

## **IgG4 cholangitis**

*New Perspectives on Biliary Tract Disease*

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## Case Report:

male, 64 yrs, truck driver and car industry worker

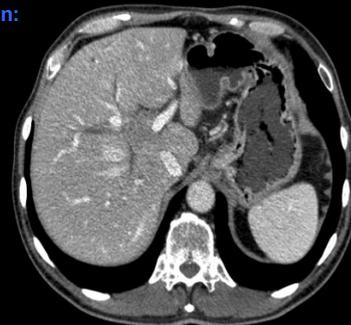
presenting with itch and jaundice



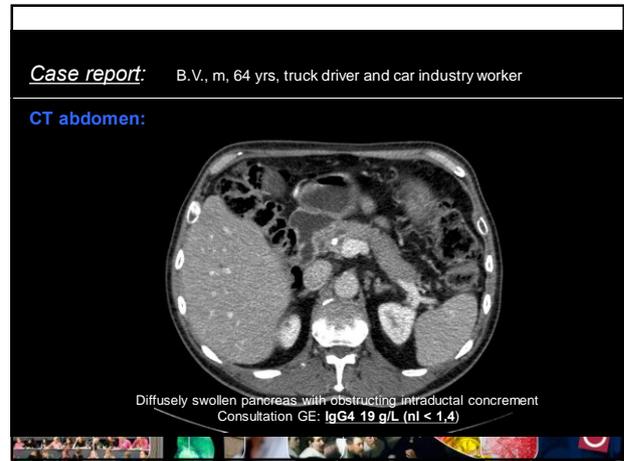
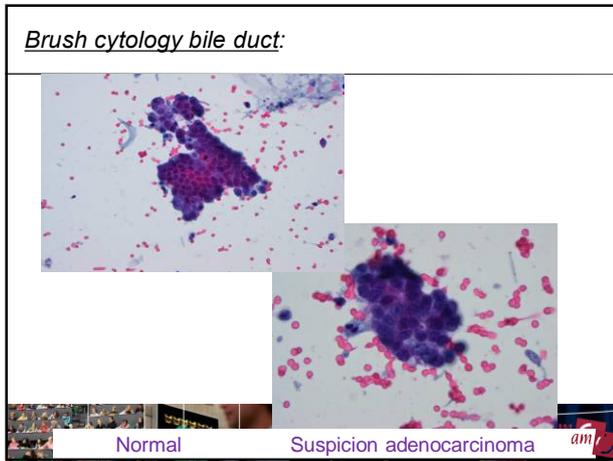
**No conflicts of interest**



**CT abdomen:**



Slightly dilated intrahepatic bile ducts with central obstruction by hypodense hilar tumor



**Diagnosis:**

Non-resectable Klatskin tumor Bismuth type 4

R/ Chemotherapy (partial regression)

FUP (3 y): Lung and submandibular involvement (histology benign)

**IgG4 cholangiopathy**

Table 1. IAC and PSC: differences in clinical presentation, immunopathological features and treatment response [10, 14–16, 19]

	PSC	IAC
Age, years	25–45	65
Gender, male	65%	80%
Response to steroids	–	+++
Association with IBD	+++	–
Association with cholangiocarcinoma	+++	?
Other organ involvement	?	+++
Histological findings	obliterative cholangitis and cirrhosis	abundant IgG4-positive plasma cells
Dominant cholangiographic findings	band-like strictures with a beaded appearance	segmental strictures and distal bile duct strictures
Elevated serum IgG4	7–9%*	around 70%

\* Of note, as the authors themselves suggest, within their cohort of PSC patients, some of the patients with elevated IgG4 levels might in fact be misdiagnosed IAC patients. IBD = Inflammatory bowel disease.

Yasser A. Alderfeste Bram D.J. van den Elzen Erik A.J. Rauws Ulrich Beuers. Immunoglobulin G4-Associated Cholangitis: One Variant of Immunoglobulin G4-Related Systemic Disease. Digestion 2009;79:220–228

**IgG4 disease; clinical relevance?**

**IgG4-Associated Cholangitis in Patients Resected for Presumed Perihilar Cholangiocarcinoma: a 30-Year Tertiary Care Experience**

Eva Roos, MD, MSc<sup>1</sup>, Lowiek M. Hubers, MD, MSc<sup>2</sup>, Robert J. S. Coelen, MD, PhD<sup>1</sup>, Marieke E. Doorenspleet, MD, PhD<sup>3</sup>, Niek de Vries, MD, PhD<sup>4</sup>, Joanne Verheij, MD, PhD<sup>4</sup>, Ulrich Beuers, MD<sup>5</sup> and Thomas M. van Gulik, MD, PhD<sup>1</sup>

*Am J Gastroenterol*. 2018 May;113(5):765-772.

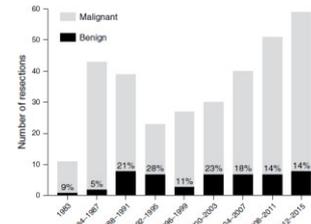


Fig. 2 Resections for presumed PHC over time

Liver and bile duct resections for PHC during three decades disclosed in 15% benign biliary disorders mimicking PHC of which 42% were definitely diagnosed as IAC. IgG4-RD remains active in the majority of patients with IAC years after surgery. Novel diagnostic tests for IAC might reduce misdiagnosis, unnecessary surgery, and life-threatening complications.

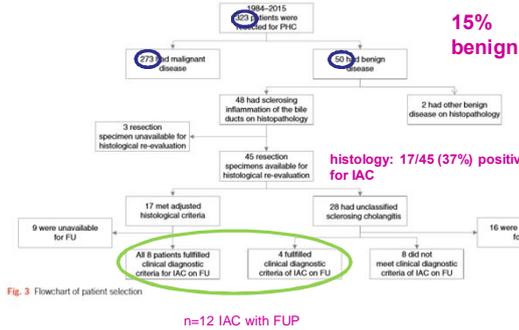


Fig. 3 Flowchart of patient selection



**IgG4-associated cholangitis (IAC):**

Hepatobiliary manifestation of immunoglobulin G4-related disease (IgG4-RD).

Systemic fibroinflammatory disorder with a wide variety of clinical presentations and organ manifestations.

IgG4-RD predominantly affects the hepatobiliary tract (IAC) and pancreas (autoimmune pancreatitis) mimics hepatobiliary, pancreatic and other malignancies.



### HISORt criteria

**Diagnostic criteria**

**Histology**

At least one of the following:

- Periductal lymphoplasmacytic infiltrate with obliterative phlebitis and storiform fibrosis
- Lymphoplasmacytic infiltrate with storiform fibrosis with abundant IgG4 cells ( $\geq 10$  IgG4 cells/hpf)

**Imaging**

Typical: diffusely enlarged gland with delayed rim enhancement, diffusely irregular, attenuated main pancreatic duct  
 Other: focal pancreatic mass/enlargement, focal pancreatic ductal stricture, pancreatic atrophy, calcification, pancreatitis

**Serology**

Elevated serum IgG4 level (normal 8–140 mg/dl)

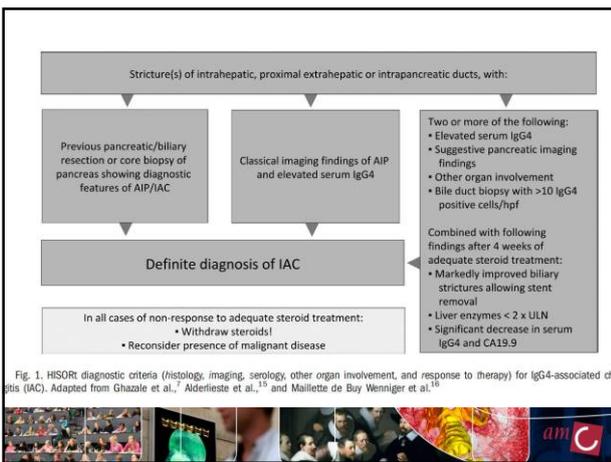
**Other organ involvement**

Hilar/intrahepatic biliary strictures, persistent distal biliary stricture, parotid/lacrimal gland involvement, mediastinal lymphadenopathy, retroperitoneal fibrosis

**Response to steroid therapy**

Resolution or marked improvement of pancreatic/extrapancreatic manifestation with corticosteroid therapy

## Histology



MODERN PATHOLOGY (2012) 25, 1181–1192

### Consensus statement on the pathology of IgG4-related disease

*Deshpande V et al –international symposium Boston 2011:*

*“The primary purpose of this statement is to provide practicing pathologists with a set of guidelines for the diagnosis of IgG4-related disease”*

Although the combination of **histopathological features** and immunohistochemical stain results can provide strong **supportive evidence** for the diagnosis of IgG4-related disease...

...

.. careful **correlation with the clinical scenario** and imaging characteristics of a particular patient is often required to arrive at a definitive diagnosis.

...

**neither an increase in serum IgG4 nor the finding of elevated numbers of IgG4 positive plasma cells in tissue is specific for IgG4-related disease...**

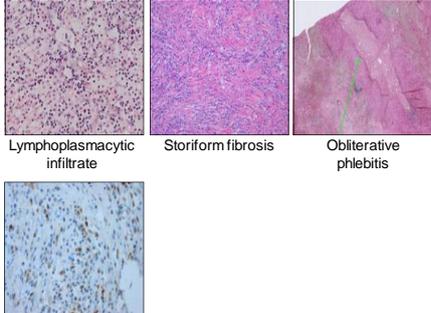


### Consensus criteria: Histology of IgG4-related disease

**2 of 3 major histological features**

- Lymphoplasmacytic infiltrate
- Storiform fibrosis
- Obliterative phlebitis

**>10-50 IgG4+ plasma cells (biopsy/resection specimen)**




### 3 major histopathological features:

- (1) Dense lymphoplasmacytic infiltrate
- (2) Fibrosis, arranged at least focally in a storiform pattern
- (3) Obliterative phlebitis

### Other histopathological features:

- (1) Phlebitis without obliteration of the lumen
- (2) Increased numbers of eosinophils



Characteristic histological features  
 1. Dense lymphoplasmacytic infiltrate  
 2. Fibrosis, usually storiform in character  
 3. Obliterative phlebitis

Cases with ≥ 2 pathology features      Cases with 1 pathology feature

	Numbers of IgG4+ plasma cells (/HPF)		Ref
	<10	>10	
Meninges	Green	Yellow	55
Lacrimal gland	Green	Yellow	28
Salivary gland	Green	Yellow	17,34
Lymph node	Green	Yellow	27
Lung (surgical specimen)	Green	Yellow	10,35
Lung (biopsy)	Green	Yellow	10,35
Pleura	Green	Yellow	6
Pancreas (surgical specimen)	Green	Yellow	30,32
Pancreas (biopsy)	Green	Yellow	55,57
Bile duct (surgical specimen)	Green	Yellow	49
Bile duct (biopsy)	Green	Yellow	58,59
Liver (surgical specimen)	Green	Yellow	49
Liver (biopsy)	Green	Yellow	12,60
Kidney (surgical specimen)	Green	Yellow	13
Kidney (biopsy)	Green	Yellow	61
Aorta	Green	Yellow	18,51,52
Retropertoneum	Green	Yellow	6
Skin	Green	Yellow	62,63

IgG4+/IgG+ plasma cell ratio ≥40% a mandatory for histological diagnosis of IgG4-RD

Green boxes = Histologically highly suggestive of IgG4-RD  
 Orange boxes = Probable histological features of IgG4-RD

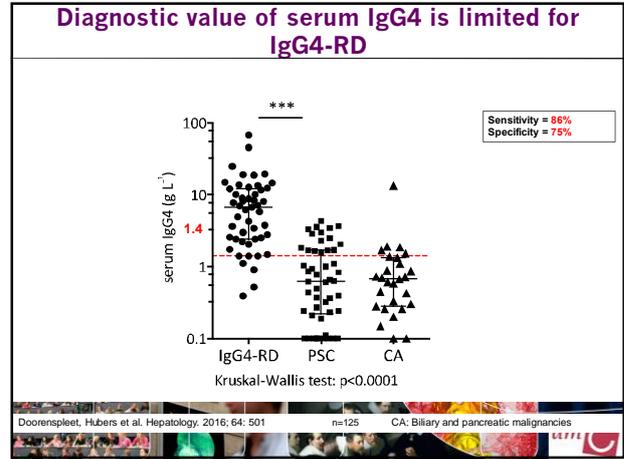


**Table 3 Features of IAC on histopathology**

Features of IAC on histopathology	n = 45
<b>Major histological criteria</b>	
Lymphoplasmacytic infiltration	44 (93%)
Storiform fibrosis	18 (38%)
Obliterative phlebitis	10 (21%)
<b>Minor histological criteria</b>	
Phlebitis without obliteration of the lumen	22 (44%)
Eosinophilia	27 (60%)
<b>IgG4+ plasma cells infiltration</b>	
>10 IgG4+ cells/hpf	19 (42%)
50 IgG4+ cells/hpf	6 (13%)
<b>Meeting IAC criteria</b>	
2 of 3 major criteria & >10 IgG4+ cells/hpf	17 (36%)
2 of 3 major criteria & >50 IgG4+ cells/hpf	6 (13%)

*hpf* high-power field

HISORT criteria and International Consensus Diagnostic Criteria (ICDC) recommend a lower cutoff of >10 IgG4+ plasma cells. In our experience, a high threshold of >50 IgG4+ cells/hpf drastically decreases sensitivity.



**Serology**

**CCA** in the setting of PSC: elevated levels of **IgG4** (in up to **22%** of patients)

**sIgG4** elevated in **15%** of patients with an unchallenged PSC diagnosis

Other organs



Prostatitis and Other Benign Diseases

**Immunoglobulin G4-related Prostatitis: A Case-control Study Focusing on Clinical and Pathologic Characteristics**

Jorie Buijs, Lucas Maillette de Buy Wenniger, Geert van Leenders, Joanne Verheij, Ilze van Omsa, Bettina Hansen, Marianne van Heerde, Nanda Krak, Ulrich Beuers, Marco Bruno, and Henk van Buuren

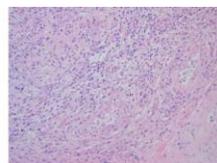
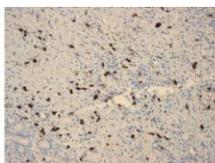
**CONCLUSION** Prostatic involvement might not be rare in patients with pancreatic or biliary IgG4-RD. Clinicians should consider this disease entity in patients with IgG4-RD and prostatic symptoms. UROLOGY 83: 521–527, 2014. © 2014 Elsevier Inc.



Images in Clinical Urology

**Testicular Inflammation as a New Manifestation of IgG4-associated Disease**

Lucas Maillette de Buy Wenniger, Johannes M. Scheltema, Joanne Verheij, and Ulrich Beuers



**Figure 1.** Revision of the surgical specimen of pancreatic tissue collected 5 years earlier during the Whipple procedure. Immunohistochemistry for IgG4 revealed a maximum of 50 IgG4-positive plasma cells per high-powered field, supporting the diagnosis of IgG4-related disease.

**Figure 2.** Hematoxylin-eosin staining of the tissue of the right testis showing a plasma cell-rich infiltrate and myofibroblastic spindle cell proliferation around the seminiferous tubules. These changes were distributed unevenly over the tissue and affected the largest part of the testis.

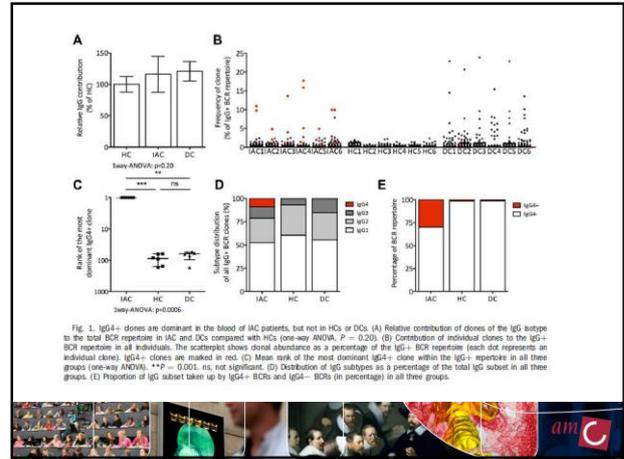


30 y AMC experience : Of the 12 patients with IAC who were followed-up, 9 patients suffered from recurrent disease after surgery;

they required immunosuppressive treatment years after surgery, underlining the importance of a correct and timely diagnosis of IAC



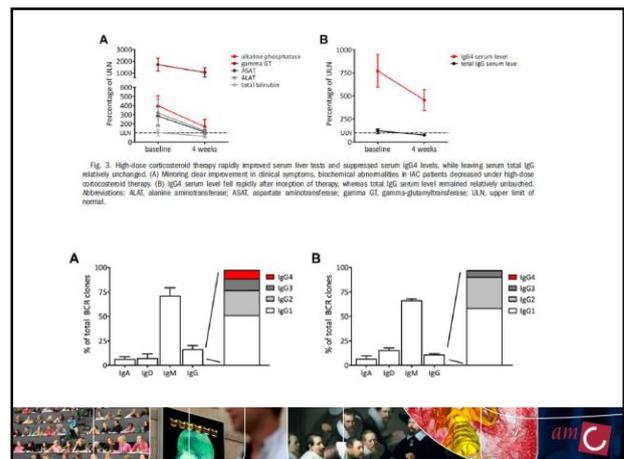
# New developments



## Immunoglobulin G4<sup>+</sup> Clones Identified by Next-Generation Sequencing Dominate the B Cell Receptor Repertoire in Immunoglobulin G4 Associated Cholangitis

Lucas J. Maillette de Buy Wenniger,<sup>1\*</sup> Marieke E. Doorenspleet,<sup>2-3\*</sup> Paul I. Klarenbeek,<sup>2,3</sup> Joanne Verheij,<sup>4</sup> Frank Baas,<sup>3</sup> Ronald P. Oude Elferink,<sup>1</sup> Paul P. Tak,<sup>3</sup> Nick de Vries,<sup>2†</sup> and Ulrich Beuers<sup>4†</sup>

HEPATOLOGY, Vol. 57, No. 6, 2013



### Exposure to Occupational Antigens Might Predispose to IgG4-Related Disease

HEPATOLOGY, Vol. 60, No. 4, 2014

Job history (>1 year)	Recalled regular occupational exposures (>1 year)
1. Musician, painter, metal worker, carpenter	car paint, metal, solvents, pigments
2. Carpenter	sawdust, wood, chipboard, solvents
3. Glass worker, project manager at multinational	glass dust, glass components, lead, barium, cobalt, nickel, lead, silica, industrial dust, building sites
4. Plasterer	chalk dust, sawdust, wood, chipwood, solvents
5. Industrial fuel/waste oil laboratory skipper	crude oil, ship waste oil, solvents, chemicals
6. Miner, boiler, bath superintendent	silica dust, mine dust, asbestos, solvents, glue, chlorine
7. Metal worker, textile worker	metal dust, solvents, textiles, pigments, paints
8. Shipping	solvents, asbestos, crude oil
9. Painter, army officer, flight arrangements, tomato farmer	paint, pigments, solvents, kerosene, pesticides, friction plate dust
10. Painter	paint, pigments, solvents, dust
11. Small machine factory owner	car paint, metal dust, solvents, asbestos, oils
12. Builder, plumber	plumbing materials, dust, sawdust, chipboard, glue, lead
13. Self-employed ophthalmician	lense glass dust, lense plastic dust, acetone
14. Carpenter	sawdust, chipboard, glue, solvents
15. Bricklayer, industrial cleaner of house walls	silica dust, concrete dust, brick dust, solvents, asbestos
16. Mud worker, shipping, mud industry manager	solvents, oil products, dust
17. Builder, painter	solvents, sawdust, chipboard, paints
18. Car industry worker	solvents, oil products
19. Historian, rebuilt 3 houses during last 20 years	sawdust, silica dust, solvents, paint
20. Builder, wall miller	silica dust, sawdust, dust, solvents
21. Metal worker	

HEPATOLOGY, VOL. 44, NO. 2, 2004

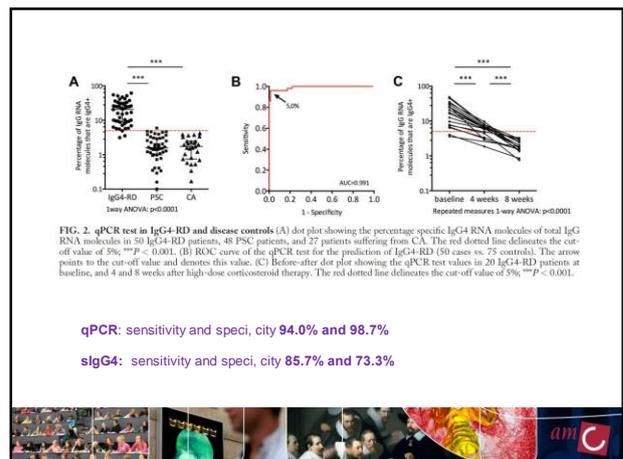
AUTOIMMUNE CHOLESTATIC AND BILIARY DISEASES

## Immunoglobulin G4<sup>+</sup> B-Cell Receptor Clones Distinguish Immunoglobulin G4-Related Disease From Primary Sclerosing Cholangitis and Biliary/Pancreatic Malignancies

Masaki E, Dzonogova<sup>1,2</sup>, Laskik M, Habes<sup>3</sup>, Emami L, Cabac<sup>4</sup>, Lasa J, Mellini de Ruy Wainiger<sup>2</sup>, Paul L, Klambuck<sup>5</sup>, Rogge W, Chapman<sup>6</sup>, Frank Rein<sup>7</sup>, Siro F, van de Grint<sup>8</sup>, Joana Verbeq<sup>9</sup>, Dominik M, van Gabel<sup>9</sup>, Elvener Bann<sup>10</sup>, Ulrich Bauer<sup>11</sup> and Niko de Vries<sup>12</sup>

IgG4-associated cholangitis/autoimmune pancreatitis (n = 34)  
 Primary sclerosing cholangitis (n = 17)  
 CA (n = 17).

Given our observed high rate of chronic occupational exposure of two independent cohorts of IgG4-RD patients suggests that **chronic exposure to occupational antigens may play a role in the initiation and/ or maintenance of IgG4-RD in susceptible individuals.**



### Annexin A11 is targeted by IgG4 and IgG1 autoantibodies in IgG4-related disease

Lowiek M Hubers,<sup>1</sup> Harmjan Vos,<sup>2</sup> Alex R Schuurman,<sup>1</sup> Robin Erken,<sup>1</sup> Ronald P Oude Elferink,<sup>1</sup> Boudewijn Burgering,<sup>2</sup> Stan F J van de Graaf,<sup>1</sup> Ulrich Beuers<sup>1</sup>

Hubers LM, *et al. Gut* 2018;**67**:728–735.

### Conclusions

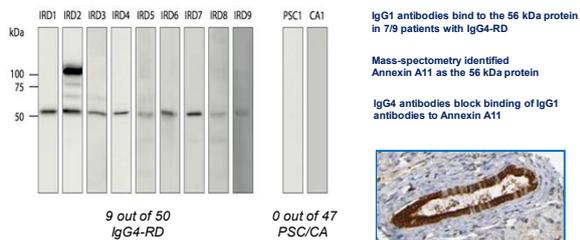
IgG4-associated cholangitis is a manifestation of IgG4-RD, a multiorgan disease characterized by highly specific B-cell responses.

Environmental risk factors might explain the typical gender and age distribution.

Number of IgG4 positive plasma cells/HPF always should be interpreted in the context of the other histomorphological criteria (lymphoplasmacellular infiltrates, storiform fibrosis and obliterative phlebitis)

**Histology contributes to diagnosis, but clinical correlation is needed!!**

### Serum IgG4 antibodies in IgG4 cholangiopathy recognize a ~56 kDa protein in human H69 cholangiocyte lysates



### Interpretation liver biopsy

*It takes two to tango..*



[www.liverpathology.org](http://www.liverpathology.org)

www.proteinatlas.com  
IRD = IgG4-RD CA = biliary/pancreatic malignancies

## Role of IgG4 within IgG4-RD:

smallest fraction (< 5%) of IgG antibodies



On the role of IgG4 in inflammatory conditions: lessons for IgG4-related disease<sup>®</sup>

David C. Trampert<sup>1</sup>, Lowiek M. Hubers<sup>1</sup>, Stan F.J. van de Graaf, Ulrich Beuers<sup>2</sup>

Allergies/hypersensitivities	
Advantageous suppression	
Beekeepers	
Animal laboratory workers	
Allergen-specific immunotherapy	
Malignancies and Parasitic infections	Autoimmune/immune-mediated diseases
Disadvantageous suppression	Pathogenic
Melanoma and cholangiocarcinoma	Pemphigus vulgaris and foliaceus
Helminthic infections	MuSK-myasthenia gravis



BBA - Molecular Basis of Disease 1864 (2018) 1401-1409