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Recurrent Fever Syndrome/ Autoinflammatory disease (HLH & MAS)

Recurrent Fever Syndrome (RFS) is a subtype of the Autoinflammatory Diseases (AD). RF is characterized as the occurrence of episodic fevers that do not have an infectious cause. Onset can range from infancy to adulthood presenting with cyclical or random attacks of fevers (above 39 degrees Celsius) and localized inflammation lasting days to months. RFS is a genetically heterogeneous condition and can be associated with a range of clinical features including: rash, edema, arthritis, skin lesions, pulmonary complications gastrointestinal irritation and hematological abnormalities.

Hemophagocytic Lymphohistiocytosis (HLH) is a disorder related to the accumulation of lymphocytes and macrophages often with hemophagocytosis involving the spleen, lymph nodes, bone marrow, liver and cerebral spinal fluid. Diagnostic criteria for HLH based on the recommendations of the Histiocyte Society include having at least five out of the following eight symptoms: Fever, splenomegaly, Cytopenias, hypertriglyceridemia, hemophagocytosis, low natural killer cell function, hyperferratinemia and high levels of soluble IL-2r. Macrophage activation syndrome (MAS) is a form of HLH associated with juvenile idiopathic arthritis (JIA) and other rheumatologic conditions. MAS is characterized by, but not limited to, high fevers, hepatosplenomegaly, lymphadenopathy and hematological anomalies.

Genetics of RFS, HLH & MAS

The genetics of Autoinflammatory Disease, including RFS and HLH & MAS are complex; autosomal dominant, autosomal recessive and X-linked modes of inheritance have been described. The targeted Next-Generation Sequencing (NGS) panels at our laboratory include genes associated with all three modes of inheritance.

Test Methods

Complete sequencing of the coding region and flanking intron/exon boundaries of the genes listed below. This is done via NGS of the targeted gene panels. Testing can be requested for one or both panels based on clinical features and the suspected mode of inheritance. Please refer to our "A Guide to Next-Generation Sequencing" information sheet available on our website, for further details.

Who Should be Tested?

- Individuals clinically suspected of being affected with RFS and HLH & MAS .
- The relatives of a proband with identified pathogenic variants in an RFS and HLH & MAS -associated gene
- Pregnancies at increased risk due to a family history of RFS and HLH & MAS.

Interpretation of Test Results

Genetic testing may reveal one or more variants in the Autoinflammatory disease /HLH genes, which should be interpreted in the context of the suspected inheritance pattern, clinical findings, family history and other experimental data.

Please refer to our "A Guide to Interpreting Sequence Variations" information sheet available on our website, for further details.

Genes associated with AD, MAS, RFS & HLH

See table on page 2

For More Information

Hereditary Periodic Fever Syndromes: http://emedicine.medscape.com/article/952254-overview

Hemophagocytic Lymphohistiocytosis (HLH): http://www.ncbi.nlm.nih.gov/books/NBK1444/

Macrophage Activation Syndrome (MAS): http://emedicine.medscape.com/article/1380671-overview

SickKids Genomic Diagnostics Laboratory: www.sickkids.ca/genome-diagnostics

To locate a genetics center near you:

Canadian Association of Genetic Counsellors (CAGC): www.cagc-accg.ca

National Society of Genetic Counselors (NSGC): www.nsgc.org

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1. Current molecular testing may not detect all possible mutations for this disease. A negative test does not rule out the possibility of RFS , MAS or HLH.

2. The clinical course or severity of symptoms cannot be predicted by molecular analysis.

3. Test results should be interpreted in the context of clinical findings, family history and other laboratory data.

4. This test was developed and its performance characteristics validated by the Molecular Genetics Laboratory at the Hospital for Sick Children. It has not been cleared or approved by the U.S. Food and Drug Administration. The FDA has determined that such clearance or approval is not necessary. This test is used for clinical purposes.

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NGS Panel 1: Recurrent fever

		Gene name	Disease
Autoinflammatory Disease Genes	**Autosomal Recessive**	LPIN2	Majeed Syndrome
		CECR1	Polyarteritis nodosa, Cat Eye Syndrome
		PSMB8	CANDLE syndrome
		IL1RN	Deficiency of Interleukin-1 receptor antagonist
		IL36RN	Deficiency of Interleukin-36 receptor antagonist
		RAB27A	Griscelli disease, type 2
	Autosomal Dominant	PSTPIP1	Pyogenic sterile arthritis, pyoderma gangrenosum, and acne (PAPA) syndrome
		CARD14	CARD14-mediated pustular psoriasis, Pityricisis Rubra Pilaris (PRP)
		TMEM173	Sting-Associated Vasculopathy, Infantile-Onset
		NOD2	Blau syndrome
Recurrent Fever Syndrome (RFS) Genes	**Autosomal Recessive**	MVK	Hyper IgD Syndrome
		MEFV	Familial Mediterranean Fever syndrome
	Autosomal Dominant	TNFRSF1A	Tumour necrosis factor receptor associated periodic syndrome (TARPS)
		NLRP3	Cryopyrin Associated Periodic Syndromes (CAPS), Muckler-Wells syndome
		ELANE	Cyclic Neutropenia, Severe Congenital Neutropenia
		MEFV	Familial Mediterranean Fever syndrome
		NLRP12	Familial Cold Autoinflammatory syndrome 2
		NLRC4	Autoinflammation with infantile enterocolitis

NGS Panel 2: Hemophagocytic Lymphohistiocytosis

Autosomal Dominant	NLRC4	Autoinflammation with infantile enterocolitis
Autosomal Recessive	AP3B1	Hermansky-Pudlak syndrome Type 2
	BLOC1S6	Hermansky-Pudlak syndrome Type 9
	CD27	CD27 deficiency
	ITK	Lymphoproliferative syndrome type 1
	LYST	Chediak-Higashi syndrome
	PRF1	Familial hemophagocytic lypmphohistiocytosis 2*
	UNC13D	Familial hemophagocytic lymphohistiocytosis 3*
	STX11	Familial hemophagocytic lypmphohistiocytosis 4*
	SLC7A7	Lysinuric protein intolerance
	STXBP2	Familial hemophagocytic lypmphohistiocytosis 5*
	RAB27A	Griscelli disease, type 2
X-linked	SH2D1A	Lymphoproliferative syndrome type 1 or Duncan disease
	XIAP	Lymphoproliferative syndrome type 2

*MAS has been associated with the four Familial hemophagocytic lypmphohistiocytosis genes listed above.