クリオピリン関連周期熱症候群の遺伝子診断の手引き

国際的なNGSベースの遺伝子検査ガイドラインの報告を踏まえて、我が国の遺伝学的バックグランドの事情も踏まえた遺伝子診断の手引きを症候群別に作成する(1)。

クリオピリン関連周期熱症候群ではモザイク変異を少なからず認めるため、上記国際ガイドラインに従い、NGS ベースの遺伝子解析を行う(1)。登録衛生検査所であるかずさ遺伝子検査室では遺伝子診断ガイドラインにあわせる形で、クリオピリン関連周期熱症候群の遺伝子検査はNLRP3 全エクソンを対象として、次世代シークエンシングで診断目的の遺伝学的検査を行っている。

次世代シーケンシングによる原因遺伝子の分析的妥当性評価系（小原、土方ら、論文準備中）を用いてNLRP3 を評価したが、イルミナ型の短鎖リードシーケンサーでも 1 塩基置換ならびに短配列の挿入欠失についてはほぼ全域が高精度で解析可能な遺伝子であることを確認した。(図 1)。

次に、クリオピリン関連周期熱症候群のモザイクにおいて、そのモザイク率は末梢血で平均 12.1%（1.8 -35.8%)、成人発症の遅発型でも平均 12.1％(3.3-27.0%)である(2, 3)。かずさ遺伝子検査室でのクリオピリン関連周期熱症候群でのモザイク変異の検出における実際は、上記検査系にて 5%以上のモザイク変異の検出は可能であり、1-5%の NLRP3 体細胞モザイクも結果的に検出できている。しかしながら、1 - 5%のモザイク変異が診断目的の遺伝学的検査において安定的に検出できるかは今後の検討課題である。このような低頻度モザイクでは、シークエンシングエラーとの鑑別が問題となるため、分子バーコード法等による評価を行い、臨床研究として診断法の確立を試みる。

さらに上記ガイドラインにあるように、遺伝子検査で得られた変異の疾患関連性の分類が重要である。国際遺伝子診断ガイドラインで記載されているようにACMG ガイドラインに沿って作成されたInfevers データベースの分類(表１－1)(4)、ClinVar(表１－2)でpathogenic もしくは likely pathogenic と記載された病的遺伝子変異リストを作成、疾患関連性を評価する。

既報にない稀なVUS については、国際的なガイドラインにて機能解析による評価が推奨されている。そのようなまれなVUS については、臨床研究として既報の in vitro の NLRP3 変異機能解析系を用いて評価を行う（THP-1 細胞での細胞死誘導、HEK293 細胞での強制発現系で ASC 依存性 NF-κB 活性上昇）(5)。

以上の解析でNLRP3 遺伝子の疾患関連変異が同定されない場合は、自己炎症性疾患遺伝子パネルでの解析を行う。特に、クリオピリン関連周期熱症候群と類似した表現型を示す疾患としてNLRC4 異常症(6)、PLCG2 異常症(7)、NLRP12 異常症(8)の報告があるため、鑑別診断としてこれらの遺伝子での変異の有無をNLRP3 解析と並行して進めることが望ましい。なお、これらの遺伝子解析はクリオピリン関連周期熱症候群の保険による遺伝子検査で

鑑別診断として行われている。

以上でも変異が同定されない場合は、全エクソーム解析など他の遺伝子をふくめた網羅的な遺伝子解析を検討する。

文献

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図1

NGSによるクリオピリン関連周期熱症候群遺伝子診断の分析的妥当性の検討

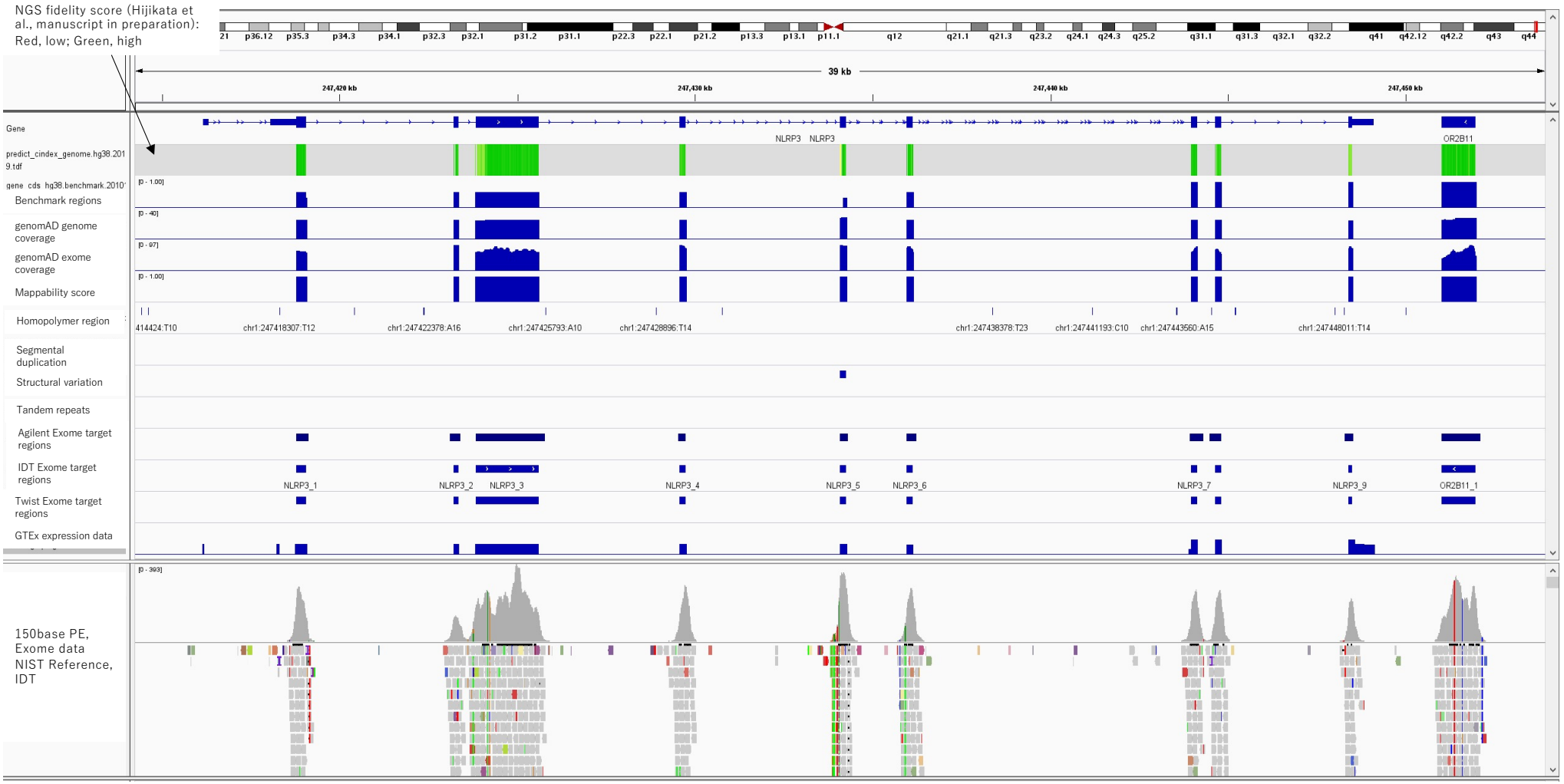

表1−1

NLRP3遺伝子の疾患関連変異の集積（Infevers 1）

CAPS – The registry of NLRP3 (CIAS1/NALP3/PYPAF1/CLR1.1) sequence variants

Location	Usual name	protein name	Sequence change	Alteration	Base substituted	Classification	Status	Associated phenotype
Exon 1	D19H	p.(Asp19His)	c.55G>C	substitution	G>C	Likely pathogenic		keratoendotheliitis fugax hereditaria
Exon 3	R168Q	p.(Arg168Gln)	c.503G>A	substitution	G>A	Likely pathogenic	PROVISIONAL	NLRP3-AID-severe (CINCA/NOMID)
Exon 3	R170S	p.(Arg170Ser)	c.508C>A	substitution	C>A	Likely pathogenic	VALIDATED	NLRP3-AID-moderate (MWS)
Exon 3	I172T	p.(Ile172Thr)	c.515T>C	substitution	T>C	Likely pathogenic	PROVISIONAL	NLRP3-AID-severe (CINCA/NOMID)
Exon 3	C259W	p.(Cys259Trp)	c.777T>G	substitution	T>G	Likely pathogenic	VALIDATED	NLRP3-AID-mild (FCAS)
Exon 3	R260W	p.(Arg260Trp)	c.778C>T	substitution	C>T	Pathogenic	VALIDATED	NLRP3-AID-mild (FCAS) NLRP3-AID-moderate (MWS)
Exon 3	R260L	p.(Arg260Leu)	c.779G>T	substitution	G>T	Pathogenic	VALIDATED	NLRP3-AID-moderate (MWS)
Exon 3	R260P	p.(Arg260Pro)	c.779G>C	substitution	G>C	Pathogenic	VALIDATED	NLRP3-AID-severe (CINCA/NOMID)
Exon 3	V262A	p.(Val262Ala)	c.785T>C	substitution	T>C	Likely pathogenic	VALIDATED	NLRP3-AID-severe (CINCA/NOMID)
Exon 3	V262G	p.(Val262Gly)	c.785T>G	substitution	T>G	Likely pathogenic	PROVISIONAL	NLRP3-AID-mild (FCAS) NLRP3-AID-moderate (MWS)
Exon 3	L264F	p.(Leu264Phe)	c.790C>T	substitution	C>T	Likely pathogenic	VALIDATED	NLRP3-AID-severe (CINCA/NOMID)
Exon 3	L264V	p.(Leu264Val)	c.790C>G	substitution	C>G	Likely pathogenic	VALIDATED	NLRP3-AID-moderate (MWS)
Exon 3	L264H	p.(Leu264His)	c.791T>A	substitution	T>A	Pathogenic	VALIDATED	NLRP3-AID-severe (CINCA/NOMID)
Exon 3	L264R	p.(Leu264Arg)	c.791T>G	substitution	T>G	Likely pathogenic	VALIDATED	NLRP3-AID-severe (CINCA/NOMID)
Exon 3	L264P	p.(Leu264Pro)	c.791T>C	substitution	T>C	Likely pathogenic	VALIDATED	CAPS
Exon 3	T266P	p.(Thr266Pro)	c.796A>C	substitution	A>C	Likely pathogenic	PROVISIONAL	NLRP3-AID-moderate (MWS) MWS/NOMID
Exon 3	F302C	p.(Phe302Cys)	c.905T>G	substitution	T>G	Likely pathogenic		NLRP3-AID-moderate (MWS)
Exon 3	F302L	p.(Phe302Leu)	c.906C>A	substitution	C>A	Likely pathogenic		NLRP3-AID (CAPS undefined)
Exon 3	D303N	p.(Asp303Asn)	c.907G>A	substitution	G>A	Pathogenic	VALIDATED	NLRP3-AID-severe (CINCA/NOMID) NLRP3-AID-moderate (MWS)
Exon 3	D303H	p.(Asp303His)	c.907G>C	substitution	G>C	Likely pathogenic	VALIDATED	NLRP3-AID-severe (CINCA/NOMID)
Exon 3	D303G	p.(Asp303Gly)	c.908A>G	substitution	A>G	Pathogenic	VALIDATED	NLRP3-AID-severe (CINCA/NOMID) Mild
Exon 3	D303A	p.(Asp303Ala)	c.908A>C	substitution	A>C	Likely pathogenic	VALIDATED	NLRP3-AID-moderate (MWS)
Exon 3	E304K	p.(Glu304Lys)	c.910G>A	substitution	G>A	Pathogenic	VALIDATED	NLRP3-AID-severe (CINCA/NOMID)
Exon 3	L305P	p.(Leu305Pro)	c.914T>C	substitution	T>C	Pathogenic	VALIDATED	NLRP3-AID-mild (FCAS)
Exon 3	Q306K	p.(Gln306Lys)	c.916C>A	substitution	C>A	Likely pathogenic	PROVISIONAL	NLRP3-AID-severe (CINCA/NOMID)
Exon 3	Q306E	p.(Gln306Glu)	c.916C>G	substitution	C>G	Likely pathogenic	PROVISIONAL	NLRP3-AID-severe (CINCA/NOMID)
Exon 3	G307S	p.(Gly307Ser)	c.919G>A	substitution	G>A	Likely pathogenic	VALIDATED	NLRP3-AID-severe (CINCA/NOMID)
Exon 3	G307V	p.(Gly307Val)	c.920G>T	substitution	G>T	Likely pathogenic	VALIDATED	NLRP3-AID-severe (CINCA/NOMID)
Exon 3	F309S	p.(Phe309Ser)	c.926T>C	substitution	T>C	Likely pathogenic	VALIDATED	NLRP3-AID-severe (CINCA/NOMID)
Exon 3	F309Y	p.(Phe309Tyr)	c.926T>A	substitution	T>A	Likely pathogenic	VALIDATED	NLRP3-AID-severe (CINCA/NOMID) NOMID with atypical features (congenital hearing loss, autoantibodies, hepatitis)
Exon 3	G309_F311del	p.(Phe309_His312delinsTyr)	c.926_934del	deletion	TTGACGAGC	Likely pathogenic		NLRP3-AID (CAPS undefined)
Exon 3	E311K	p.(Glu311Lys)	c.931G>A	substitution	G>A	Likely pathogenic	VALIDATED	NLRP3-AID-moderate (MWS)
Exon 3	H312P	p.(His312Pro)	c.935A>C	substitution	A>C	Likely pathogenic	VALIDATED	NLRP3-AID-moderate (MWS)
Exon 3	R325W	p.(Arg325Trp)	c.973C>T	substitution	C>T	Likely pathogenic	VALIDATED	NLRP3-AID-moderate (MWS)
Exon 3	G326E	p.(Gly326Glu)	c.977G>A	substitution	G>A	Likely pathogenic	VALIDATED	NLRP3-AID-severe (CINCA/NOMID)

Infevers website: https://infevers.umai-montpellier.fr/web/search.php?n=4

表1−1

NLRP3遺伝子の疾患関連変異の集積 (Infevers 2)

Location	Usual name	protein name	Sequence change	Alteration	Base substituted	Classification	Status	Associated phenotype
Exon 3	S331R	p.(Ser331Arg)	c.993C>A	substitution	C>A	Likely pathogenic	PROVISIONAL	NLRP3-AID-severe (CINCA/NOMID)
Exon 3	I334V	p.(Ile334Val)	c.1000A>G	substitution	A>G	Likely pathogenic	PROVISIONAL	NLRP3-AID-severe (CINCA/NOMID)
Exon 3	T347I	p.(Thr347Ile)	c.1040C>T	substitution	C>T	Likely pathogenic		NLRP3-AID (CAPS undefined)
Exon 3	T348M	p.(Thr348Met)	c.1043C>T	substitution	C>T	Pathogenic	VALIDATED	NLRP3-AID-moderate (MWS)
Exon 3	V351M	p.(Val351Met)	c.1051G>A	substitution	G>A	Likely pathogenic	PROVISIONAL	NLRP3-AID-severe (CINCA/NOMID)
Exon 3	V351L	p.(Val351Leu)	c.1051G>C	substitution	G>C	Likely pathogenic	PROVISIONAL	NLRP3-AID-severe (CINCA/NOMID)
Exon 3	V351LGT	p.(Val351Leu)	c.1051G>T	substitution	G>T	Likely pathogenic		NLRP3-AID (CAPS undefined)
Exon 3	A352T	p.(Ala352Thr)	c.1054G>A	substitution	G>A	Likely pathogenic	VALIDATED	NLRP3-AID-severe (CINCA/NOMID)
Exon 3	A352S	p.(Ala352Ser)	c.1054G>T	substitution	G>T	Likely pathogenic		NLRP3-AID-moderate (MWS)
Exon 3	A352V	p.(Ala352Val)	c.1055C>T	substitution	C>T	Pathogenic	VALIDATED	NLRP3-AID-moderate (MWS)
Exon 3	L353P	p.(Leu353Pro)	c.1058T>C	substitution	T>C	Likely pathogenic	VALIDATED	NLRP3-AID-mild (FCAS)
Exon 3	E354D	p.(Glu354Asp)	c.1062G>T	substitution	G>T	Likely pathogenic	VALIDATED	NLRP3-AID-severe (CINCA/NOMID)
Exon 3	K355T	p.(Lys355Thr)	c.1064A>C	substitution	A>C	Likely pathogenic	VALIDATED	NLRP3-AID-moderate (MWS)
Exon 3	K355N	p.(Lys355Asn)	c.1065A>T	substitution	A>T	Likely pathogenic	PROVISIONAL	NLRP3-AID-severe (CINCA/NOMID)
Exon 3	H358R	p.(His358Arg)	c.1073A>G	substitution	A>G	Likely pathogenic	VALIDATED	NLRP3-AID-severe (CINCA/NOMID)
Exon 3	L359V	p.(Leu359Val)	c.1075T>G	substitution	T>G	Likely pathogenic		NLRP3-AID (CAPS undefined)
Exon 3	A374D	p.(Ala374Asp)	c.1121C>A	substitution	C>A	Likely pathogenic	VALIDATED	NLRP3-AID-severe (CINCA/NOMID)
Exon 3	T405P	p.(Thr405Pro)	c.1213A>C	substitution	A>C	Likely pathogenic	VALIDATED	NLRP3-AID-severe (CINCA/NOMID)
Exon 3	M406V	p.(Met406Val)	c.1216A>G	substitution	A>G	Likely pathogenic	VALIDATED	NLRP3-AID-severe (CINCA/NOMID)
Exon 3	M406I	p.(Met406Ile)	c.1218G>C	substitution	G>C	Likely pathogenic	VALIDATED	NLRP3-AID-severe (CINCA/NOMID)
Exon 3	L411V	p.(Leu411Val)	c.1231C>G	substitution	C>G	Likely pathogenic	PROVISIONAL	CAPS
Exon 3	L411F	p.(Leu411Phe)	c.1231_1233delinsTTT	delins	CTG / TTT	Likely pathogenic		NLRP3-AID-moderate (MWS)
Exon 3	L411M	p.(Leu411Met)	c.1231C>A	substitution	C>A	Likely pathogenic		NLRP3-AID-severe (CINCA/NOMID)
Exon 3	W414L	p.(Trp414Leu)	c.1241G>T	substitution	G>T	Likely pathogenic	PROVISIONAL	NLRP3-AID-moderate (MWS)
Exon 3	T433I	p.(Thr433Ile)	c.1298C>T	substitution	C>T	Likely pathogenic	PROVISIONAL	NLRP3-AID-severe (CINCA/NOMID)
Exon 3	T436P	p.(Thr436Pro)	c.1306A>C	substitution	A>C	Likely pathogenic	VALIDATED	NLRP3-AID-severe (CINCA/NOMID)
Exon 3	T436A	p.(Thr436Ala)	c.1306A>G	substitution	A>G	Likely pathogenic	VALIDATED	NLRP3-AID-mild (FCAS)
Exon 3	T436DEL	p.(Thr438del)	c.1306_1308del	deletion	ACC	Likely pathogenic	PROVISIONAL	NLRP3-AID-severe (CINCA/NOMID)
Exon 3	T436N	p.(Thr436Asn)	c.1307C>A	substitution	C>A	Likely pathogenic	VALIDATED	NLRP3-AID-severe (CINCA/NOMID)
Exon 3	T436I	p.(Thr436Ile)	c.1307C>T	substitution	C>T	Pathogenic	VALIDATED	NLRP3-AID-severe (CINCA/NOMID) Mild
Exon 3	A439T	p.(Ala439Thr)	c.1315G>A	substitution	G>A	Likely pathogenic	VALIDATED	NLRP3-AID-moderate (MWS)
Exon 3	A439P	p.(Ala439Pro)	c.1315G>C	substitution	G>C	Likely pathogenic	VALIDATED	NLRP3-AID-severe (CINCA/NOMID)
Exon 3	A439V	p.(Ala439Val)	c.1316C>T	substitution	C>T	Pathogenic	VALIDATED	NLRP3-AID-mild (FCAS)
Exon 3	F443L	p.(Phe443Leu)	c.1329C>G	substitution	C>G	Likely pathogenic	VALIDATED	NLRP3-AID-severe (CINCA/NOMID)
Exon 3	F444V	p.(Phe444Val)	c.1330T>G	substitution	T>G	Pathogenic		Recurrent fever
Exon 3	N477K	p.(Asn477Lys)	c.1431C>A	substitution	C>A	Likely pathogenic	VALIDATED	NLRP3-AID-severe (CINCA/NOMID)
Exon 3	I480F	p.(Ile480Phe)	c.1438A>T	substitution	A>T	Likely pathogenic	VALIDATED	NLRP3-AID-severe (CINCA/NOMID) NLRP3-AID-moderate (MWS)
Exon 3	F523C	p.(Phe523Cys)	c.1568T>G	substitution	T>G	Pathogenic	VALIDATED	NLRP3-AID-moderate (MWS)
Exon 3	F523Y	p.(Phe523Tyr)	c.1568T>A	substitution	T>A	Likely pathogenic	VALIDATED	NLRP3-AID-severe (CINCA/NOMID)

Infevers website: https://infevers.umai-montpellier.fr/web/search.php?n=4

表1−1

NLRP3遺伝子の疾患関連変異の集積 (Infevers 3)

Location	Usual name	protein name	Sequence change	Alteration	Base substituted	Classification	Status	Associated phenotype
Exon 3	F523LC>A	p.(Phe523Leu)	c.1569C>A	substitution	C>A	Likely pathogenic	VALIDATED	NLRP3-AID-severe (CINCA/NOMID)
Exon 3	F523LC>G	p.(Phe523Leu)	c.1569C>G	substitution	C>G	Likely pathogenic	VALIDATED	NLRP3-AID-severe (CINCA/NOMID) Schnitzler's syndrome
Exon 3	E525K	p.(Glu525Lys)	c.1573G>A	substitution	G>A	Likely pathogenic	VALIDATED	NLRP3-AID-mild (FCAS)
Exon 3	E525V	p.(Glu525Val)	c.1574A>T	substitution	A>T	Likely pathogenic	VALIDATED	NLRP3-AID-severe (CINCA/NOMID)
Exon 3	R554X	p.(Arg554*)	c.1660C>T	substitution	C>T	Likely pathogenic	VALIDATED	FMF atypical Triggered by exposure to cold
Exon 3	Y563N	p.(Tyr563Asn)	c.1687T>A	substitution	T>A	Likely pathogenic	VALIDATED	NLRP3-AID-mild (FCAS)
Exon 3	G564D	p.(Gly564Asp)	c.1691G>A	substitution	G>A	Likely pathogenic		NLRP3-AID (CAPS undefined)
Exon 3	F566Y	p.(Phe566Tyr)	c.1697T>A	substitution	T>A	Likely pathogenic		NLRP3-AID-moderate (MWS)
Exon 3	F566L	p.(Phe566Leu)	c.1698C>A	substitution	C>A	Likely pathogenic	VALIDATED	NLRP3-AID-severe (CINCA/NOMID)
Exon 3	E567K	p.(Glu567Lys)	c.1699G>A	substitution	G>A	Likely pathogenic	VALIDATED	NLRP3-AID-moderate (MWS)
Exon 3	E567Q	p.(Glu567Gln)	c.1699G>C	substitution	G>C	Likely pathogenic		NLRP3-AID (CAPS undefined)
Exon 3	E567A	p.(Glu567Ala)	c.1700A>C	substitution	A>C	Likely pathogenic	VALIDATED	NLRP3-AID-moderate (MWS)
Exon 3	E567G	p.(Glu567Gly)	c.1700A>G	substitution	A>G	Likely pathogenic		NLRP3-AID (CAPS undefined)
Exon 3	K568N	p.(Lys568Asn)	c.1704G>C	substitution	G>C	Likely pathogenic	VALIDATED	NLRP3-AID-severe (CINCA/NOMID)
Exon 3	G569R	p.(Gly569Arg)	c.1705G>C	substitution	G>C	Pathogenic	VALIDATED	NLRP3-AID-moderate (MWS)
Exon 3	G569A	p.(Gly569Ala)	c.1706G>C	substitution	G>C	Likely pathogenic	VALIDATED	NLRP3-AID-severe (CINCA/NOMID)
Exon 3	G569V	p.(Gly569Val)	c.1706G>T	substitution	G>T	Likely pathogenic		NLRP3-AID (CAPS undefined)
Exon 3	Y570N	p.(Tyr570Asn)	c.1708T>A	substitution	T>A	Likely pathogenic	VALIDATED	CAPS
Exon 3	Y570C	p.(Tyr570Cys)	c.1709A>G	substitution	A>G	Likely pathogenic	VALIDATED	NLRP3-AID-severe (CINCA/NOMID)
Exon 3	Y570F	p.(Tyr570Phe)	c.1709A>T	substitution	A>T	Likely pathogenic	VALIDATED	NLRP3-AID-severe (CINCA/NOMID)
Exon 3	L571F	p.(Leu571Phe)	c.1713G>T	substitution	G>T	Likely pathogenic	VALIDATED	NLRP3-AID-severe (CINCA/NOMID)
Exon 3	L571FG>C	p.(Leu571Phe)	c.1713G>C	substitution	G>C	Likely pathogenic	VALIDATED	NLRP3-AID-severe (CINCA/NOMID)
Exon 3	I572F	p.(Ile572Phe)	c.1714A>T	substitution	A>T	Likely pathogenic	VALIDATED	NLRP3-AID-severe (CINCA/NOMID)
Exon 3	F573S	p.(Phe573Ser)	c.1718T>C	substitution	T>C	Likely pathogenic	VALIDATED	NLRP3-AID-severe (CINCA/NOMID)
Exon 3	T587I	p.(Thr587Ile)	c.1760C>T	substitution	C>T	Likely pathogenic	PROVISIONAL	NLRP3-AID-severe (CINCA/NOMID)
Exon 3	S595G	p.(Ser595Gly)	c.1783A>G	substitution	A>G	Likely pathogenic	VALIDATED	NLRP3-AID-severe (CINCA/NOMID)
Exon 3	I598F	p.(Ile598Phe)	c.1792A>T	substitution	A>T	Likely pathogenic	VALIDATED	NLRP3-AID-severe (CINCA/NOMID) NLRP3-AID-moderate (MWS)
Exon 3	R605G	p.(Arg603Gly)	c.1807A>G	substitution	A>G	Likely pathogenic		NLRP3-AID-moderate (MWS)
Exon 3	E627Q	p.(Glu627Gln)	c.1879G>C	substitution	G>C	Likely pathogenic		NLRP3-AID-moderate (MWS)
Exon 3	E627G	p.(Glu627Gly)	c.1880A>G	substitution	A>G	Pathogenic	VALIDATED	NLRP3-AID-mild (FCAS)
Exon 3	E627D	p.(Glu627Asp)	c.1881A>T	substitution	A>T	Likely pathogenic	VALIDATED	NLRP3-AID-severe (CINCA/NOMID)
Exon 3	L632F	p.(Leu632Phe)	c.1896G>T	substitution	G>T	Pathogenic	VALIDATED	NLRP3-AID-severe (CINCA/NOMID) Mild
Exon 3	M659K	p.(Met659Lys)	c.1976T>A	substitution	T>A	Pathogenic	VALIDATED	NLRP3-AID-mild (FCAS)
Exon 3	M662T	p.(Met662Thr)	c.1985T>C	substitution	T>C	Likely pathogenic	VALIDATED	NLRP3-AID-severe (CINCA/NOMID)
Exon 3	E688K	p.(Glu688Lys)	c.2062G>A	substitution	G>A	Likely pathogenic	VALIDATED	NLRP3-AID-severe (CINCA/NOMID)
Exon 4	G755RG>C	p.(Gly755Arg)	c.2263G>C	substitution	G>C	Pathogenic	VALIDATED	NLRP3-AID-severe (CINCA/NOMID)
Exon 4	G755RG>A	p.(Gly755Arg)	c.2263G>A	substitution	G>A	Pathogenic	VALIDATED	NLRP3-AID-severe (CINCA/NOMID)
Exon 4	G755A	p.(Gly755Ala)	c.2264G>C	substitution	G>C	Likely pathogenic	VALIDATED	NLRP3-AID-severe (CINCA/NOMID)
Exon 4	G767S	p.(Gly767Ser)	c.2299G>A	substitution	G>A	Likely pathogenic		NLRP3-AID (CAPS undefined)
Exon 6	Y859H	p.(Tyr859His)	c.2575T>C	substitution	T>C	Likely pathogenic	VALIDATED	CAPS
Exon 6	Y859C	p.(Tyr859Cys)	c.2576A>G	substitution	A>G	Likely pathogenic	VALIDATED	NLRP3-AID-severe (CINCA/NOMID) arthralgias, headache, intracranial hypertension, hearing loss, short stature

Infevers website: https://infevers.umai-montpellier.fr/web/search.php?n=4

表1−2

NLRP3遺伝子の疾患関連変異の集積（ClinVar 1）

Name	Gene(s)	Protein change	Condition(s)	Clinical significance (Last reviewed)
NM_004895.4(NLRP3):c.784C>T (p.Arg262Trp)	NLRP3	R260W, R262W	Cryopyrin associated periodic syndrome|Familial amyloid nephropathy with urticaria AND deafness|not provided|Familial cold urticaria	Pathogenic(Last reviewed: Mar 13, 2019)
NM_004895.4(NLRP3):c.785G>C (p.Arg262Pro)	NLRP3	R262P, R260P	Familial cold urticaria|not provided|Chronic infantile neurological, cutaneous and articular syndrome	Likely pathogenic(Last reviewed: Dec 11, 2018)
NM_001243133.1(NLRP3):c.902G>A (p.Gly301Asp)	NLRP3	G303D, G301D	Familial cold urticaria|not specified	Likely pathogenic(Last reviewed: May 18, 2019)
NM_004895.5(NLRP3):c.911T>G (p.Phe304Cys)	NLRP3	F304C, F302C	Cryopyrin associated periodic syndrome	Pathogenic(Last reviewed: Dec 29, 2019)
NM_004895.4(NLRP3):c.913G>A (p.Asp305Asn)	NLRP3	D303N, D305N	Cryopyrin associated periodic syndrome|not provided|Familial cold urticaria|Familial amyloid nephropathy with urticaria AND deafness|Chronic infantile neurological, cutaneous and articular syndrome	Pathogenic(Last reviewed: Sep 19, 2019)
NM_004895.4(NLRP3):c.916G>A (p.Glu306Lys)	NLRP3	E306K, E304K	Familial cold urticaria|not provided	Pathogenic(Last reviewed: Apr 27, 2017)
NM_004895.4(NLRP3):c.920T>C (p.Leu307Pro)	NLRP3	L307P, L305P	Familial cold urticaria|not provided	Likely pathogenic(Last reviewed: Aug 11, 2016)
NM_004895.4(NLRP3):c.925G>C (p.Gly309Arg)	NLRP3	G309R, G307R	not provided	Likely pathogenic(Last reviewed: Jan 18, 2017)
NM_004895.4(NLRP3):c.926G>T (p.Gly309Val)	NLRP3	G309V, G307V	Familial cold urticaria|Cryopyrin associated periodic syndrome	Likely pathogenic(Last reviewed: May 4, 2019)
NM_001243133.1(NLRP3):c.926T>C (p.Phe309Ser)	NLRP3	F309S, F311S	Chronic infantile neurological, cutaneous and articular syndrome|Familial cold urticaria	Pathogenic(Last reviewed: Jul 1, 2002)
NM_004895.4(NLRP3):c.983G>A (p.Gly328Glu)	NLRP3	G328E, G326E	Familial cold urticaria|Cryopyrin associated periodic syndrome	Pathogenic(Last reviewed: Apr 24, 2019)
NM_001243133.2(NLRP3):c.1000A>G (p.Ile334Val)	NLRP3	I334V, I336V	Cryopyrin associated periodic syndrome	Likely pathogenic(Last reviewed: Sep 20, 2019)
NM_004895.4(NLRP3):c.1049C>T (p.Thr350Met)	NLRP3	T350M, T348M	not provided|Familial amyloid nephropathy with urticaria AND deafness|Familial cold urticaria|Cryopyrin associated periodic syndrome	Pathogenic(Last reviewed: Apr 1, 2020)
NM_004895.4(NLRP3):c.1061C>T (p.Ala354Val)	NLRP3	A352V, A354V	not provided|Familial amyloid nephropathy with urticaria AND deafness|Cryopyrin associated periodic syndrome|Familial cold urticaria	Pathogenic/Likely pathogenic(Last reviewed: Aug 9, 2019)
NM_004895.4(NLRP3):c.1064T>C (p.Leu355Pro)	NLRP3	L353P, L355P	not specified|not provided|Familial cold urticaria|Chronic infantile neurological, cutaneous and articular syndrome|DEAFNESS, AUTOSOMAL DOMINANT 34, WITH OR WITHOUT INFLAMMATION|Familial cold urticaria|Familial amyloid nephropathy with urticaria AND deafness|Keratitis fugax hereditaria|Cryopyrin associated periodic syndrome	Pathogenic(Last reviewed: Oct 25, 2019)
NM_004895.4(NLRP3):c.1071A>C (p.Lys357Asn)	NLRP3	K357N, K355N	not provided	Pathogenic(Last reviewed: May 4, 2017)
NM_004895.4(NLRP3):c.1219A>C (p.Thr407Pro)	NLRP3	T407P, T405P	not provided|Familial cold urticaria	Likely pathogenic(Last reviewed: Aug 28, 2018)
NM_004895.4(NLRP3):c.1313C>T (p.Thr438Ile)	NLRP3	T438I, T436I	Familial cold urticaria|Cryopyrin associated periodic syndrome	Pathogenic(Last reviewed: Mar 13, 2019)
NM_004895.4(NLRP3):c.1322C>T (p.Ala441Val)	NLRP3	A439V, A441V	Cryopyrin associated periodic syndrome|not specified|not provided|Familial cold urticaria	Pathogenic(Last reviewed: Nov 27, 2019)
NM_004895.4(NLRP3):c.1579G>A (p.Glu527Lys)	NLRP3	E527K, E525K	Familial cold urticaria|Cryopyrin associated periodic syndrome	Likely pathogenic(Last reviewed: Oct 29, 2018)
NM_004895.4(NLRP3):c.1705G>A (p.Glu569Lys)	NLRP3	E569K, E567K	Familial cold urticaria|Cryopyrin associated periodic syndrome	Pathogenic(Last reviewed: Aug 26, 2019)
NM_004895.4(NLRP3):c.1711G>A (p.Gly571Arg)	NLRP3	G571R, G569R	not provided	Pathogenic(Last reviewed: Jul 9, 2013)
NM_001243133.1(NLRP3):c.1705G>C (p.Gly569Arg)	NLRP3	G569R, G571R	Familial cold urticaria|Familial amyloid nephropathy with urticaria AND deafness	Pathogenic(Last reviewed: Jun 1, 2002)
NM_001243133.1(NLRP3):c.1718T>C (p.Phe573Ser)	NLRP3	F573S, F575S	Chronic infantile neurological, cutaneous and articular syndrome|Familial cold urticaria	Pathogenic(Last reviewed: Jul 1, 2002)
NM_004895.4(NLRP3):c.1789A>G (p.Ser597Gly)	NLRP3	S597G, S595G	not provided	Likely pathogenic(Last reviewed: Jul 25, 2017)
NM_001079821.2(NLRP3):c.1805A>G (p.Gln602Arg)	NLRP3	Q602R, Q600R	Pleural effusion|Pericardial effusion|Fever	Likely pathogenic(Last reviewed: Jan 4, 2016)
NM_001243133.1(NLRP3):c.1880A>G (p.Glu627Gly)	NLRP3	E627G, E629G	Familial cold urticaria	Pathogenic(Last reviewed: Nov 1, 2001)
NM_004895.4(NLRP3):c.2582A>G (p.Tyr861Cys)	NLRP3	Y861C, Y859C, Y804C	not provided|Familial cold urticaria	Pathogenic(Last reviewed: Jan 9, 2019)