTable23.09.2026.docx