A genetic database and clinical findings for immunodeficiency due to mutations in interleukin-10, interleukin-10 receptor A, and interleukin-10 receptor B genes

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ABSTRACT

Defects in interleukin (IL)-10 cytokine and receptors are associated with severe immune dysregulation, with affected patients presenting mainly with very early onset inflammatory bowel disease (VEO-IBD), arthritis, and skin manifestations such as dermatitis and folliculitis. We have created a database of published mutations in the genes encoding for IL-10, IL-10 receptor A (IL-10RA), and IL-10 receptor B (IL-10RB). All published mutations were reviewed and clinical as well as laboratory phenotypes recorded. Many variants in these genes are reported to be associated with IBD, as well as other diseases and pathologies. However, in this review we have focused on mutations considered harmful to the gene product and which lead to the classic presentation of VEO-IBD. This database can assist clinicians in the diagnosis of patients with specific features of immunodeficiency. A yearly update of new mutations and phenotypes will be performed.

Statement of novelty: The presented database and short review is the first extensive collection of reported mutations and the clinical features of Very Early Onset IBD due to IL10 related genes.

Introduction

Interleukin (IL)-10 is an important anti-inflammatory mediator. Deleterious defects in IL-10 cytokine and receptors are associated with severe immune dysregulation, with affected patients presenting mainly with the phenotype of very early onset inflammatory bowel disease (VEO-IBD). Other prominent features include skin manifestations, such as dermatitis and folliculitis, and in some patients arthritis may be significant (Glocker et al. 2009).

Inflammatory bowel disease is a group of several disorders afflicting mainly the gastrointestinal tract, alongside the well characterized Crohn's disease and Ulcerative Colitis, there is a group of patients with very early onset inflammatory bowel disease (VEO-IBD), which is encountered by pediatricians and gastroenterologists worldwide. These patients present with severe gastrointestinal involvement, eczema, arthritis and sometimes infections. As many as 20% carry mutations in IL-10, IL-10 receptor A (IL-10RA), or IL-10 receptor B (IL-10RB). These defects are considered primary

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immunodeficiency diseases and carry a poor prognosis if left untreated. Unfortunately, response to conventional IBD treatment regimens is poor, thus, hematopoietic stem cell transplantation (HSCT) is considered a curative treatment for these patients.

Immunologic studies

The routine immune workup in the majority of patients is unremarkable. 2 studies reported changes in immunoglobulins; in 2 cases IgG was low, and in 1 case IgA or IgG was elevated. As for lymphocyte surface markers, 1 study reported reduced numbers of FOXP3 expressing CD4 lymphocytes in both blood and tissue (Kelsen et al. 2015) and another study reported low CD4/CD8 ratio (Engelhardt et al. 2013). Lymphocyte proliferation assay results have been reported to be normal.

Clinical features

VEO-IBD, which is refractory to conventional treatment modalities, is the most significant finding, with most reports describing the disease as beginning during the very first months of life. Severe perianal disease with fistula formation and severe colitis, and in some patients oral aphthous lesions, all appeared in infants younger than 6 months. In many cases, this was described during the first 3 months of life and progressed rapidly. One interesting report of a patient from Korea described a relatively late presentation at the age of 6 years without the common finding of severe perianal disease. The pathogenic mutation occurred before the splice site, resulting in skipping and fusion of exon 3 and 5 of the *IL10* RA gene (Oh et al. 2016).

All known treatments for IBD, such as steroids, immunomodulators, and anti-tumor necrosis factor (TNF) therapy failed to achieve substantial effects. In many patients, surgical treatment was undertaken to alleviate some of the symptoms. In as much as a third of patients, a prominent feature is arthritis affecting the large joints. Eczema and folliculitis are also very common and this may involve large portions of body area.

Malignancy with B cell lymphoma in patients with IL-10 defects have been reported by Neven et al. (2013). These involved mostly non-Epstein-Barr virus (EBV)-related B cell lymphomas, and occurred after several years of disease (around 5 years). Most were

treated and cured, although 1 patient was reported to experience several recurrences, and was cured after HSCT. The exact mechanism has not been elucidated, although it may well be related to IL-10 regulatory, or rather, lack of regulatory activity in these patients. All had non-EBV-related diffuse large B cell lymphoma. The current consensus for treating these patients is with HSCT, however, in some patients not all manifestations resolve post-transplant, such as in the case reported by Kim et al. (2014). This group of patients reinforces the need for early diagnosis and curative treatment with HSCT.

Other less frequent findings including autoimmune hepatitis, idiopathic thrombocytopenic purpura (ITP), pyoderma gangrenosum, Gram-negative sepsis, and recurrent pneumonia were all described in sporadic patients (see Table 1).

There are, however, some limitations in our attempt to summarize this large group of patients (Table 1). Since the discovery of this group of diseases, the increasing availability of diagnostic tools, as well as early diagnosis and treatment, has changed the natural course and phenotype of these inherited defects. Furthermore, the mutations and patients presented here are by no means a reflection of the extent of this group of diseases or their prevalence. It is reasonable to conclude that once a mutation is found in a population, many more patients will be identified by direct sequencing of the known mutation, rather than whole exome sequencing, and therefore may not be reported.

Summary

VEO-IBD related to mutations in IL-10 and IL-10 receptors have a unique presentation and carry a grave prognosis, unless diagnosed early and treated appropriately. The current main curative treatment is HSCT, with good results reported by several centers.

The subject of polymorphisms in these genes was not covered in this manuscript, but is an important issue (Moran et al. 2013). Undoubtedly, some of these changes cause increased susceptibility to IBD and are worth studying in further detail. We have focused on the changes that were studied biologically and were proven to be a direct cause for IBD.

Table 1: Mutations in IL-10, IL10RA, IL10RB, clinical and immunologic features.

	Ethnicity	Gene mutation	Lymphocyte cell numbers	Immunoglobulins/Antibodies	Clinical features	References
IL-10RA	Caucasian	169I>T (missense), 431E>X (nonsense)	Lymphocyte populations-normal	Normal	VEO-IBD, eczema, food intolerance/allergy, pyoderma gangrenosum, sepsis	Lee et al. 2014
	Black	Compound heterozygous 169I>T (missense)				
	Turkish	64Y>X			VEO-IBD	Beser et al. 2015
	N/A	45W>G			VEO-IBD	Beser et al. 2015
	Korean	91Y>C/262R>C. Compound heterozygous			VEO-IBD	Shim et al. 2013 Shim and Seo 2014
	Arab, Lebanon	141G>R			Folliculitis, infantile VEO-IBD	Glocker et al. 2009
	Caucasian, Germany	84T>I			Folliculitis, infantile VEO-IBD	Glocker et al. 2009
	N/A	262R>C				Begue et al. 2011
	Turkish	101R>W		Normal		Kotlarz et al. 2012
	Brazilian	57W>C		Normal	Arthritis, VEO-IBD	Kotlarz et al. 2012
		117R>C. Compound heterozygous				
	Black	169I>T		Normal	VEO-IBD, atopic dermatitis, folliculitis	Kotlarz et al. 2012
	Caucasian, Canada	206P>X			VEO-IBD, arthritis, folliculitis	Moran et al. 2013
	Chinese	84T>I; 101R>T. Compound heterozygous			VEO-IBD, no other symptoms	Mao et al. 2012
	Afghanistan	Intron 3 c.368-10C>G	Normal lymphocyte population, proliferation	Normal	VEO-IBD, B cell lymphoma, recurrent pneumonia	Murugan et al. 2014
	Arabic	Aberrant trafficking of receptor Ex1-3 deleted. Homozygous		Low IgG	VEO-IBD	Engelhardt et al. 2013
	Caucasian	Val23fsX31 (Del. Ex 2_4)		High IgA	VEO-IBD	Engelhardt et al. 2013
	Pakistani	Tyr57Cys. Heterozygous		Low IgG	VEO-IBD	Engelhardt et al. 2013 Engelhardt et al. 2013
		125L>R 125G>R				Oh et al. 2016
	Korean	p.T179T aberrant splice site mutation			Early onset-IBD, probably less severe, older age	
		537G>A				
	Japanese	Same as above			VEO-IBD, ITP, JML	Yanagi et al. 2016
	Caucasian	412R>W. Heterozygous	Normal B, T, NK Low FOXP3+ cells	Normal Ig	VEO-IBD, eczema, folliculitis	Kelsen et al. 2015
	Chinese	100V>G 64Y>C			VEO-IBD	Xiao et al. 2016

(continued)

Table 1: (Continued)

	Ethnicity	Gene mutation	Lymphocyte cell numbers	Immunoglobulins/Antibodies	Clinical features	References
IL-10RB	Indian	117R>H	CD4/CD8 ratio—low	Normal	VEO-IBD	Engelhardt et al. 2013
	Arabic	Leu59fsX72 Skipped exon 3	B and NK low	High IgA	VEO-IBD	
	Pakistani	Trp18fsX29		High IgA	VEO-IBD	
	Turkish	193G>R	N/A	N/A	VEO-IBD	
	Kurdish	159W>X 141E>X			Folliculitis, arthritis, VEO-IBD, autoimmune hepatitis VEO-IBD, B cell lymphoma	Glocker et al. 2009 ; Kotlarz et al. 2012 Begue et al. 2011 ; Neven et al. 2013 Kotlarz et al. 2012
	Asian, Bangladesh	66C>Y	Normal	Normal	Folliculitis, VEO-IBD	
	Arabic	3'UTR: C52T	Normal	Normal	Arthritis, IBD	Kotlarz et al. 2012
	Caucasian Germany/ Poland	204W>X 230S>X	Normal lymphocyte population and proliferation	Normal/ hypergammaglobulinemia	Dermatitis, folliculitis, VEO-IBD	Kotlarz et al. 2012
	Turkish	c.331+907_574 del	Normal		VEO-IBD, folliculitis	Kotlarz et al. 2012
	N/A	59Y>C F269fsX275 204W>C g.11930-17413 del	Normal lymphocyte population and proliferation	Normal	VEO-IBD, B cell lymphoma VEO-IBD, B cell lymphoma VEO-IBD, B cell lymphoma	Neven et al. 2013 Neven et al. 2013 Neven et al. 2013
IL-10	Pakistani	113G>R	Normal		VEO-IBD, no extraintestinal manifestations	Glocker et al. 2010 Kotlarz et al. 2012
	Arab	153G>D				

Note: VEO-IBD, very early onset inflammatory bowel disease, consisting frequently with severe inflammation, severe perianal disease with fistulae. Patients often suffer from FTT, failure to thrive; 3'UTR, untranslated region; AI, autoimmune; JML, juvenile myelogenous leukemia; ITP, immune thrombocytopenic purpura.

In this short review, we have collated all reported mutations found in several journal databases with a short description of the patients' ethnicity, main immunological features and most important their clinical presentation. We hope this increases awareness to the spectrum of the disease, and the importance of early diagnosis and treatment.

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