

Review Article

Genetic Profile of Familial Multiple Sclerosis

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Abstract

The leading cause of motor disability in young adults, multiple sclerosis (MS) is an inflammatory, autoimmune disease of the central nervous system which mainly affects women and usually begins between the ages of 25 and 35. Familial MS accounts for 12.6% of MS cases worldwide. This study aims to provide a comprehensive overview of familial MS, identifying some of the implicated genes through various analytical approaches, and comparing them with the number of candidate genes reported. Over a period of 10 years (2014 to 2024), data on sporadic and familial MS, candidate genes and the genetic analysis methods used to identify them have been collected for 24 countries spread across five continents, with 5 countries (Africa), 8 countries (Europe), 6 countries (Asia), 4 countries (America) and 1 country (Oceania). Like sporadic MS, familial MS has the highest frequency in Canada (32.7%) compared with other countries, and it would appear that the more relatives there are to the affected person, the greater the risk of developing the disease. GWAS has proved to be the most effective and promising analysis method, since it has been able to identify the majority of candidate genes (more than 200).

Key words: MS, Familial, Sporadic, Molecular genetics, Candidate genes.

المخلص

كونه السبب الرئيسي للإعاقة الحركية لدى الشباب، هو مرض التصلب، ومناعي ذاتي يصيب الجهاز العصبي المركزي، ويؤثر بشكل رئيسي على النساء وعادة ما يبدأ بين سن 25 و 35 عامًا. يمثل التصلب المتعدد العائلي 12.6% من حالات التصلب المتعدد في جميع أنحاء العالم. تهدف هذه الدراسة إلى تقديم نظرة عامة وشاملة حول التصلب المتعدد العائلي، وتحديد بعض الجينات المتضمنة من خلال مقاربات تحليلية مختلفة، ومقارنتها بعدد الجينات المرشحة المبلغ عنها. تم جمع بيانات حول التصلب المتعدد العائلي، والجينات المرشحة، وطرق التحليل الجيني المستخدمة لتحديد، على مدى فترة 10 سنوات من 2014 إلى 2024، وذلك لـ 24 دولة موزعة عبر خمس قارات بواقع 5 دول بإفريقيا، و 8 دول بأوروبا، و 6 دول بآسيا، 4 دول بأمريكا، ودولة واحدة بأوقيانوسيا مثل التصلب المتعدد المتقطع فإن التصلب المتعدد العائلي يتمتع بأعلى تكرار له في كندا 32,7% مقارنة بالبلدان الأخرى ويبدو أنه كلما زاد درجة القرابة إلى الشخص المصاب كلما زادت خطورة إصابته بالمرض وقد أثبتت دراسة الارتباط على مستوى الجينوم بأكمله (GWAS) أنها الطريقة التحليلية الأكثر فعالية واعدة، حيث تمكنت من تحديد غالبية الجينات المرشحة أكثر من 200

الكلمات الرئيسية: التصلب المتعدد، عائلي، متقطع، علم الوراثة الجزيئي، الجينات المرشحة.

Introduction

Multiple sclerosis (MS) is an inflammatory, demyelinating and degenerative disease of the central nervous system (CNS). It is a disease of young adults, preferentially affecting women (sex ratio 1/3) and generally occurring between the ages of 25 and 35 (Leprieur, 2019).

Its causes are multifactorial, combining a predisposing genetic background that plays a role in its development with acquired factors, the majority of which appear to be present during childhood and

adolescence (Mathey, 2021). Its risk depends on the degree of genetic proximity to the index case (Balcerac & Louapr , 2022).

In multiple sclerosis, the immune system malfunctions and attacks myelin, a protective sheath that covers many axons. This sheath is made up of concentric clusters of oligodendrocyte extensions, a membrane structure that promotes nerve transmission, increasing its speed up to a hundred times. Therefore, the deterioration of myelin in multiple sclerosis delays the transmission of nerve signals. Inflammation affects certain areas of the nervous system, resulting in plaque lesions that can turn into scars and lead to neurodegeneration.

Multiple sclerosis has a complex and varied epidemiology. The frequency, onset, risk factors and course of the disease differ significantly depending on the populations examined and geographical areas. A deeper understanding of these

factors may help to optimise the prevention, early diagnosis and management of multiple sclerosis (Freysse, 2024)

Whether relapsing-remitting, secondary progressive or primary progressive its main players are T and B lymphocytes (Talmont, 2020). It affects 2.8 million people worldwide, 12.6% of whom have a familial form (Barka, 2018; Balc rac & Louapr , 2021), defined by the presence of another family member affected to the third degree or less (Balc rac & Louapr , 2022). There is a difference in clinical presentation between familial and sporadic cases, with familial forms having a more multifocal onset (Wellek et al., 2011), more relapses, earlier worsening of disability and more severe long-term disability. It should be noted that there is a shorter delay in diagnosis, probably due to awareness of the disease, and there are also more brain lesions detected on MRI (Andrijauskis et al., 2019; Steenhof et al., 2019).

Research into familial forms of multiple sclerosis, particularly that conducted in 2024, corroborates the idea that the disease is not transmitted in a one-dimensional way (such as a single defective gene).

In recent years, extensive research has shed light on some of the mystery surrounding this condition and clarified the immunopathological mechanisms underlying it, particularly the triggering factors. This paves the way for the development of more targeted and effective treatments for this often-devastating disease (Hoballah, 2018)

Also the existence of multiple cases within the same family is due to the confluence of various predisposing genes and environmental influences. Recent research has also established a link between family structures and consanguinity in certain areas, reinforcing the hypothesis of a polygenic genetic involvement (Vahebet et al., 2024).

The aim of this work is to establish a global overview of familial multiple sclerosis and to list the genes responsible as well as the different methods of detecting causal mutations.

Materials and Methods:

The subjects chosen for this study represent all patients in the global population

from families with at least two cases of multiple sclerosis without demographic or ethnic exclusion.

Data collect: The international databases consulted were: Google Scholar, Pubmed, ResearchGate using the following keywords: Multiple sclerosis, sporadic, familial, genes, polymorphism, sequencing. This study was based on epidemiological (Tab. 1 and 2) and genetic (Tab. 3) data recorded in a number of countries around the world over a period from 2014 to 2024 (10 years).

The influence of certain environmental factors such as higher latitude, low serum levels of vitamin D, childhood obesity, infection with the Epstein Barr virus and herpes simplex viruses, smoking and diet (salt, saturated fatty acids) (Dobson, 2019; Librizzi, 2020). This leads us to say that being related to a person affected by this disease and being exposed to the environmental factors mentioned, increases the risk of developing multiple sclerosis compared with that of the general population exposed to the same factors (Lubetzki & Stankoff, 2017; Tizaoui, 2018; Leprieur, 2019; Gouideret et al., 2020).

To this end, in the present study, we attempt to highlight the different genes involved in familial MS, as well as their similarities, detected by different analysis methods, the example of GWAS (Genome-Wide Association studies), WES (Whole Exome Sequencing), ...

Results:

Distribution of Multiple Sclerosis:

Worldwide, the sporadic form of multiple sclerosis is more common than the familial form. Of the 2.8 million people affected, 12.6% have the familial form (Barka, 2018 ; Balc rac & Louapr , 2021).

The figure below (Fig. 01) and Tab. 01 shows the distribution of the sporadic form of MS in a few countries spread across different continents (www.atlasofms.org). It has a heterogeneous distribution (Fig.1), with a relatively high rate in Canada and Denmark and a rather low rate in China, India and Niger, thus confirming epidemiological studies which speak of a high frequency of the disease in Caucasians and a much lower frequency in Asia and sub-Saharan Africa (Leray et al., 2016).

Although MS seems to manifest with greater severity and aggressiveness in patients of North African origin (Gouider et al., 2020), epidemiological data from this region remain limited.

In this study, we aim to point out the genes linked to familial MS and show their similarities, using different analysis methods such as GWAS and WES

Table 1 Distribution of sporadic MS in selected countries worldwide (www.atlasofms.org).

	Country	Population	Patients	Proportion (1patient/inhabitants)	Reference
Africa	Algeria	44,18 millions	15000	1/3000	www.atlasofms.org
	Tunisia	12,26 millions	3251	1/5000	
	Egypt	109,3 millions	59671	1/1500	
	Nig�ria	213,4 millions	10048	1 /20000	
	South Africa	59,39 millions	4685	1 /12000	
Europe	France	67,75 millions	100000	1 /700	
	Belgium	11,59 millions	12000	1 /1000	
	Romania	19,12 millions	8000	1 /2500	
	Denmark	5,857 millions	17747	1/300	
Asia	Iran	87,92 millions	86256	1 /1000	
	China	1,425 billion	42440	1 /34000	
	India	1,428 billion	145800	1 /9500	
	Russia	143,4 millions	78914	1 /2000	
America	Canada	38,25 millions	90000	1 /400	
	United States	331,9 millions	400000	/	
	Brazil	214,3 millions	40000	1/5500	
	Australia	25,69 millions	25607	1/1000	

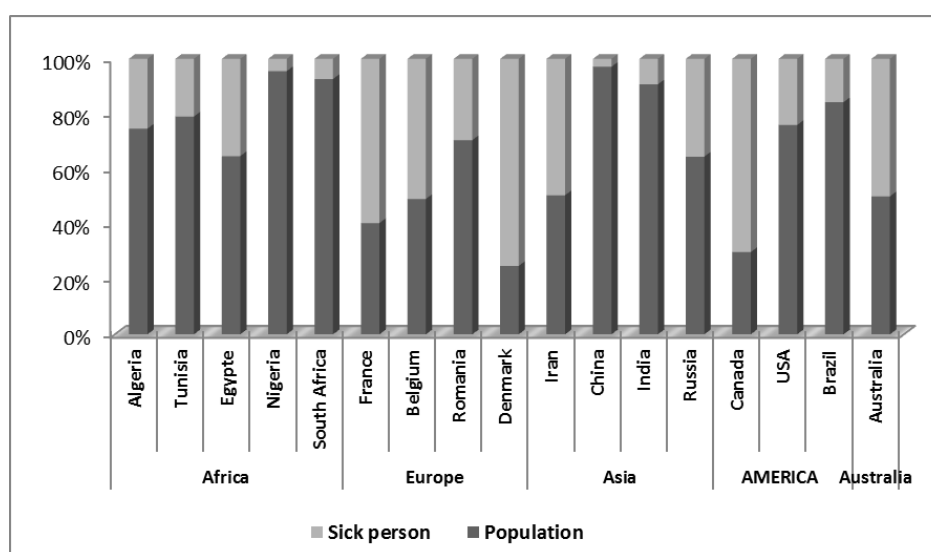


Figure 01. The sporadic form in a number of countries around the world.

Like sporadic MS, familial MS has a heterogeneous distribution (Tab. 02); for example, the rate is 32.7% in Canada, 29% in Finland, 28.7% in Croatia and Slovenia (Relatively high), 21% in Saudi Arabia, 12.2% in Iran, 10.4% in Qatar (Moderately high); 6.12% in Brazil, 3.3% in Mexico and 2% in Hungary (Low) (Harirchian et al., 2018). This form remains high in Caucasians, moderate in North Africans and much lower in Asians and sub-Saharan (Cambron, 2015; Hentati et al., 2018; Harirchian et al. 2018; Gouider et al., 2020).

Table 2: Distribution of familial forme of MS in some countries around the world

	Country	Familial MS (%)	Number of patients studied	References
Africa	Algeria	5%Blida	806	Gouider et al.2020 Benyahia, 2019
		9,2%Oran	291	
		14,2%Tlemcen	450	
	Tunisia	4,1% à 5,5%	27	Ben Chihi,et al.,2023
Europe	Belgium	20%	152	Cambron, 2015
	Finlande	29%		Harirchian et al., 2018
	Croatia	28,7%		Harirchian et al., 2018
	Hongrie	2%		Harirchian et al., 2018
	Slovania	28,7%		Harirchian et al., 2018
	Iran	19%		Harirchian et al., 2018
Asia	Saudi Arabia	21%		Harirchian et al., 2018
	Qatar	10,4%		Harirchian et al., 2018
	Canada	32,7%		Harirchian et al., 2018
America	Brazil	6,12%		Harirchian et al., 2018
	Mexico	3,3%		Harirchian et al., 2018

Although it is not hereditary, there are genetic factors favorable to its development, as highlighted by a number of epidemiological studies revealing that 15 to 20% of affected patients also had an affected family member.

Genetic Factors

The importance of genetic inheritance was established following the observation of a 10 to 15-fold increase in risk among children with one parent affected by multiple sclerosis (Mathey G.)

From a genetic point of view, it is clear that the worldwide prevalence of MS varies according to geographical area (Damotte, 2014). Namely, very high in North America and Europe and rather low in East Asia and sub-Saharan Africa.

It has been pointed out that in cases of familial MS, the disease may be transmitted from generation to generation, so a genetic influence would be more obvious, which would explain the higher frequency of this condition observed in relatives of people with the disease (Sawcer, 2014; Leray et al., 2016; Leprieur, 2019). The genetic contribution to the risk of developing MS is currently estimated at around 50% (Fagnani et al., 2015; Balc rac & Louapr , 2021) and patients with at least one relative affected are estimated at 20% (Damotte, 2014).

According to Leprieur A. 2019, for a person with MS, first-degree relatives have a risk of developing the disease of around 3% (i.e. 4% for siblings, 2% for children and 2% for parents). The risk is about three times higher than that of second- or third-degree relatives (around 1%), and 10 to 30 times greater than in the general population (0.1–0.3%). The risk increases further when both parents are affected. Finally, an estimate of around 30% has been demonstrated for monozygotic twins. This implies that the risk of the disease developing in relatives of the affected person increases with the amount of

genetic material shared (Leprieur, 2019).

Recently, using GWAS analysis, 233 candidate genes have been recognized for MS, including 32 genes that are part of the major histocompatibility complex, 200 have been found in somatic chromosomes and only one carried by the X chromosome (IMSGC, 2019) and appear to contribute to a significant risk for the development of this disease. This supports the multifactorial nature of MS, as the results indicate a higher prevalence in men, despite epidemiological studies reporting the opposite. Such findings point to a significant hormonal influence in disease expression.

In this research, the study, which focuses on the analysis of rare RNAs, shows that in some individuals with MS, abnormal gene expression in immune cells responsible for destroying pathogens is associated with abnormalities in the Integrator complex, a protein complex essential for the maturation of non-coding RNAs. Because of this problem, the RNAs generated from the DNA sequences that regulate gene expression are longer and more numerous. These sequences, also known as 'enhancers', are partly derived from ancient viruses, which have been tamed and exploited by the cell to better regulate gene expression. Therefore, the imperfect maturation of enhancer RNAs could explain the regular production of viral genes in patients with MS. However, the Integrator complex also has an impact on the activity of RNA polymerase II, the enzyme responsible for transcribing genes that code for proteins. Without effective action by the Integrator, RNA polymerase II triggers transcription more often, but encounters difficulties in completing it. This promotes the expression of short genes, such as those related to inflammation, while longer genes, which are essential for the preservation of endothelium, among other things, are not fully transcribed, thus jeopardizing their expression, so there is less integrator activity in MS patients.

Consequently, many transcriptional observations in MS patients can be explained by the same phenomenon, which greatly enriches our understanding of this complex disease (CNRS Biologie, 2024).

several analysis methods were used to detect different genes. This is described in Table 03.

Analysis Methods Used:

GWAS (Genome-Wide Association studies)

Genome-wide association studies are a technique that enables rapid analysis of markers across the DNA of several individuals, making it possible to identify genetic variations relating to specific traits or diseases.

Using this method, the genome is examined in its entirety to identify single nucleotide polymorphisms (SNPs) that could be associated with certain diseases such as neurodegenerative diseases, heart disease, diabetes and asthma. For some diseases, this would enable prevention, while for others it would enable early treatment and a better therapeutic strategy.

Whole Exome Sequencing (WES):

Whole Exome Sequencing (WES) allows the analysis of all protein coding sequences in the human genome.

Whole exome sequencing (WES) is widely used and is being progressively optimized for the detection of rare and common genetic variants in humans (Belkadi et al., 2015).

Whole exome sequencing is used to perform massive screening of structural and regulatory genes to identify allelic frequencies of disease-associated polymorphisms in diverse populations and detect possible mutations or polymorphisms leading to defective protein sequences. In this way, exome sequencing now makes it possible both to diagnose monogenic diseases (MD) and to examine apparently healthy populations to reveal potential risks before the disease manifests itself (Oleget et al., 2023).

Exome sequencing (WES) is effective for study diseases, as exonic regions can contain up to 85% of

functional variants responsible for disease, even though they represent only 2% of the entire genome (Jacob, 2020).

Table 3. Distribution of analysis methods used for the detection of some candidate familial MS genes throughout the world.

Country	Analysis Methods	genes	Chromosomes	References
CANADA	WES	MASP1	3	Vilariño-Güell et al., 2019
		PLAU	10q22.2	
		C2	6p21.33	
		NILRP12	19q13.42	
		UBR2	6	
		CTNNA3	10q21.3	
		NFATC2	16p11.2	
		RNF213	17q25.3	
		NCOA3	20q13.12	
		SLC24A6	12q24.13	
		SLC8B1	12q24.13	
		KCNG4	16q24.1	
		P2RX4	12q24.32	
		P2RX7	12q24.31	
		GALR2	17q25.3	
AUSTRIA	WES	NLRP1	17	Zrzavy et al., 2020
		DPH3	3	
		MBP	18	
		INPP4B	4	
		ThyN1	11	
		NFAT5	16	
IRAN	qPCR	TTC21A	3	Khalilian et al., 2021
		YAP1	11q22.1	
		TAZ		
		CRB3	19	
ALGERIA		VDR	12q13.11	Bourokba et al., 2015
		HLA DRB1*		
		HLA DRB1*07	6p21.3	
		HLA A26		
		HLA B18		
AUSTRALIA, UK, US, EUROPE	GWAS	HLA B40		Cotsapas, 2018
		IL2	4q27	
		IL7R	5p13.2	
		GALC	14	
		TYK2	19	
		NLRP8	19	
		PRF1	10	
		PRKRA	2	
		HDAC7	12	

The Major Histocompatibility Complex (MHC) has been recognised for several years as the main genetic locus linked to MS, in particular the HLA-DRB1*15:01 class II allele which, in addition to its significant susceptibility, was the first to be associated with this pathology, making it the predominant genetic risk factor while being responsible for practically 50% of the genetic predisposition. (Patsopoulos et al., 2017; Tizaoui, 2018; Leprieur, 2019; Librizzi, 2020) with an additive effect in the case of homozygous genotype (Hollenback et al., 2015; Song et al., 2019; Balcerac & Louapre, 2022); this allele is found in the following haplotype: HLA DRB1*15:01 DQA1*01:02 DQB1*06:02 HLA-DR2 which represents an association of genes located close to each other and often transmitted together, this haplotype is often present in leucoderms (30%) with a clear female predominance.

It is likely that the HLA-DRB1*15 01 allele may have a common affinity for two structural proteins, an EBV protein (EBNA1) and a myelin protein (MBP), so this allele (HLA DRB1*15 01) transforms the influence of certain environmental factors; The odds ratio for smoking is 2.8 for the development of MS

in carriers of this allele and 1.4 in non-carriers; in addition, the herpes simplex virus increases the risk of MS in patients who do not carry the HLA DRB1*15 01 antigen (Balcerac & Louapre, 2022).

Other chromosomal locations have been identified, most of which are involved in immune system mechanisms. These genes code for other HLA class I or II serotypes (DRB1 or not), or other immune system molecules (receptors for interleukins, tumor necrosis factor, etc.) (Tizaoui, 2018; Mathey, 2021; Balcerac & Louapre, 2022).

Through whole-exome sequencing (WES) conducted by Carles Vilariño-Güell in 2019, twelve genes of the innate immune system responsible for regulating the transcription and activation of inflammatory mediators were identified as likely pathogenic variants associated with MS. These variants have been identified in genes for fibrinolysis and complement pathways (PLAU, MASP1, C2), inflammasome assembly (NLRP12), Wnt signalling (UBR2, CTNNA3, NFATC2, RNF213), nuclear receptor complexes (NCOA3) and cation channels and exchangers (KCNG4, SLC24A6, SLC8B1). These genes are thought to be responsible for disrupting interconnected immunological and pro-inflammatory pathways, while contributing to the initial event in the pathophysiology of familial MS.

The GWAS analysis carried out by the research team of the International Multiple Sclerosis Genetics Consortium recognized the involvement of 233 genes, one of the candidate genes found being carried by the X chromosome.

Using the same analysis method (whole exome sequencing), a research study conducted by Tobias Zrzavy in 2020, in Austria, on 4 families with a history of multiple sclerosis, identified other candidate genes (DPH3, MBP, INPP4, ThyN1, NFATS, TTC21A).

The qPCR technique was used on 13 families, some of whose members had this condition and who were followed up at the neurology department of the CHU Annaba (north-east Algeria) in 2015 (Bourokba et al., 2015). This team demonstrated (by comparing affected vs. unaffected individuals) a significant rate of DRB1*01 allele frequency (33.3% vs. 12% $p = 0.05$) DRB1*07 (25% vs. 6% $p = 0.05$) A26 (12.5% vs. 0% $p = 0.03$) B18 (29.1% vs. 2% $p = 0.001$) and B40 (12, 5% vs 0% $p = 0.03$) were found, while the DRB1*15 alleles (0% vs 26% $p = 0.006$) A24 (8.3% vs 40% $p = 0.005$) and B35 (16.6% vs 42% $p = 0.03$) had a protective effect on multiple sclerosis susceptibility in this sample.

Furthermore, a qPCR analysis conducted in an Iranian population by Sheyda Khalilian and colleagues in 2021 identified additional genes (YAP1, TAZ, CRB3, and VDR), each implicated in MS through distinct mechanisms. For example, the VDR (vitamin D receptor) gene encodes the vitamin D receptor protein, which enables the body to respond to vitamin D. This vitamin contributes to cerebral activity in the embryonic and adult brain, by helping the connectivity of neuronal circuits responsible for locomotor and emotional behavior. Low serum levels of VD have been observed in patients suffering from Alzheimer's disease, Parkinson's disease and multiple sclerosis.

The work carried out for this study is complex and requires a meticulous approach.

This work is essential to advance our understanding of the mechanisms responsible for familial MS and the differences that exist around the world.

In this systematic review, certain limitations must be noted, the most notable being the significant difference in population size between countries that have been the subject of genetic studies on familial multiple sclerosis.

Conclusion:

Multiple sclerosis is a complex chronic disease, neurodegenerative which is the leading cause of acquired motor disability in young adults. It is thought to be due to a genetic predisposition combined with environmental factors: infection by the Epstein-Barr virus, smoking, serum vitamin D levels, childhood obesity and eating habits (Dobson, 2019; Librizzi, 2020; Gouider, et al., 2020).

According to Professor Gourraud P.A. (2021), even though genetic knowledge of this disease has clearly evolved, it would be impossible to say whether or not an individual will develop multiple sclerosis on the basis of genetic data alone, since some patients have all the known genetic markers while others do not. Genetic studies are currently needed to improve prevention, diagnosis, management and treatment of the disease, in order to reduce the frequency and severity of relapses, slow disease progression and relieve symptoms. It is important to emphasize that the genes and polymorphisms associated with MS

must take into account the ethnic aspect, which plays an important role in calculating the risk of predisposition to the disease. This leads us to say that it is imperative for countries where a GWAS has not been carried out not to use the results of other countries to assess the risk in their patients, especially if they are of a different ethnic group.

Of all the genetic studies carried out by researchers, GWAS is still the only one to have identified the most candidate genes (233 genes), which leads us to conclude that the genome-wide association study is the most conclusive.

Reference

- Andrijauskis, D., Balnyte, R., Keturkaite, L., Vaitkus, A. Clinical and diagnostic features of patients with familial multiple sclerosis. *Medical hypothesis review* Revue volume 131 :109310 . DOI : 10.1016/j.mehy.109310 (2019).
- Atlas of MS 3rd edition <https://www.atlasofms.org/map/global/epidemiology/number-of-people-with-ms> (2022).
- Balcerac, A. Louapre, C. Genetics and familial distribution of multiple sclerosis *Neurological Review* Volume 178, Issue 6, 512-520 (2022).
- Barka Bedrane, Z., Saadi, K., Reguig, A., Louhibi, C., Boudjelal, M., Allal, S. & Bouchenak Khelladi, D. Caractéristiques cliniques et profil évolutif de la sclérose en plaques familiale à l'extrême ouest d'Algérie *Neurological review*, Volume 174, additionnal 1, p.S91, ISSN 0035-3787, <https://doi.org/10.1016/j.neurol.2018.01.206> (2018).
- Belkadi, A., Bolze, A., Itan, Y., Cobat, A., Vincent, Q., Antipenko, A., Shang, L., Boisson, B., Casanova, J.L. & Abel, L. Whole genome sequencing is more powerful than whole exome sequencing for detecting exome variants. Ref : 25827230 PMCID : PMC4418901 DOI : 10.1073/pnas.1418631112 (2015).
- Benyahia, H., et al. "Sclérose en plaques familiale : Caractéristiques cliniques et évolutives dans l'ouest algérien à propos de 64 cas." *Revue Neurologique*, vol. 175, no. 10, 2019, pp. 696-702. DOI: 10.1016/j.neurol.2019.06.012.
- Ben Chihi, F., Derbali, H., Chnitir, S., Messelmani, M., Bedoui, I., Mansour, M., Zaouali, J., Mrissa, R., L'héritage Que Personne n'a Demandé ! Caractéristiques Cliniques de la Sclérose en Plaques Familiale Service de Neurologie, Hôpital Militaire Principal d'Instruction de Tunis. *Revue Neurologique*, Volume 180, Supplement, April 2024, Page S14
- Bourokba, S., Retima, A., Lakehal, M., Merriche, H., Guediri-Merriche, S., Ouelaa, H. & Toubal, N. Sclérose en plaques familiale et typage HLA : à propos de 24 patients algériens. *Revue Neurologique* Volume 171, Supplement 1 Page A62 <https://doi.org/10.1016/j.neurol.2015.01.137> (2015).
- Cambron, B. Formes familiales de sclérose en plaques : caractéristiques démographiques, cliniques et paracliniques. Faculté de médecine et médecine dentaire, Université catholique de Louvain. Prom.: VanPesch, Vincent. <http://hdl.handle.net/2078.1/thesis:39080> (2015).
- CNRS Biologie. Sclérose en plaques : un défaut dans la lecture des gènes mise en évidence chez les patients (2024).
- Dobson, R. Giovannoni, G. Multiple sclerosis - a review. *European Journal of Neurology*. Jan;26(1):27-40. Doi: 10.1111/ene.13819. Epub 2018 Nov 18. PMID: 30300457 (2019).
- Drai, R. Etude clinique et profil évolutif des patients suivis pour une sclérose en plaques au niveau du CHU de Blida, avec une estimation de la prévalence dans la commune de Blida. Thesis in Medicine, Blida University, Algeria, 262p (p101) <https://di.univ-blida.dz/jspui/handle/123456789/9693> (2018).
- Fagnani, C., Neale, M.C., Nisticò, L., Stazi, M.A., Ricigliano, V.A., Buscarinu, M.C., Salvetti, M. & Ristori, G. Twin studies in multiple sclerosis: a meta-estimation of heritability and environmentality. *Multiple sclerosis journal*, Volume 21 , number 11, pp. 1404 – 1413. <https://doi.org/10.1177/1352458514564492J> (2015).

- Freysseline, L. La rééducation cognitive dans la prise en charge de la sclérose en plaques : Enjeux et impact sur le quotidien des personnes. Mémoire de fin d'études. 63p (p15) Université de Limoge, Institut Limousin de FORMation aux MÉtiers de la Réadaptation Ergothérapie. (juin 2024)
- Gouider, R., Mrabet, S., Sidhom, Y., Kacem, I., Lubetzki, C. & Papeix, C. Specific characteristics of multiple sclerosis in North Africa: Role of genetic and environmental factors. *Bulletin de l'Académie Nationale de Médecine* Volume 204, Issue 4, pp.421-427 (2020).
- Gourraud P.A. Susceptibilité génétique à la sclérose en plaques : Les connaissances actuelles <https://www.sep-ensemble.fr/lasep-c-est-quoi/susceptibilite-genetique-a-la-sep> (2021).
- Guillaume M. Nouvelle histoire “naturelle” de la sclérose en plaques à l'ère des nouvelles classifications et des thérapeutiques. Médecine humaine et pathologie. Université de Lorraine, 2021. Français. fNNT : 2021LORR0367ff. ffiletel-04452731f HAL Id: tel-04452731 <https://theses.hal.science/tel-04452731v1> Submitted on 12 Feb 2024).
- Hirichian, M.H., Fatehi, F., Sarraf, P., Honarvar, N.M. & Bitarafan, S. Worldwide prevalence of familial multiple sclerosis: A systematic review and meta-analysis. *Review Mult Scler Relat Disord.*;20:43-47 doi: 10.1016/j Epub Dec 24. PMID: 29291483.(2017).
- Hentati, E., Ben Sassi, S., Nabli, F., Mabrouk, T., Zouari, M., Hentati, F., Disability progression in multiple sclerosis: a Tunisian prospective cohort study *Neurol Sci*, 39 (5) (2018), pp. 879-884.
- Hoballah N. La sclérose en plaques : histoire, physiopathologie et thérapeutiques actuelles thèse présentée pour l'obtention du titre de docteur en pharmacie diplôme d'état . Faculté de pharmacie de grenoble le: 27/08/2018 148P. p26.
- Hollenbach J.A., Oksenberg J.R. The Immunogenetics of Multiple Sclerosis: A Comprehensive Review. *J Autoimmun.* (2015) Nov;64. pp13–25.
- International Multiple Sclerosis Genetics Consortium. Multiple sclerosis genomic map implicates peripheral immune cells and microglia in susceptibility. *Science*. Sep 27;365(6460):eaav7188. doi: 10.1126/science.aav7188. PMID: 31604244; PMCID: PMC7241648 (2019).
- Jacob, A. Apport du séquençage d'exome pour le diagnostic et le traitement des maladies complexes. Médecine humaine et pathologie. Université de Lille. Français. fNNT : 2020LILUS011ff. ffiletel-03267865f (2020).
- Khalilian, S. , Hojati, Z. , Dehghanian, F., Shaygannejad, V, Hosseini Imani, S.Z., Kheirollahi, M., Khorrami, M., Mirmosayyeb, O. Gene expression profiles of YAP1, TAZ, CRB3 and VDR in familial and sporadic multiple sclerosis in an Iranian population. 11: 7713. doi: 10.1038/s41598-021-87131-z PMCID: PMC8032816 PMID: 33833274 (2021).
- Léocadie, A. and Segard, S. La génétique : les techniques et les outils de séquençage en biologie clinique <https://doi.org/10.1016/j.irbmnw.2024.100576>.
- Leprieur, A. Sclérose en plaques : la maladie et les avancées thérapeutiques. P. 6-9-10-11- ffdumas-02459204 (2019).
- Leray, E., Moreau, T., Fromont, A., Edan, G. Epidemiology of multiple sclerosis. *Rev. Neurol* (Paris).172(1):3-13.PMID: 26718593 DOI : 10.1016/j.neurol.2015.10.006 (2016).
- Librizzi, T. Sclérose en plaques : prise en charge globale et accompagnement du patient à l'officine. Sciences pharmaceutiques. P: 30-33-34-37-38-39-40 dumas-03035129 (2020).
- Magy, L. Épidémiologie de la sclérose en plaques. Dossier: Nouvelle ère pour la sclérose en plaques *La revue du praticien* 72 (4) P.: 379-416 https://santepsy.ascodocpsy.org/index.php?lvl=bulletin_display&id=30289 (2022).
- Mathey, G. Nouvelle histoire “naturelle” de la sclérose en plaques à l'ère des nouvelles classifications et des thérapeutiques. Médecine humaine et pathologie. Université de Lorraine, 2021. Français. fNNT : 2021LORR0367.
- Oudrer-Tabti, N. Profil clinico-épidémiologique et évolutif de la sclérose en plaques à Oran. Thèse de doctorat en sciences médicales, université d'Oran. <https://theses.univ-oran1.dz/document/1012018002t>. (2018).

- Oleg, S. Glotov, Alexandre, N. Tchernov, Andreï, S. Glotov. Human exome sequencing and perspectives of predictive medicine: analysis of international data and our own experience. PMID: 37623486 PMCID: PMC10455459 DOI: 10.3390/jpm13081236 (2023).
- Sawcer, S. Franklin, R.J.M. Ban, M. Génétique de la sclérose en plaques Volume 13, Issue 7P700-709 July. 2014. PMID: 24852507 DOI : 10.1016/S1474-4422(14)700419(2014).
- Song, J., Westerlind, H., McKay, K.A., Almqvist, C., Stridh, P., Kockum, I., Hillert, J., Manouchehrinia, A.J. Familial risk of early- and late-onset multiple sclerosis: a Swedish nationwide study. *Journal of Neurology* 266(Suppl 195) DOI:10.1007/s00415-018-9163-6.
- Steenhof, M., Stenager, E., Munk Nielsen, N., Kyvik, K., Möller, S., Hertz, J.M., Familial multiple sclerosis patients have a shorter delay in diagnosis than sporadic cases PMID: 31078918 DOI: 10.1016/j.msard (2019).
- Talmont, F., Hatzoglou, A. et Cuvillier, O. La sclérose en plaques et les médicaments immuno-modulateurs des récepteurs de la sphingosine 1-phosphate. Multiple sclerosis and immuno-modulators of sphingosine 1-phosphate receptors. *Med Sci (Paris)* 2020 ; 36 : 243-252 DOI <https://doi.org/10.1051/medsci/2020026>
- Institut de pharmacologie et de biologie structurale, UMR 5089 CNRS, Université de Toulouse, 205 route de Narbonne, 31077 Toulouse, France.
- Tizaoui, K. Multiple sclerosis genetics: Results from meta-analyses of candidate-gene association studies. *Cytokine* 106:154-164. doi: 10.1016/j.cyto.2017.10.024. Epub 2017 Nov 2. PMID: 29103823 (2018).
- Vaheb, S. Panah, MY. Afshari-Safavi, A. Moases Ghaffary, E. Shaygannejad, A. Shaygannejad, V. Mirmosayyeb, O. Role of parental consanguinity and familial aggregation in development of multiple sclerosis: a case-control study Publication : *European Journal of Medical Research*, volume 29, article n°503. Date : octobre 2024 DOI : 10.1186/s40001-024-02094-x.
- Vilariño-Güell, C., Zimprich, A., Martinelli-Boneschi, F., Herculano, B., Wang, Z., Matesanz, F., Urcelay, E., Vandenbroeck, K., Leyva, L., Gris, D., et al (2019). Exome sequencing in multiple sclerosis families identifies 12 candidate genes and nominates biological pathways for the genesis of disease. *PLoS Genetics*, 15(6), e1008180. <https://doi.org/10.1371/journal.pgen.1008180>
- Wellek, A., Korsukewitz, C., Bach, J.P., Schock, S., Eienbröcker, C., Seitz, F., Spengler, A., Hemmer, B., Schlegel, K., Oertel, W.H., Sommer, N., Tackenberg, B. Sibling disability risk at onset and during disease progression in familial multiple sclerosis. *Mult Scler J*. PMID: 21561958 DOI: 10.1177/1352458511405088 (2011).