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Original Article

Postitive impact of impact of expert reference centre validation on performance of next-generation sequencing for genetic diagnosis of autoinflammatory diseases

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Supplementary Materials: The following are available online at www.mdpi.com/xxx/s1, Table S1: List of the 55 genes and transcripts used for variant annotation and nomenclature included in our next-generation sequencing targeted panel and association with OMIM diseases. Table S2: Genetic diagnosis yield of targeted panels for AIDs reported in the literature. Figure S1. Workflow reporting the decisional tree for genetic testing.

Table S1. List of the 55 genes and transcripts used for variant annotation and nomenclature included in our next-generation sequencing targeted panel and association with OMIM diseases.

GENETICS			PHENOTYPE					
Gene (locus)	**RefSeq transcript**	**OMIM**	**Inheritance**	**Disease**	**Name of disease**	**OMIM**	**Aliases**	**Name of aliases**
ACP5 (19p13.2)	NM_001111035.2	171640	Recessive	SPENCDI	Spondyloenchondrodysplasia With Immune Dysregulation	607944		
ADA2 (22q11.1)	NM_001282225.1	607575	Recessive	VAIHS	Vasculitis, Autoinflammation, Immunodeficiency, And Hematologic Defects Syndrome	615688	DADA2	Deficiency of adenosine deaminase 2
			Recessive	SNDNS	Sneddon Syndrome	182410		
			Recessive	PAN	Polyarteritis Nodosa, Childhood-Onset			
ADAM17 (2p25.1)	NM_003183	603639	Recessive	NISBD	Inflammatory Skin And Bowel Disease, Neonatal	614328		
ADAR (1q21.3)	NM_001111	146920	Recessive	AGS6	Aicardi-Goutieres Syndrome 6	615010		
			Dominant	DSH	Dyschromatosis Symmetrica Hereditaria	127400		
AP1S3 (2q36.1)	NM_001039569.1	615781	Dominant	PSORS15	Psoriasis 15, Pustular, Susceptibility To	616106		
CARD14 (17q25.3)	NM_024110.4	607211	Dominant	PSOR2	Psoriasis 2	602723	CAMPS	CARD14-mediated pustular psoriasis
			Dominant	PRP	Pityriasis Rubra Pilaris	173200		
CASP1 (11q22.3)	NM_001257118	147678	Candidate					
COPA (1q23.2)	NM_001098398.1	601924	Dominant	AILJK	Autoimmune Interstitial Lung, Joint, And Kidney Disease	616414		
DDX58 (9p21.1)	NM_014314	609631	Dominant	SGMRT2	Singleton-Merten Syndrome 2	616298		

FAS (10q23.31)	NM_000043.5	134637	Dominant/ Recessive	ALPS	Autoimmune Lymphoproliferative Syndrome	601859		
FASLG (1q24.3)	NM_000639.2	134638	Recessive	ALPS	Autoimmune Lymphoproliferative Syndrome	601859		
FBLIM1 (1p36.21)	NM_017556.3	607747	Candidate (AR)	CRMO	Chronic Recurrent Multifocal Osteomyelitis			
IFIH1 (2q24.2)	NM_022168.3	606951	Dominant	AGS7	Aicardi-Goutieres Syndrome 7	615846		
			Dominant	SGMRT1	Singleton-Merten Syndrome 1	182250		
IL10 (1q32.1)	NM_000572.2	124092	Candidate	IL10 deficiency				
IL10RA (11q23.3)	NM_001558.3	146933	Recessive	IBD28	Inflammatory Bowel Disease 28, Autosomal Recessive	613148		
IL10RB (21q22.11)	NM_000628.4	123889	Recessive	IBD25	Inflammatory Bowel Disease 25, Autosomal Recessive	612567		
IL1RN (2q14.1)	NM_173841.2	147679	Recessive	OMPP	Osteomyelitis, Sterile Multifocal, With Periostitis And Pustulosis	612852	DIRA	Deficiency of IL1 Receptor Antagonist
IL36RN (2q14.1)	NM_173170.1	605507	Recessive	PSORP14	Pustular Psoriasis, Generalized	614204	DITRA	Deficiency of IL36 Receptor Antagonist
LACC1 (13q14.11)	NM_001128303.1	613409	Candidate (AR)	SJIA	Systemic Juvenile Inflammatory Arthritis			
LPIN2 (18p11.31)	NM_014646.2	605519	Recessive	MJDS	Majeed Syndrome	609628	LPIN2-CNO	LPIN2-Chronic non-bacterial osteomyelitis
MDFIC (7q31.1-q31.2)	NM_199072.4	614511	Candidate					
MEFV (16p13.3)	NM_000243.2	608107	Recessive	FMF	Familial Mediterranean Fever	249100		
			Dominant	FMF	Familial Mediterranean Fever, Autosomal Dominant	134610		

			Dominant	PFAD	Periodic Fever With Autoinflammatory Disease			
			Dominant	PAAND	Pyrin-Associated Autoinflammation With Neutrophilic Dermatosis			
MVK (12q24.11)	NM_000431.3	251170	Recessive	MEVA	Mevalonic Aciduria	610377	MKD	Severe Mevalonate kinase deficiency
				HIDS	Hyper-Igd Syndrome	260920	MKD	Mild Mevalonate kinase deficiency
NCSTN (1q23.2)	NM_015331.2	605254	Dominant	ACNINV1	Acne Inversa, Familial, 1	142690	PASH	Pyoderma gangrenosum acne suppurative hidradenitis
NLRC4 (2p22.3)	NM_021209.4	606831	Dominant	AIFEC	Autoinflammation With Infantile Enterocolitis	616050		
				FCAS4	Familial Cold Autoinflammatory Syndrome 4	616115		
NLRP1 (17p13.2)	NM_033004.3	606636	Dominant/ Recessive	AIADK	Autoinflammation With Arthritis And Dyskeratosis;	617388	NAIAD	NLRP1-associated autoinflammation with arthritis and dyskeratosis
NLRP12 (19q13.42)	NM_144687.3	609648	Dominant	FCAS2	Familial Cold Autoinflammatory Syndrome 2	611762		
NLRP3 (1q44)	NM_001243133.1	606416	Dominant	CINCA	Cinca Syndrome	607115	NOMID	Neonatal onset multisystem inflammatory disease
							Severe NLRP3-AID	NLRP3-associated autoinflammatory disease (NLRP3-AID)
			Dominant	MWS	Muckle-Wells Syndrome	191900	Moderate NLRP3-AID	
			Dominant	FCAS1	Familial Cold Autoinflammatory Syndrome 1	120100	Mild NLRP3-AID	
NOD2 (16q12.1)	NM_022162.2	605956	Dominant	Blau	Blau Syndrome	186580		NOD2-associated granulomatous disease

OTULIN (5p15.2)	NM_138348	615712	Recessive	AIPDS	Autoinflammation, Panniculitis, And Dermatosis Syndrome	617099		
PLCG2 (16q23.3)	NM_002661.4	600220	Dominant	APLAID	Autoinflammation, Antibody Deficiency, And Immune Dysregulation, Plcg2-Associated	614878		
				FCAS3	Familial Cold Autoinflammatory Syndrome 3	614468	PLAID	PLCG2 associated antibody deficiency and immune dysregulation
POMP (13q12.3)	NM_015932.5	613386	Recessive	KLICK	Keratosis Linearis With Ichthyosis Congenita And Sclerosing Keratoderma	601952		
			Dominant	PRAAS2	Proteasome-Associated Autoinflammatory Syndrome 2	618048	CANDLE	Chronic Atypical Neutrophilic Dermatosis with Lipodystrophy and Elevated temperature
PSENEN (19q13.12)	NM_172341.2	607632	Dominant	ACNINV2	Acne Inversa, Familial, 2	613736		
PSMA3 (14q23.1)	NM_002788.3	176843	Candidate (AR)	PRAAS				
PSMB4 (1q21.3)	NM_002796.2	602177	Recessive	PRAAS3	Proteasome-Associated Autoinflammatory Syndrome 3	617591	CANDLE	Chronic Atypical Neutrophilic Dermatosis with Lipodystrophy and Elevated temperature
PSMB8 (6p21.32)	NM_148919.3	177046	Recessive	PRAAS1	Proteasome-Associated Autoinflammatory Syndrome 1	256040	CANDLE	Chronic Atypical Neutrophilic Dermatosis with Lipodystrophy and Elevated temperature
PSMB9 (6p21.32)	NM_002800.4	177045	Recessive	PRAAS3	Proteasome-Associated Autoinflammatory Syndrome 3	617591	CANDLE	Chronic Atypical Neutrophilic Dermatosis with Lipodystrophy and Elevated temperature
PSMG2 (18p11.21)	NM_020232.4	609702	Candidate (AR)	PRAAS	Proteasome Associated Autoinflammatory Syndrome			
PSTPIP1 (15q24.3)	NM_003978.4	606347	Dominant	PAPA	Pyogenic Sterile Arthritis, Pyoderma Gangrenosum, And Acne	604416	PAPA	PSTPIP1-associated arthritis, pyoderma gangrenosum and acne
PYCARD (16p11.2)	NM_013258.4	606838	Candidate					
RBCK1 (20p13)	NM_031229.3	610924	Recessive	PGBM1	Polyglucosan Body Myopathy 1 With Or Without Immunodeficiency	615895	PBMEI	Polyglucosan Body Myopathy, Early-Onset, With or Without Immunodeficiency

RNASEH2A (19p13.13)	NM_006397.2	606034	Recessive	AGS4	Aicardi-Goutieres Syndrome 4	610333		
RNASEH2B (13q14.3)	NM_024570.3	610326	Recessive	AGS2	Aicardi-Goutieres Syndrome 2	610181		
RNASEH2C (11q13.1)	NM_032193.3	610330	Recessive	AGS3	Aicardi-Goutieres Syndrome 3	610329		
RNF31 (14q12)	NM_017999.4	612487	Candidate (AR)	HOIP Deficiency				
SAMHD1 (20q11.23)	NM_015474.3	606754	Recessive	CHBL2	Chilblain Lupus 2	614415		
				AGS5	Aicardi-Goutieres Syndrome 5	612952		
SERPING1 (11q12.1)	NM_000062.2	606860	Dominant	HAE1	Angioedema, Hereditary, Type I	106100		
SH3BP2 (4p16.3)	NM_003023.4	602104	Dominant		Cherubism	118400	SDCM	SH3BP2 deficiency with multilocular cystic disease of the mandibles
SLC29A3 (10q22.1)	NM_018344.5	612373	Recessive	H syndrome	Histiocytosis-Lymphadenopathy Plus Syndrome	602782		
TMEM173 (5q31.2)	NM_198282.3	612374	Dominant	SAVI	Sting-Associated Vasculopathy, Infantile-Onset	615934		
TNFAIP3 (6q23.3)	NM_001270508.1	191163	Dominant	AISBL	Autoinflammatory Syndrome, Familial, Behcet-Like	616744	HA20	Deficiency in HA20 protein
TNFRSF11A (18q21.33)	NM_003839.3	603499	Recessive	OPTB7	Osteopetrosis, Autosomal Recessive 7	612301	TRAPS11	TNFRSF11A-associated hereditary fever disease
			Dominant	FEO	Familial Expansile Osteolysis	174810		
TNFRSF1A (12p13.31)	NM_001065.3	191190	Dominant		Periodic Fever, Familial, Autosomal Dominant	142680	TRAPS	TNF receptor-associated periodic fever syndrome
TNFRSF9 (1p36.23)	NM_001561	602250	Candidate					

TREX1 (3p21.31)	NM_016381.5	606609	Dominant/ Recessive	CHBL1	Chilblain Lupus 1	610448
			Dominant	AGS1	Aicardi-Goutieres Syndrome 1	225750
			Dominant	RVCL	Vasculopathy, Retinal, With Cerebral Leukodystrophy	192315
TRNT1 (3p26.2)	NM_182916.2	612907	Recessive	RPEM	Retinitis Pigmentosa And Erythrocytic Microcytosis	616959
			Recessive	SIFD	Sideroblastic Anemia With B-Cell Immunodeficiency, Periodic Fevers, And Developmental Delay	616084

AR, Autosomal recessive. OMIM, Online Mendelian Inheritance in Man, OMIM®. McKusick-Nathans Institute of Genetic Medicine, Johns Hopkins University (Baltimore, MD), {13/09/2019}. World Wide Web URL: https://omim.org/

Table S2. Genetic diagnosis yield of targeted panels for AIDs reported in the literature.

Reference	No of AIDs genes in the panel	Library enrichment method	NGS equipment	Software for raw data analysis	Variant pathogenicity assessment	Inclusion of frequent VOUS	Segregation analysis	Coverage, depth of reads	No. of patients tested	No. of patients with genetic confirmation	Genetic diagnosis yield
Omoyinmi et al., 2017	32	Capture (QXT, Agilent technologies)	MiSeq (Illumina)	Galaxy, in-house pipeline and Agilent SureCall v3.5.1.46	ACGS 2013 guidelines	Yes	Yes if available	97%, >30X	50	11	22%
Nakayama et al., 2017	12	Amplification (Multiplex PCR, Takara)	MiSeq (Illumina)	Blat (aligner) and Sommelier (variant caller)	ND	Yes	ND	90%, >20X	108	22	20%
Ozyilmaz et al., 2019	3	NEXTflex Periodic Fever-1 NGS Amplicon Panel (Bioo Scientific)	MiSeq (Illumina)	"SEQ" variant analysis (Genomize)	ND	Yes	Yes if available	ND	64	12	19%
Karacan et al., 2019	15	Amplification (Ion AmpliSeq, Thermo Fisher Scientific)	Ion S5 (Thermo Fisher Scientific)	Torrent Suite 5.4.0 (Life Technologies)	Frequencies, HGMD, ClinVar, Infevers	No	ND	95%, >50X	196	14	7%
Papa et al., 2019	41	Amplification (Ion AmpliSeq, Thermo Fisher Scientific)	Ion PGM™ (Thermo Fisher Scientific)	Ion Reporter™ 5.0 (Thermo Fisher Scientific)	In-house criteria (Frequencies, *in silico* software tools, CADD score, ClinVar)	No	Yes if available	4 amplicons at <10X analyzed by Sanger sequencing	50	2	4%

ND, not determined; ACGS, Association for Clinical Genomic Science; HGMD, Human Gene Mutation Database.

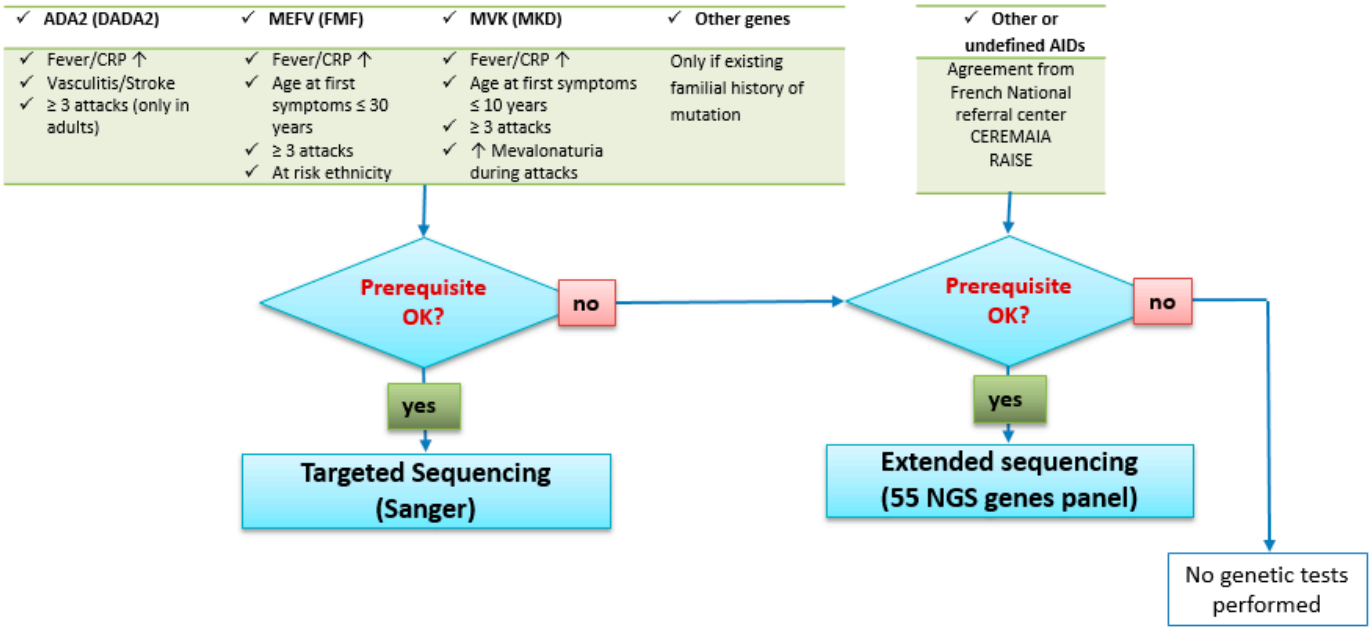

Figure S1. Workflow reporting the decisional tree for genetic testing. CEREMAIA, Reference centre for AIDs; CRP, C-reactive protein; RAISE, Reference centre for juvenile arthritis and pediatric rare autoimmune diseases.