

## Review Article

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# Genes associated as risk factor Morbus Hansen's disease: A review article

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## Abstract

**Introduction:** Morbus Hansen is a chronic infectious disease caused by the bacteria *Mycobacterium leprae* and *Mycobacterium lepromatosis*. Morbus Hansen is still a health problem in endemic areas, such as Africa, Southeast Asia and Latin America. Morbus Hansen (MH) is named after the founder of this disease in the 19th century, a doctor from Norway named Gerhard Henrik Armauer Hansen. An increase in the incidence of Morbus Hansen occurs in people with household contacts with Morbus Hansen sufferers. This manuscript review which gene had a role in morbus Hansen disease.

**Discussion:** Morbus Hansen disease is characterized by a granulomatous inflammatory process in the peripheral nerves and mucosa of the upper respiratory tract and lesions on the skin are the main clinical signs that can be seen. *Mycobacterium leprae* is intracellular, namely in reticuloendothelial cells, for example macrophages and on peripheral nerves, namely on the Schwann cell. *Mycobacterium leprae* infection can also attack the eye and testes. Risk factors for the occurrence of Morbus Hansen disease include: living in an endemic area of Morbus Hansen, low socio-economic conditions, such as poor living facilities, contaminated water, poor nutrition, other diseases that can reduce the body's immune system, contact with morbus Hansen patient's and gene risk. Several genes have been studied and are associated with individual susceptibility to infection with the bacteria *Mycobacterium leprae*.

**Conclusion:** Several genes are associated with individual susceptibility to infection with Morbus Hansen Disease. Recent studies have this gene could defects in the cellular immune response more vulnerable to infection with bacteria *Mycobacterium leprae*. These defect came from genes that are thought to be associated with Morbus Hansen disease. Furthermore, research studies must confirm these genes.

**Keywords:** Risk factors, Genes, Morbus Hansen.

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## Introduction

Morbus Hansen is a chronic infectious disease caused by the bacteria *Mycobacterium leprae* and *Mycobacterium lepromatosis*. Morbus Hansen is still a health problem in endemic areas, such as Africa, Southeast Asia and Latin America. Morbus Hansen (MH) is named after the founder of this disease in the 19th century, a doctor from Norway named Gerhard Henrik Armauer Hansen [1-3].

*Mycobacterium lepromatosis* was found as a Morbus Hansen pathogen in an endemic case that occurred in Mexico and the Caribbean in 2008 [1,4,5]. In Ziehl-Nielsen staining, *Mycobacterium leprae* will be red [1]. *Mycobacterium sp.* has a characteristic rod-shaped, gram-positive, covered by a cell membrane consisting of a waxy layer, is acid resistant, aerobic, and intracellular obligate. there are Country still sufferers until right now, such as in India, Egypt, Nepal, Somalia, Liberia, and Vietnam [3].

Morbus Hansen is rarely found in very young children because of the long incubation period before the onset of clinical manifestations [1,3]. Morbus Hansen cases are more common in males than in females. The incidence rate is higher in contacts with multibacillary cases (MB) than in paucibacillary (PB) 5-14 times. Morbus Hansen disease can occur at any age and children are more susceptible to contracting *Mycobacterium leprae* infection than adults [3,6].

An increase in the incidence of Morbus Hansen occurs in people with household contacts with Morbus Hansen sufferers. This disease is transmitted from one person to another through airborne droplets. The spread of *Mycobacterium leprae* can also be influenced by several factors, including socioeconomic status, population density, nutrition, and immune response. The BCG immunization attainment rate in a region also affect this disease [7,8]. This manuscript review which gene had a role in morbus Hansen disease.

## Discussion

### Epidemiology and prevalence

The global Morbus Hansen disease control program which was launched between 2006 and 2010 has successfully collected data on the description of Morbus Hansen cases worldwide, especially data originating from endemic countries of Morbus Hansen. In total, there were 244.796 new cases reported in 2009 (a total of 16.115 new MH cases came from South and Southeast Asia), while in early 2010 there were 211.903 new Morbus Hansen cases worldwide. Currently, Morbus Hansen is endemic in more than 15 countries around the world, but around 83% of Morbus Hansen cases are found in three countries, namely India, Brazil and Myanmar. India accounts for about 64% of all Morbus Hansen cases worldwide [9,10].

Morbus Hansen disease is characterized by a granulomatous inflammatory process in the peripheral nerves and mucosa of the upper respiratory tract and lesions on the skin are the main clinical

signs that can be seen [1,2]. *Mycobacterium leprae* is intracellular, namely in reticuloendothelial cells, for example macrophages and on peripheral nerves, namely on the Schwann cell. *Mycobacterium leprae* infection can also attack the eye and testes [6].

The classic clinical signs of Morbus Hansen play an important role in establishing the diagnosis of Morbus Hansen, although the presence of *Mycobacterium leprae* on skin smears, histopathological features and Polymerase Chain Reaction (PCR) are sometimes needed to assist diagnosis [3]. Morbus Hansen should be suspected in patients with the following signs and symptoms: skin lesions in the form of pale or reddish spots; decrease or loss of sensation in the skin lesions; numbness in the arm or leg; weakness in the arms, legs or eyelids; painful nerves; swelling of the face or earlobes; numb sores on the arms and legs; as well as skin stiffness [1].

Based on the WHO 1997 diagnostic criteria, the diagnosis of Morbus Hansen (MH) was made if there were one or more of the three cardinal signs of Morbus Hansen as follows: numb hypopigmented (or erythematous) skin lesions; thickening or enlargement of the peripheral nerves accompanied by loss of sensation and / or weakness in the muscles it supplies; and the discovery of acid-resistant stem bacteria in skin smears [2,3,10].

### Pathophysiology & clinical manifestation of Morbus Hansen

Hansen's Morbus is a disease that is quite complex and has a clinical picture that varies depending on the type and strength of the body's immune response [2,3]. A strong immunocellular response can effectively inhibit the multiplication of *Mycobacterium leprae* and is associated with PB type MH (paucibacillary). Weak cellular immune response does not inhibit germ replication so that the MB type MH (multibacillary) appears [3].

In 1981, WHO classified MH into MB and PB types according to the degree of positivity of *Mycobacterium leprae* on skin smears. The MB type MH consists of lepromatous leprosy (LL), borderline lepromatous (BL), and mid-borderline leprosy (BB) according to Ridley-Jopling's classification with a bacteriological index of +2 or more for each skin lesion. Whereas PB type MH consists of intermediate leprosy (I), tuberculoid leprosy (TT), and borderline tuberculoid (BT) according to Ridley-Jipley's classification with a bacteriological index <2 for each skin lesion [11].

Intermediate (I) type MH is characterized by multiple hypopigmented macules that may heal spontaneously or develop into other types. MH type TT is characterized by multiple hypopigmented macules, sometimes large and numb, sometimes accompanied by nerve manifestations in the form of enlarged nerves. This type of Hansen Morbus can sometimes heal spontaneously within a few years, sometimes persists and often develops into other types. The BT type MH is similar to the TT type MH but the skin lesions are more numerous and smaller and the peripheral nerve thickening is less common [1].

BB type MH is characterized by many reddish plaques with asymmetric distribution, sometimes numbness and accompanied

by regional adenopathy (enlarged lymph nodes). Meanwhile, BL type MH is characterized by numerous skin lesions, which can be macules, papules, plaques or nodules, may or may not be accompanied by numbness (anesthesia). The early LL-type MH is characterized by symmetrical, diffuse, diffuse macular lesions, sometimes with alopecia. In advanced LL type MH, the nerves are also affected, marked by areas of numbness and limb weakness. Sometimes also accompanied by tissue necrosis and lepromas (skin nodules) [1].

Although the resulting skin lesions are not generally fatal, Morbus Hansen is the most common cause of peripheral neuropathy worldwide. Neuropathy occurs not only due to infection and damage to peripheral nerves caused directly by *Mycobacterium leprae* but also due to inflammatory processes and the body's immune response to infection [2,12].

If left unchecked and untreated, *Mycobacterium leprae* infection will continue to develop and cause permanent damage to the skin, nerves, extremities and also the eyes. *Mycobacterium leprae* infection will cause the fingers and toes to shorten and change shape because the tissue will be absorbed by the body. In 1995, WHO estimated that at least 2 to 3 million people worldwide became permanently disabled because of Morbus Hansen [1].

The clinical and histopathological features of Morbus Hansen's disease depend on the immunological status of the patient at the time of *Mycobacterium leprae* infection and according to disease progression. The body's immune response to *Mycobacterium leprae* varies and gives a clinical picture that changes spontaneously and is called the Morbus Hansen reaction. This Morbus Hansen reaction is also responsible for the permanent nerve damage and deformity caused by the *Mycobacterium leprae* infection. This fluctuating immune response is influenced by several things, including: response to Morbus Hansen treatment, stress, and pregnancy [10,11].

The Morbus Hansen reaction is broadly divided into type 1 and type 2 MH reactions. Type 1 MH reactions (also called reverse reactions: RR) are mediated by type IV hypersensitivity reactions. In this type I reaction, cytokines in the blood will increase, including interferon- $\gamma$  and tumor necrosis factor and CD4 + T cells will be activated. MH type 1 reactions can be found in patients with MH type PB and MH type MB (borderline group) [1,8].

Meanwhile, MH type 2 reaction (erythema nodosum leprosum = ENL) is mediated by type III hypersensitivity reactions, which are characterized by immune complex deposits accompanied by systemic toxicity, increased tumor necrosis factor, and increased neutrophil infiltration and complement deposits in the skin. This type 2 MH reaction can be found in the MB type MH, namely the LL [1,8].

Although in laboratory studies, mice and some primates can be infected by the bacteria *Mycobacterium leprae*, *Mycobacterium leprae* naturally only infects humans. The Morbus Hansen patient is a major source of transmission of the *Mycobacterium leprae* bacteria to other humans. The level of infection in Morbus Hansen patients is related to the population of *Mycobacterium leprae* in these patients. Contact with MH type MB patients increases the risk 5-10 fold for contracting *Mycobacterium leprae*, whereas contact with MH type PB patients increases the risk 2-3 times for acquiring *Mycobacterium leprae* bacteria in individuals who live in endemic areas of Morbus Hansen [8,9].

*Mycobacterium leprae* infection in Morbus Hansen patients is suspected mainly through respiratory tract, but there is also evidence that *Mycobacterium leprae* infection can also be through wounds on the skin. The transmission of Morbus Hansen is suspected through several mechanisms, including: air droplets, child to parent, parent to child, between siblings, length of exposure to Morbus Hansen patients, genetics and environmental conditions [1,3,8].

**Table 1:** Characteristics of every type of Morbus Hansen [10].

Characteristics	Tuberculoid	Borderline tuberculoid	Midborderline	Borderline lepromatous	Lepromatous leprosy
Number of lesions	Single or upto 3	A Few (up to J O)	Several (10-30)	Numerous asymmetrical (>30)	Innumerable, symmetrical
Size	Variable, usually large	Variable, some are large	Variable	Small, some can be large	Small
Surface changes	Hypopigmented	Dry, scaly, look bright, and infiltrated	Dull or slightly shiny	Shiny	Small
Sensations	Absent	Markedly diminished	Markedly diminished	Slightly diminished	Minimally diminished
Hair growth	Nil	Markedly diminished	Markedly diminished	Slightly diminished	Not affected initially
Skin smear	Negative	Negative or 1+	1-3+	3-5+	Plenty, including globi (6+)
Lepromin test	Strongly positive	Weakly positive	Negative	Negative	Negative

## Gene associated of Morbus Hansen disease

Several genes have been studied and are associated with individual susceptibility to infection with the bacteria *Mycobacterium leprae*. Recent studies have shown that Morbus Hansen patients have defects in the cellular immune response that make them more susceptible to infection with the bacteria *Mycobacterium leprae*. Approximately 10 percent of the world's population is actually at risk for developing Morbus Hansen disease. The genes that are thought to be associated with Morbus Hansen disease can be seen in table 2.

**Table 2:** Gen Associated Morbus Hansen Disease [1].

Name	Locus	OMJM	Gene
LPRS1	10p13	609888	
LPRS2	6q25	607572	PARK2, PACRG
LPRS3	4q32	246300	TLR2
LPRS4	6p21.3	610988	LTA
LPRS5	4p14	613223	TLR1
LPRS6	13q14.11	613407	

Contact with a patient with Morbus Hansen is undoubtedly a risk factor for contracting Morbus Hansen disease. 1-15 Risk factors for the occurrence of Morbus Hansen disease include: living in an endemic area of Morbus Hansen, low socio-economic conditions, such as poor living facilities, contaminated water, poor nutrition and other diseases that can reduce the body's immune system [3,16,17].

### Conclusion

Several genes are associated with individual susceptibility to infection with Morbus Hansen Disease. Recent studies have this gene could defects in the cellular immune response more vulnerable to infection with bacteria *Mycobacterium leprae*. These defect came from genes that are thought to be associated with Morbus Hansen disease. Furthermore, research studies must confirm these genes.

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