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Genetic diagnosis of systemic autoinflammatory diseases and underlying primary immunodeficiency

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Systemic autoinflammatory diseases (SAIDs) are characterized by unprovoked inflammatory episodes such as recurrent/periodic fever, serositis, skin lesions, abdominal symptoms, arthritis/arthralgia, and central nervous system involvement. Genetic diagnosis of SAIDs has been challenging because disease manifestations overlap among themselves and with other immunological disease categories, such as infection and autoimmune diseases. However, the advent of next-generation sequencing (NGS) technologies and expanding knowledge about the innate immunity and inflammation have made the routine genetic diagnosis of SAIDs possible. Here, we review the recurrent/periodic fevers, other recently identified autoinflammatory diseases, and type I interferonopathies, and discuss the clinical usefulness of NGS targeted sequencing for SAIDs, and recent advance of understandings for this heterogeneous disease group as for underlying primary immunodeficiency.

Key words: Inflammation, Innate immunity, Genetic testing.

Introduction

Systemic autoinflammatory diseases (SAIDs) are characterized by unprovoked inflammatory episodes such as recurrent/periodic fever, serositis, skin lesions, abdominal symptoms, arthritis/arthralgia, and central nervous system involvement [1-4]. In this expanding and still ongoing disease category, genetic diagnosis has been challenging because disease manifestations overlap among themselves and with other immunological disease categories, such as infection and autoimmune diseases. Differential diagnosis with laboratory findings of this disease category has not been so helpful because their underlying pathophysiology shares a common immunological defect [5]. Prior to the dissemination of next-generation sequencing (NGS) technologies, the genetic diagnosis was limited to genes associated with prototypic recurrent fevers (*MEFV, MVK, TNFRSF1A,* and *NLRP3* genes). In the era of NGS, we can incorporate the expanded SAID-associated genes into our targeted panel gene list, and we are now hoping to adopt the routine genetic diagnosis in this challenging category of diseases and finally, provide a genetic characterization of many previously undiagnosed patients, and give an insight to the biological mechanisms of the innate immunity and autoinflammation. Recent diagnostic approaches of SAIDs can shorten the diagnostic odyssey and provide early access to the optimal treatment adapted to the underlying disease pathophysiology of the immune system. Here, we discuss the clinical usefulness of NGS targeted sequencing for SAIDs and recent advance of understandings for this heterogeneous disease group as for underlying primary immunodeficiency.

Genetic testing for 4 prototypic hereditary recurrent fevers (HRFs).

Genetic testing using Sanger sequencing as a first-line diag-

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nostic tool was recommended for the patients with a clear clinical diagnosis of 4 prototypic HRFs. Genetic testing guidelines were suggested for two recessively inherited diseases [6]: Familial Mediterranean fever (FMF) associated with *MEFV* gene (MIM *608107) and mevalonate kinase deficiency (MKD) associated with *MVK* gene (MIM *251170), and two dominantly inherited diseases: tumor necrosis factor (TNF) receptor-associated periodic syndrome associated with *TNFRSF1A* gene (MIM *191190) and cryopyrin-associated periodic syndrome (CAPS) associated with *NLRP3* gene (MIM *606416). This guideline recommended to screen mutational hot spots (exons 2, 3, 5, 10 of the *MEFV* gene; exons 2-11 of the *MKV* gene; exons 2-4 of the *TNFRSF1A*; exon 3 of the *NLRP3*). However, such a screening approach should always consider the possibility of the presence of a causal mutation outside the defined regions of interest. We can find genotype-phenotype information of these 4 prototypic HRFs in the well-organized registry for autoinflammatory diseases (Eurofever, https://www.printo.it/eurofever/index) [7]. Genetic diagnosis of these 4 prototypic HRFs could guide the therapy according to the specific defect in immunological process. Colchicine is the first-line therapeutic modality for FMF [8]. However, IL-1 or IL-6 blockade for MKD, and IL-1 blockade for CAPS are recommended [9-13].

Genetic Testing for The Expanding List of SAID-Associated Genes

Targeted sequencing using NGS technologies is the current method of choice for SAIDs with ambiguous phenotypes and locus heterogeneity. NGS targeted gene panels usually analyze coding sequences of hundreds of genes. Therefore, we can incorporate other recently described SAID-associated genes, such as *adenosine deaminase 2* (*ADA2*, MIM *607575), *nucleotide-binding oligomerization domain protein 2* (*NOD2*, MIM *605956), *proline/serine/threonine phosphatase-interacting protein 1* (*PSTPIP1*, MIM *606347), and *tumor necrosis factor-alpha-induced protein 3* (*TNFAIP3*, MIM *191163) genes. Deficiency of plasma adenosine deaminase 2 caused by homozygous or compound heterozygous mutations of the *ADA2* gene has been identified in various systemic inflammatory diseases and immune deficiencies, manifesting fever, vasculitis, polyarteritis nodosa, recurrent stroke, and pure red cell aplasia [14-16]. Blau syndrome is a representative autoinflammatory granulomatous disease resulting from mutations of the recognition receptor NOD2, presenting with granulomatous polyarthritis, dermatitis and uveitis [17,18]. Pyogenic sterile arthritis, pyoderma gangrenosum and acne syndrome is a pleiotropic autosomal dominant autoinflammatory disease caused by mutations of CD2-binding protein PSTPIP1, which interacts with pyrin [19,20]. Haploinsufficiency of nuclear factor kappa B (NF-κB) regulatory protein A20 encoded by *TNFAIP3*, mediates a familial Behcet-like autoinflammatory syndrome, characterized by painful and recurrent mucosal ulceration affecting the oral mucosa, gastrointestinal tract, and genital areas. Several non-truncating TNFAIP3 mutations may provoke autoimmune conditions such as rheumatoid arthritis, SLE, and Sjogren associated non-Hodgkin lymphoma [21-23]. Therefore, expert practice guidelines from the International Society of Systemic Autoinflammatory Disease recommended including these 4 recently identified genes (*ADA2, NOD2, PSTPIP1*, and *TNFAIP3*) in its diagnostic scheme in addition to the 4 previously annotated HRF associated genes (*MEFV, MVK, NLRP3*, and *TNFRSF1A*) [22].

The locus specific database for SAIDs (Infevers, https://infevers.umai-montpellier.fr/web/index.php) deposited 43 additional genes into an expanding list of SAID-associated genes: *ADAM17, ALPK1, AP1S3. CARD14, CDC42, CEBPE, COPA, ELF4, F12, IKBKG, IL1RN, IL36RN, LACC1, LPIN2, NCSTN, NLRC4, NLRP1, NLRP12, NLRP7, OTULIN, PLCG2, POMP, PSMA3, PSMB4, PSMB8, PSMB9, PSMB10, PSMG2, PSTPI1, RBCK1, RELA, RIPK1, SAMD9L, SH3BP2, SLC29A3, STING1, TNFAIP3, TNFRSF1A, TNFRSF11A, TRAP1, TRNT1, UBA1, WDR1*. Most of them are associated with the players of the innate immune system, such as inflammasomes and IL-1β production (*MVK, NLRP1, NLRP3, NLRC4, PSTPIP1*), NF-κB signaling (*NOD2, TNFAIP3, TNFRSF1A, TNFRSF11A, TRAP1*), ubiquitination (*UBA1*), and type I interferon production (*COPA, POMP, STING1*) [5].

Type I Interferonopathy and Innate Immune System

Type I interferonopathy has been denoted and classified within the broader disease entity of SAIDs [5,24]. Aicardi-Goutieres syndrome (AGS) is the first defined Mendelian disease associated with type I interferon upregulation, characterized by inflammation and tissue damage in the central nervous system, brain calcification, chronic cerebrospinal fluid (CSF) lymphocytosis, increased CSF alpha-interferon. Mutations of the *ADAR, RNASEH2A, RNASEH2B, RNASEH2C, SAMHD1*, and *TREX1* can cause dysfunction of nucleases involved in the immune system, resulting in inflammatory damage to brain, skin and other body systems that lead to the characteristic features of AGS [25]. Type I interferon (IFN-I) and their cognitive receptors and

Table 1. Representative periodic fever/autoinflammatory disease panel gene list

Genes	Reference transcript	MIM *	MIM #	Associated disease	Mode of inheritance
ACP5	NM_001111035.2	171640	607944	Spondyloenchondrodysplasia with immune dysregulation	AR
ADA2	NM_001282225.2	607575	615688	Vasculitis, autoinflammation, immunodeficiency, and hematologic defects syndrome	AR
ADAM17	NM_003183.5	603639	614328	Inflammatory skin & bowel disease, neonatal, 1	AR
ADAR	NM_001111.4	146920	615010	Aicardi-Goutieres syndrome 6	AR
			127400	Dyschromatosis symmetrica hereditaria	AD
ASAH1	NM_177924.4	613468	228000	Farber lipogranulomatosis	AR
CARD14	NM_024110.4	607211	173200	Pityriasis rubra pilaris	AD
			602723	Psoriasis 2	AD
DNASE2	NM_001375.2	126350	619858	Autoinflammatory-pancytopenia syndrome	AR
ELANE	NM_001972.3	130130	162800	Neutropenia, cyclic	AD
			202700	Neutropenia, severe congenital 1, autosomal dominant	AD
HAX1	NM_006118.3	605998	610738	Neutropenia, severe congenital 3, autosomal recessive	AR
IFIH1	NM_022168.4	606951	615846	Aicardi-Goutieres syndrome 7	AD
			619773	Immunodeficiency 95	AR
IL10RA	NM_001558.3	146933	613148	Inflammatory bowel disease 28, early onset	AR
IL10RB	NM_000628.4	123889	612567	Inflammatory bowel disease 25, early onset	AR
IL1RN	NM_173841.2	147679	612852	Interleukin 1 receptor antagonist deficiency	AR
IL36RN	NM_012275.2	605507	614204	Psoriasis 14, pustular	AR
LPIN2	NM_014646.2	605519	609628	Majeed syndrome	AR
MEFV	NM_000243.2	608107	134610	Familial Mediterranean fever, AD	AD
			249100	Familial Mediterranean fever, AR	AR
			608068	Neutrophilic dermatosis, acute febrile	AD
MVK	NM_000431.3	251170	260920	Hyper-IgD syndrome	AR
			610377	Mevalonate kinase deficiency	AR
NLRP1	NM_033004.3	606636	617388	Autoinflammation with arthritis and dyskeratosis	AD, AR
NLRP12	NM_144687.3	609648	611762	Familial cold autoinflammatory syndrome 2	AD
NLRP3	NM_004895.4	606416	607115	CINCA syndrome	AD
			617772	Deafness, autosomal dominant 34, with or without inflammation	AD
			120100	Familial cold inflammatory syndrome 1	AD
			191900	Muckle-Wells syndrome	AD
NOD2	NM_022162.2	605956	186580	Blau syndrome	AD
PLCG2	NM_002661.5	600220	614878	Autoinflammation, antibody deficiency, and immune dysregulation syndrome	AD
			614468	Familial cold autoinflammatory syndrome 3	AD
PSMB8	NM_148919.4	177046	256040	Proteasome-associated autoinflammatory syndrome 1 and digenic forms	AR
PSTPIP1	NM_003978.4	606347	604416	Pyogenic sterile arthritis, pyoderma gangrenosum, and acne	AD
RNASEH2A	NM_006397.2	606034	610333	Aicardi-Goutieres syndrome 4	AR
RNASEH2B	NM_024570.3	610326	610181	Aicardi-Goutieres syndrome 2	AR
RNASEH2C	NM_032193.3	610330	610329	Aicardi-Goutieres syndrome 3	AR
SAMHD1	NM_015474.3	606754	612952	Aicardi-Goutieres syndrome 5	AR
SH3BP2	NM_003023.4	602104	118400	Cherubism	AD
SLC29A3	NM_018344.5	612373	602782	Histiocytosis-lymphadenopathy plus syndrome	AR
TNFAIP3	NM_006290.3	191163	616744	Autoinflammatory syndrome, familial, Behcet-like 1	AD
TNFRSF11A	NM_003839.3	603499	612301	Osteopetrosis, autosomal recessive 7	AR
TNFRSF1A	NM_001065.3	191190	142680	Periodic fever, familial	AD
TREX1	NM_033629.5	606609	2235750	Aicardi-Goutieres syndrome 1, dominant and recessive	AD, AR
STING1 (TMEM173)	NM_198282.4	612374	615934	STING-associated vasculopathy, infantile-onset	AD
WDR1	NM_017491.5	604734	150550	Periodic fever, immunodeficiency, and thrombocytopenia syndrome	AR

MIM *, gene/locus MIM number; MIM #, phenotype MIM number; AD, autosomal dominant; AR, autosomal recessive.

signaling pathways are the essential components of the innate immune system. Type I interferonopathy-associated genes can be grouped according to their functions as nucleic acid sensing (*IFIH1, DDK58*), nucleic acid signaling (*STING1, COPA*), nuclear acid metabolism (*RNASEH2A, RNASEH2B, RNASEH2C, POLA1, BLM, ATM, DCLRE1C, SAMHD1, TREX1, DNASE2, ADAR1, SKIV2L PTPN1, LSM11, RNU7-1*), proteasome (*PSMB4, PSMB8, PSMB9, PSMB10, PSMD12, PSMA3, PSMG2, POMP*), mitochondrial integrity (*NGLY1, ATAD3A*), and post interferon receptor signaling pathways (*ISG15, JAK1, STAT1, STAT2, USP18*).

Adoption of Targeted NGS Panel Sequencing for SAIDs

SAID is a rapidly expanding disease category that is associated with the innate immune dysregulation, encompassing hereditary recurrent/periodic fevers, other recently defined SAIDs, and type I interferonopathies. Since they share the immunological pathways and interactions, genetic diagnostic approaches are challenging. Therefore, adoption of NGS technology in this complicated disease category, having locus heterogeneity and various expressivity, is mandatory. NGS panel testings, including primary immunodeficiency panel and hemophagocytic lymphohistiocytosis panel, are now routinely performed in Korea. There were some retrospective studies and case reports to reveal the genetic cause of SAIDs [26,27]. So far, SAID NGS panel testing is not widely performed. As for SAIDs, the list of panel genes should be periodically updated because they are still expanding rapidly. The SAID panel should include classical 4 HRF-associated genes and additional SAIDs-associated genes. The inclusion of type I interferonopathy-associated genes in the panel is also recommended. Table 1 shows the representative SAID gene panel in Korea. After the adoption of this NGS panel for 18 months, they could identify the causative mutations of classical HRF-associated genes and other SAID-associated genes in the patients with recurrent fever and/or systemic inflammatory diseases (Table 2).

Conclusion

Genetic diagnosis of autoinflammatory diseases has been challenging so far. However, the advent of NGS technologies and expanding knowledge about the innate immunity and inflammation have made the routine genetic diagnosis of SAIDs possible. Here we reviewed the classical recurrent hereditary fevers and recently defined SAIDs, and type I inteferonopathies

Table 2. An example of genetic variations detected by targeted sequencing for SAIDs which was conducted at one university hospital in South Korea for 18 months

No.	Reasons of genetic testing	Test results	Genes	Sequence variations (HGVS)	Classification (ACMG)	dbSNP	Reference
1	Recurrent fever, family history	Detected	*PSTPIP1*	NM_003978.4:c.769G>A (p.Glu257Lys)	LP	N/A	[28]
2	FUO, meningitis, papilledema	ND					
3	Recurrent fever, oral ulcer, abdominal pain, diarrhea	Detected	*TNFAIP3*	NM_006290.3:c.547C>T (p.Arg183*)	P	rs1423560438	[29,30]
4	Recurrent fever, synovitis (hip joint)	ND					
5	Recurrent fever	ND					
6	Recurrent fever, FUO	ND					
7	FUO	Detected	*NLRP3*	NM_004895.4:c.2582A>G (p.Tyr861Cys)	LP	rs180177452	[31]
8	Recurrent fever, skin rash	ND					
9	FUO, skin rash, pancytopenia	ND					
10	Recurrent fever, oral ulcer	ND					
11	Recurrent fever, vomiting	ND					
12	FUO, arthralgia	Inconclusive	*MEFV*	NM_000243.2:c.250G>A (p.Glu84Lys)	VUS	rs150819742	[32]
13	Periodic fever, oral ulcer	ND					
14	Recurrent fever, cellulitis	ND					
15	Recurrent fever	Inconclusive	*TREX1*	NM_033629.4:c.-26-1G>A	VUS	rs749323787	N/A
16	Recurrent fever, oral ulcer	ND					
17	Periodic fever, conjunctivitis, periorbital edema, febrile convulsion	ND					

SAID, systemic autoinflammatory disease; HGVS, Human Genome Variation Society; ACMG, American College of Medical Genetics; FUO, fever of unknown origin; ND, not detected; LP, likely pathogenic; VUS, a variant of uncertain significance; N/A, not applicable.

with their corresponding molecular mechanisms of the innate immunity. Now is the time to adopt the targeted NGS panel testing in the routine genetic diagnosis of SAIDs in Korea.

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