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Stroke, Epidemiological and Genetical Approach

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1. Introduction

Current knowledge in genetics has began increasingly to reveal the complexity of the interaction between various risk factors. The purpose of this chapter is to present knowledge about stroke, particularly the role of genetic components as risk factors.

Despite remarkable progress in the recent years in the field of the management and treatment of Cerebral Vascular Accident (stroke), the latter remains a major cause of mortality and morbidity in many countries. In fact, it is admitted that even though the majority of strokes has been not fatal sofar, it has often been responsible for functional deficits (motor, visual and cognitive). Stroke is very common in industrialized countries (Casas J et al, 2007) and is the third leading cause of death in North America, Japan and China (Xiao Yuxin et al, 2009) (Table 1). The annual incidence in Canada is about 1/1000, and soars to 10/1000 after age 65. This incidence is much higher in Europe, (7/1000 in France, 5.6/1000 in Portugal) (Roshan Ariyaratnam et al, 2007) (Table 2).

Population	Stroke deaths Per 100 000 Population	Year of Publication *
Spain	39.2	2005
France	27.7	2006
Italy	31.9	2006
Portugal	96.1	1999
Germany	34.5	2006
Japan	56.3	2007
China	160.1	2000
Korea	93.1	2006

Table 1. International Death Rates of Stroke (Donald Lloyd-Jones et al. 2009).

Population	Stroke Incidence Per 1000	Publication*
UK	1.8	Alexander H et al, 2000
France	7.6	Lemesle M et al, 1999
Italy	2.7	Carolei A et al, 1997
Portugal	5.6	Correia M et al 2004
Germany	3.5	Kolominsky-Rabas PL et al 1998
Sweden	3.1	Johansson B et al 2000

Table 2. Stroke incidence study in Europe (Truelsen T. et al, 2006.)

In developing countries, this incidence is less well known due to the lack of adequate management of stroke patients. However, the data currently available show a frequency similar to those reported in some industrialized countries (Fig 1). They illustrate clearly that stroke is a major public health problem (Table 3). In Morocco, the incidence of stroke is estimated to 0.4 /1000 with 25% of death cases *(Stroke colloquium 2009.*

Population	Incidence Per 1000
Kuwait	0.8
Saudi Arabia	0.9
Bahrain	0.4
Qatar	0.4
Libya	0.65
Tunisia	0.54

Table 3. Stroke incidence study in Arab countries. (Hani TS Benamer et al, 2009)

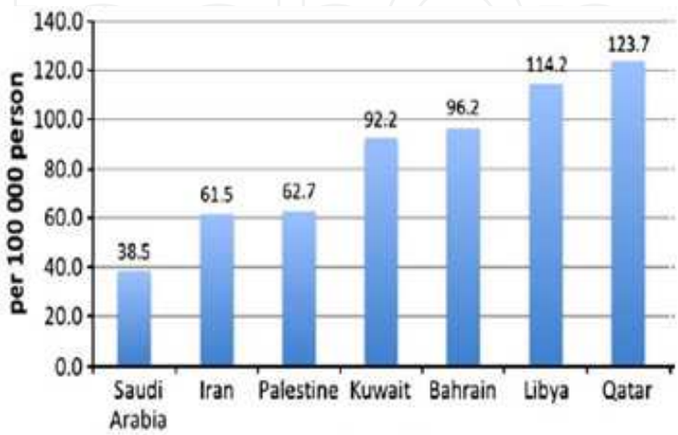


Fig. 1. Incidence rates of stroke in the Middle East and north of Africa (Tran J et al 2010)

1.1 Definition and types of stroke

Stroke is defined by the World Health Organization (WHO), on the basis of a clinical and pathophysiological approach, as "a rapid installation of neurological deficit, with symptoms lasting 24 hours or more, associated to focal or global cerebral dysfunction, that can be fatal, and the apparent cause of which is vascular" (Asplund et al, 1988). This definition encompasses a broad category of strokes:

Ischemic stroke: accounts for 80% of all strokes (M. Dichgans, 2007)
Hemorrhagic stroke (20% of all strokes) (AG Thrift, 2001),
Brain blood vessels disorders.
Ischemic strokes are related to a complete or incomplete lack of blood supply. They include ischemic stroke (AIC) and transient ischemic attack (TIA).

Stroke is thought of as a syndrome which represents a collection of disease processes all of which resulting in cerebral ischaemia. The different processes have different clinical phenotypes and different etiological mechanisms. Many symptoms can occur in stroke but not simultaneously. They depend on stroke localization in the brain and on vascular damage (Table 4).

SYMPTOMS	MANIFESTATIONS
Cognitive Disturbance	For many people, a clinical stroke elicits symptoms involving cognition. If one were to suffer a stroke, they may begin to feel dizzy or lightheaded. They may also suffer a loss of coordination, have trouble forming sentences or even lose consciousness.
Vocal Disturbance	Besides having a difficulty with words and sentences, it is also possible for a stroke to impede one's ability to speak, causing them to slur or garble their words.
Visual Disturbance	For others, a stroke causes some sort of visual disturbance, including a blurred, doubled or darkened vision. These may either be momentary or prolonged.
Mobility Issues	Sometimes, a stroke causes sudden mobility issues, triggering a paralysis or numbness to either the right or left side of the body.
Headaches	Though a headache alone is not a sure sign one is having a stroke, it is one of the common symptoms, especially when accompanied by pain or stiffness within the neck and face as well as digestive distress.
Digestive Distress	Often associated with the symptom of a headache, a stroke can cause one to experience a sudden nausea that often triggers vomiting.

Table 4. Clinical Stroke Symptoms (American Society of Neurology, 2007)

The International Classification TOAST (Table 5), classified strokes into five groups based on etiologic mechanisms (Adams et al, 1993). A subtype classification has been recommended for genetic association studies (Dichgans et al, 2005). Increasing evidence suggests that different subtypes of stroke may have both different degrees of heritability and genetic risk factor profiles.

Etiology	Caractéristique	REF
Atherosclerosis	The arteries of large and medium caliber seats of choice: the origin of the internal carotid artery, the carotid siphon, the origin and termination of the vertebral artery and the aortic arch.	(Markus et al 2001).
Lacunar Stroke	Occlusion of these arteries is responsible for brain deficiencies (small deep infarct <1.5 cm in diameter). They are located in the subcortical areas, mainly in the basal ganglia, capsules, and the brain stem). It has been suggested as an explanation to the thrombosis process, an overactive clotting in predisposed patients or an abnormality in blood vessels.	(Ward et Brown, 2002
Cardioembolic Stroke	Heart diseases that can cause embolic ischemic stroke are numerous. Atrial fibrillation is the heart disease most commonly involved (50% of cases), followed by ischemic heart disease and valvular heart disease.	(Warlow et al 2001
Indefined Stroke	Many other conditions may be responsible for stroke such as arterial dissection, arterial different nature dysplastic, inflammatory or infectious diseases or blood clotting abnormalities	(Milandre et al 1998).

Table 5. Stroke international Classification TOAST (Dichgans, 2004).

1.2 Stroke pathophysiology

In the medical literature, the term stroke refers to different events with a common pathophysiology, associated to subclinical atherosclerosis, or thromboembolic disease (MTE). As a multifactorial disease, stroke results from the synergistic combination of several risk factors, some of which are still unknown. (Fig 2)

In ischemic strokes, reduced blood flow causes a set of events that influence the severity of cerebral infarction (Lawrence R. Wechsler et al, 2011). These events are the result of interaction between vascular and cellular elements which lead to the release of amino acid neurotransmitters and to the increase in circulating calcium and free radicals. In addition, oxidative stress and inflammation contribute to the process of cellular damage and ischemia. These events have contributed to the emergence of the new concept "neurovascular unit" including astrocytes, neurons and vascular structure.

Studies of the experimental model and the analysis of brain imaging showed that brain damage depends on the infarction's duration. Thus, the areas affected by the infarct remain viable for 24 hours with the possibility of recovery after revascularization.

A phenotypic complexity is added with a gene-gene, gene-environment interactions component. The identification of environmental and genetic factors that predispose to stroke is a major research target for a better understanding of the pathophysiological mechanisms of the disease and for modulating its prevention and treatment.

1.3 Risk factors

1.3.1 The traditional risk factors

Age is the most important risk factor. The incidence of stroke doubles in men and women after 55 years of age (Wolfe 2000; Yannick Bejot, 2007). Smoking appears to increase the risk of stroke (MP Jones, 1990; Anthony Behin, 2002). However, this risk is reversible after 5 years of cessation. Tobacco may act through different mechanisms including endothelial cytotoxicity, mitogenic effect on the media, platelet activation, blood hyperviscosity, and lowering HDL blood rates (Bhat, VM, 2008). Alcohol increases the risk of hemorrhagic (relative risk × 6) or ischemic stroke (relative risk × 3) (Lowenfels, Albert B., 2000, Hart C, 1999). In addition, dietary factors play a role as well. A diet high in cholesterol, saturated fat and low in fruits, vegetables and fish increases the risk of stroke (Brigham and Women's Hospital. 2005), while a large consumption of vitamin C and folate would reduce its impact by an anti-oxidant effect and the reduction of homocysteine concentration. (Homocysteine Lowering Trialists' Collaboration, 1998). Studies, cohort and case-control, demonstrated that lack of exercise is associated with an increased risk of stroke. Such an effect could act, at least partially, by reducing blood pressure. (Chong Do Lee, 2003). Ethnicity: it is admitted that there is a genetic and environmental heterogeneity between races (Jun Z. Li, 2008, Neil Risch, 2002). Significant differences in incidence and stroke subtypes distribution have been reported among different ethnic groups (Dawn M. Bravata, 2005). The incidence is greater among African Americans and African Caribbeans versus Caucasians in the United Kingdom (Gillum et al, 1999). Personal or familial history is the best documented risk factor. In fact, the familial forms of stroke have been known since a long time (Voetsch B et al. 2003; Hassan A, 2002). The risk of stroke is higher in people with family history. (Duanping Liao, 1997). Hypertension is a major risk factor, it is present in 40-85% of patients with cerebral infarction and in 80% of those with a cerebral hematoma (Hu G, Sarti C, 2005) regardless of sex and age (Collins et MacMahon, 1994; Niclot P, 2003; HironoriImano, 2009) Similarly, diabetes mellitus increases by 2-5 the risk of stroke (B Stegmayr, 1995) (Mats Eliasson, 2003, Hu G, 2005, A Rautio, 2008). The increase in total cholesterol and low density lipoprotein (LDL-C) was strongly correlated with the risk of ischemic heart disease. (Toth PP , 2005).

1.3.2 The emerging risk factors

A number of case-control studies have shown an association between infection and acute ischemic stroke (Grau et al. 1995; IY Bova, 1996; Benoît Guillon, 2003; A. Paganini-Hill, 2003). The association is not specific to a particular type of infection resulting in a prothrombotic state and acute endothelial dysfunction (HC Emsley, 2008). Many cross-sectional and prospective studies have shown that chronic inflammation is a risk factor and suggest to assess this risk by measuring C-reactive protein and proteins of the inflammatory reaction (PIR), (Danesh et al. 2000, Ridker et al. 2000). This systematic search does not meet the consensus of professionals (Fifth Conference of the American Heart Association '(AHA) (Pearson et al, 2004). Other factors including psychosocial factors and some hormonal treatments have been implicated. Currently, there is a recent increasing interest in adhesion molecules such as the vascular endothelial growth factor (VEGF). It is one of the main factors controlling the development and maintenance of the vascular system in humans (angiogenesis). Indeed, high levels of circulating VEGF have been observed in cases of ischemic diseases such as stroke [Hojo et al. 2000; Blann et al, 2002). Currently targeted therapies, using VEGF, are undergoing clinical trials (Buysschaert et al, 2007).

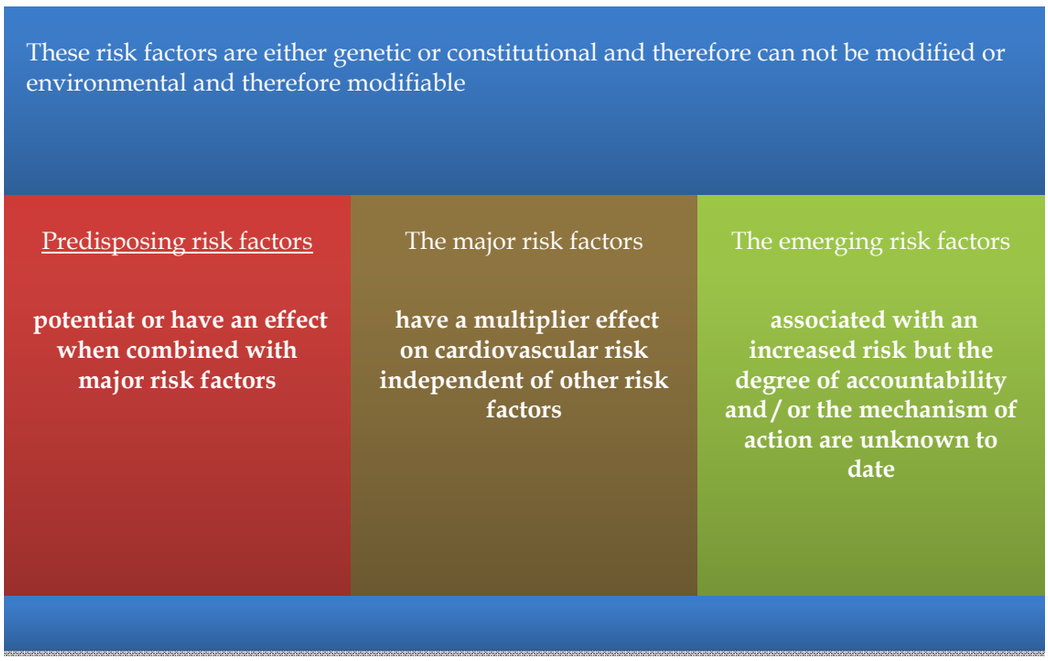
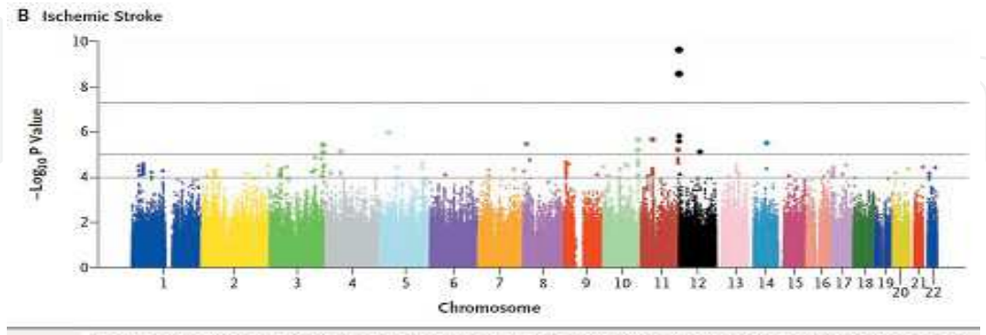


Fig. 2. Synthesis of stroke risk factors

2. Genetics of stroke

The genetics of complex diseases has known a great progress in recent years. The" Human Genome Project" is an international initiative that has enabled the sequencing of the human genome in its entirety as well as the discovery of SNP (Single nucleotide polymorphisms) which had a great success for association studies (Fig 3). The second initiative was the "HapMap project" which helped to develop a haplotype map of the human genome and allowed to describe the most common polymorphisms and the linkage disequilibrium blocks. It is currently a key for conducting further research on new genes and on both their association to disease and their response to drugs.



Results of Tests for the Association between Stroke and Each SNP Measured in the Genomewide Association Study.

P values (based on the fixed-effects model) are shown in signal-intensity (Manhattan) plots relative to their genomic position for total stroke (Panel A) and ischemic stroke (Panel B). Within each chromosome, the results are plotted left to right from the p-terminal end. The top horizontal line indicates the chosen threshold for genomewide significance, $P = 5 \times 10^{-8}$; the middle line indicates the threshold for $P = 10^{-5}$; and the bottom line indicates the threshold for $P = 10^{-4}$.

Fig. 3. Results of the association of stroke with SNP tested in GWAS (GWAS project,2009)

Apart from some rare Mendelian forms, most strokes are considered as multifactorial disease. The hypothesis of a genetic origin of stroke was based mainly on the observations of several family cases with a non-Mendelian transmission. In the Framingham project, the existence of a family history (paternal or maternal origin) of stroke was associated with an increased risk of this disease in the descendants (D. Kiely Ket al, 1993). This familial aggregation could be only the consequence of conventional risk factors like hypertension, diabetes and hypercholesterolemia. The strongest evidence has been reported by twins studies, and animal models (Rubattu S et al, 1996) (Table 6). These studies showed that the prevalence of stroke was multiplied by five in monozygotic twins compared to dizygotic (Flossmann E et al 2004, Jeff s Bet al 1997, Brass LM and al,1992).

Type of study (n)	Odds ratio (95% CI)	p-value	Stroke subclassified
Twin studies	1.65(1.2-2.3)	0.003	No
Cohort studies	1.30 (1.2-1.5)	<0.00001	2 studies
Case-control studies	1.76 (1.7-1.9)	<0.00001	15 studies

Table 6. Odds Ratios of a positive family history in different types of studies (Flossmann E et al 2004)

2.1 Rare Mendelian etiologies responsible for stroke

Many monogenic Mendelian diseases, be they autosomal dominant, autosomal recessive or X-linked, may be complicated by stroke in young patients without known risk factors (s Jeff B, 1997, Rolfs A et al, 2005, JA, Hess et al, 2006) (Table 7). Knowledge of these Mendelian forms is important. It helps in genetic counseling to identify patients at a presymptomatic stage in families with risk factors and, to discuss a preventive approach or treatment.

If expressed in the homozygous state, stroke may occur at an early stage (sometimes in infancy). Whereas, in the heterozygous state, the consequences of the genetic defect may be mild or even indistinguishable from conventional risk factors' effects. (Perry IJ et al. 1995.). Apart from this disease, cerebral autosomal dominant arteriopathy (CADASIL), sickle cell disease, Fabry disease (deficiency of lysosomal alpha-galactosidase) and mitochondrial diseases as MELAS syndrome are probably the most common metabolic causes of stroke.

CADASIL: The cerebral autosomal dominant arteriopathy with leukoencephalopathy and subcortical infarcts is a hereditary autosomal dominant cerebral arteriolopathy. Notch 3 gene was located on chromosome 19 (Tournier-Lasserve E, 1993), and the first mutations were identified in 1996 (Joutel A, 1996). The disease has been described in different families of European, African, North African, American (Arcos-Burgos OM, 2001), Indian, and Asian origin (Kotorii S, 2001). But its prevalence remains largely under-estimated, about 1 to 24,000. It occurs on an average of 42 years of age (Chabriat H, 1996, Chabriat H, 1997, Chabriat H, 1995), with extremes of 20 and 65 years (Chabriat H, 1995, Desmond DW, 1999, M Dichgans, 1998).

	diseases	Frequence	transmission	GENE	
metabolic diseases	-Fabry disease (Neuropathic pain, cardiac failure, cataract, renal failure, reduction of α-Gal enzyme activity, mechanisms of ischemic stroke unknown -Mitochondrial diseases (MELAS, Development delay, sensorineural hearing loss, short stature, seizures, migraine. Pathophysiolog disruption of the blood-brain barrier a decrease in cerebral blood flow autoregulation of primary defects in neuronal oxidative metabolism - homocystinuria, -sulphite oxidase deficiency - aciduriesméthylmalonique, propionic	Frequent Frequent Frequent Frequent? Occasional	XL Mat. AR MT,AD ,AR AR		GAL Mitoc hondr ial
Coagulopathies :	deficiency of factor V Leiden (resistance to activated protein C) Sneddon's syndrome (familial syndrome of antipholipides) fibrinogen deficiency deficiency of factor VIII, IX, X and VIII deficit in protein C, S	Frequent? Frequent Frequent Occasional	AD AD AR ARLX, AR AD		
neuro-cutaneous syndromes	Telangiectasies heorragic hereditary (Rendu-Osler-Weber) -syndrome de Bannayan-Zonana -sclérose tubéreuse de bourneville -neurofibromatose de type I -syndrome de Van Hippe I-Lindau	Frequent Occasional Rare Rare Rare	AD AD AD AD AD		
Primary disease of the cerebral vessels	fibromuscular dysplasia pseudo - xanthoma type I -Ehlers-Danlos disease (particularly type IV) cerebral-amyloidosis Icelandic type (deficiency cystatineC) Dutch type (B deficiency protein precursor amyloidal, APP B) cerebral vascular malformations, arterial dissection, familial forms of cavernous angioma adult polycystic kidney disease (APKD1 and APKD2) syndrome of arterial dissections and lentigines	Frequent Frequent Frequent Frequent Frequent Rare ? Rare Frequent	AD AD, AR AD, AR AD AD AD AD AD		

CADASIL	Migraine with aura is the principal sign, PATHOPHYSIOLOGY abnormal drainage of the portion of the Notch extramembranous 3 protein accumulation of the fragment extramembranous vessels	Frequent	AD	NOT CH3
Sickle-cell disease	Clinical feature Pain crisis, bacterial infection, VasoOclusive Crisis, pul Pathophysiology Deformation of red blood cell intimal hyperplasia proliferation of smooth muscle cells thrombosis. monary and abdominal crises, anaemia, myelopathy, seizure	Frequent	AR	HBB

Table 7. Etiologies responsible for rare mendelian stroke (Natowicz M et al, 1987)

Sickle cell disease is a common cause of stroke in children (JA Switzer, 2006), either in its homozygous or compound heterozygous form with hemoglobin C (HbC) or α-thalassemia (Old J. 2002). Hemoglobin S is due to a mutation by substitution of adenine for thymine in codon 6 of the β-globin gene on chromosome 11p15.4, resulting in the substitution of a valine by a glutamic acid in the protein chain. This alteration of the protein causes a deformation of the red cell that becomes sickle-shaped. Brain stroke appears to be a consequence of an abnormal interaction between sickle red blood cells and vascular endothelium (JA Switzer, 2006; Hebbel RP, 2004). The sickled red cells tend to clump together and adhere to the endothelium. The endothelial activation further promotes remodeling of the arterial wall and vascular disease. The typical atherothrombotic stroke is often located in the internal carotid artery and the proximal, middle and anterior portions of cerebral arteries. It is associated with hyperplasia of intima, fibroblasts proliferation and smooth muscle cells. (Stockman JA et al 1972). Many patients develop lacunar small-vessel disease (JA Switzer, 2006; J Schatz, 2002).

Fabry disease is a lysosomal disease, due to a deficiency of α-galactosidase A enzyme (GLA). Most patients are carriers of missense and nonsense mutations, large and small rearrangements or splicing defects in the coding region of α-galactosidase gene on the X chromosome (GLA) (Desnick et al 2001, Schaefer, 2005; Human Gene Mutation Database). Clinical signs include an acroparesthesia, angiokeratoma, and hypohidrosis, which often develop in childhood or adolescence before the systemic complications leading to heart and renal failure and ischemic stroke (Rolfs A et al 2005; Crutchfield KE et al 1998, Grewal RP et al 1994; Mitsias P et al, 1996). Ischemic stroke predominates in the vertebrobasilar circulation (Rolfs A, 2005).

MELAS syndrome: Mitochondrial Encephalomyopathy, Lactic Acidosis, and Stroke-like episodes, is a mitochondriopathy caused by many mutations, transmitted by maternal inheritance in mitochondrial DNA (Pavlakis SG, 1984, Martinez-Fernandez E, 2001). Over 80% of patients carry the A3243G mutation; an A to G transition at position 3243 of the gene MT-TL1. MELAS syndrome is associated with various symptoms. However, in monosymptomatic cases, ischemic stroke is the only existing expression (Martinez-

Fernandez E, 2001). In MELAS, the episodes of ischemic stroke are different from those of a typical cerebral infarction with the cortex being always involved.

Primitive genetic diseases of the cerebral vessels: an increasing number of genetic diseases of the cerebral vessels responsible for stroke have been identified in the last few years. Fibromuscular dysplasia is characterized by the presence of dilatations in small and medium arteries due to the destruction of the media, fibrosis and muscular hyperplasia. The occurrence of aneurysm rupture is a relatively common event in various forms of Ehlers-Danlos disease; especially type IV that is characterized by a deficiency of collagen type 3. Some forms of amyloidosis are characterized by a predominantly cerebral localization of amyloidal deposits in the vessels causing hemorrhagic or ischemic stroke. These disorders are genetically heterogeneous; some are due to mutations in cystatin C (an inhibitor of several cysteine proteinases), others are due to mutations in the precursor of the beta-amyloid protein (beta-APP) (Levy E et al. 1990, M. Abrahamson, 1992).

2.2 Stroke model of multifactorial disease with polygenic component

More than 2300 candidate polymorphisms are currently listed in association with stroke (Matthew B et al, 2010). These factors have been listed on the bases of their involvement in known metabolic pathways or through pangenomics studies. Most of them have been analyzed in different populations by association studies. The genes studied are typically those involved in the coagulation (Fig 4), homocysteine and lipid metabolism. Among those genes, the most explored with consensus were: FV, FII, MTHFR, ApoE, ACE (Fig 5) and fibrinogen, PAI1. Others have been explored without consensus (Enos, PON, LPL, FGA / FGB / FGG, F7, F13A1, vWF, F12, SERPINE1, ITGB3, PLA2, ITGA2B, ITGA2, GP1BA, AGT, NOS3, LPL, PON1, PDE4D, ALOX5AP, MTR, CBS, NINJ2) (Bersano et al. 2008). The results published today are often controversial depending on the population studied, the age of patients and stroke subtypes.

a- Factor V Leiden Mutation: is one of the most studied thrombotic variants. It is the main genetic risk factor for deep vein thrombosis. (JP Casas, 2004; Ye Z, 2006, Paluku T, 2011). Several meta-analyses were conducted to study the association between FVL and stroke. The results are controversial and are population age dependent; this Association was absent in Morocco (Paluku et al, 2011), weak in Asia (Jul K, 2002, Kim RJ, 2003). It is found highly significant with an OR of 1.33 (95% CI, 1.12 to 1.58) in the Caucasian population (Casas JP, 2004, Paul Bentley et al.).

The data published on the FV Leiden mutation showed a great diversity in geographical repartition. it is very common in Europeans, with a north-south gradient: 4.4% in the UK versus 1.7 % in Italy and is absent in sub-Saharian Africans and East-Asians. For Arab populations in the eastern basin of the Mediterranean, this mutation is high especially in Jordan (12.3%) (AWID, 1999), Syria (13.6%) (Irani-Hakim, 2000) and Lebanon (14.2%) (Irani-Hakim 2000, 2002 Tamim). Prevalence decreases as the distance from these regions of the Mediterranean basin increases. It is present in Tunisia, Algeria, and absent in Morocco (Mathonnet F, Nadifi S. et al, 2002). This geographical difference in the Maghreb could be explained by the region's history, including the presence of the Ottoman Empire (Turkish) since the XVIth century in Tunisia and Algeria (Cavalli et al, 1994), but not in Morocco (Mathonnet F, Nadifi S 2002). This mutation is probably due to a founder effect, which

would have occurred in the eastern Mediterranean sea, 21000 to 34000 years ago (Zivelin 1997) and spread across the migration flows to other parts of the world (Castoldi 1997, Irani Hakim, 2000).

b- Mutation G20210A of prothrombin gene: Prothrombin G20210A mutation is considered as the second cause of inherited thromboembolic disease. This mutation is found at the heterozygous state in 4 to 8% of subjects with a first episode of venous thrombosis. The estimated relative risk is 2-7 times higher in carriers (De Moerloose, 2000, Emmrich 2001, Paluku et al, 2011). The homozygous forms are rarely observed (0.014% -0.0025%) (Poort SR, 1996) and risk associated with homozygosity is currently unknown. The mechanism of hypercoagulability is due to an increase in the formation of thrombin. However, there are conflicting results in the role of the G20210A prothrombin gene in ischemic stroke pathogenesis.

c-: fibrinogen: Studies have shown a strong link between high plasma fibrinogen and stroke (Wilhelmsen L, 1984 Gregory W. Albers 2009). The relative risk was estimated to 2.06 (1.83-2.33) (CO Fibrinogen Studies, 2005). This relationship is controversial because the levels of fibrinogen are influenced by tobacco, obesity, diabetes, inflammation and infection (L Wilhelmsen, 1984, Rothwell PM, 2004).

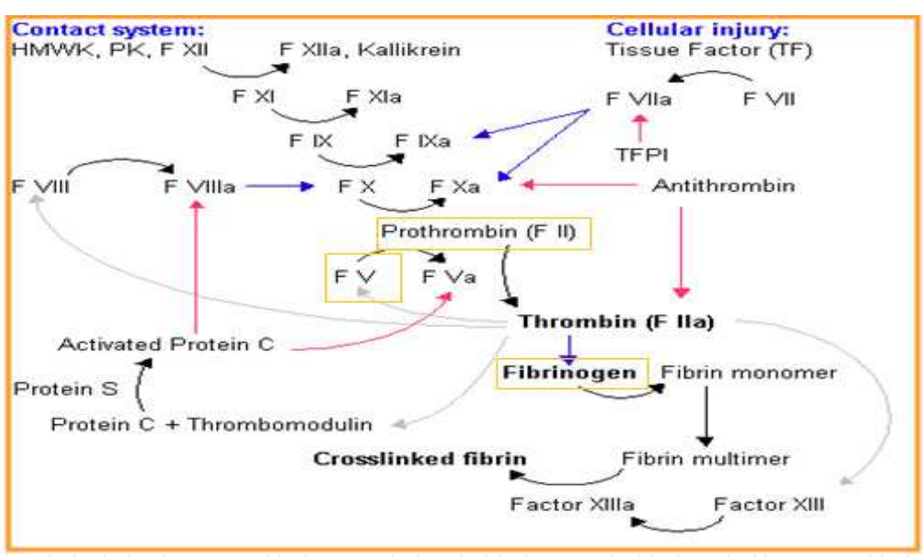


Fig. 4. Schema of cascade of coagulation with different factors

d- Mutations in the PAI1 gene: The Plasminogen activator inhibitor type 1 (PAI1) is a potent inhibitor of fibrinolysis (Dichgans et al, 2008). It was shown that a high activity of PAI1 is associated with an important cerebral risk and coronary vascular disease (Casas JP et al 2004). The 4G/5G polymorphism in the PAI1 gene promoter is most frequently studied in association with stroke (Roshan A et al, 2007). The data of association studies (Case-control) were not unanimous about the involvement of the 5G polymorphism in stroke (Dichgans, 2008).

e- Molecular mechanism of C667T Variant of MTHFR gene: The 5, 10-methylenetetrahydrofolate reductase (MTHFR) is an enzyme catalyzing the reduction of 5, 10 - methylenetetrahydrofolate (MTHF), to 5-MTHF, which is the predominant form of

folate. The MTHFR gene is located in 1p36.3 (Goyette et al, 1994). It comprises 11 exons and extends over a length of 2.2 Kb (Goyette, 1998). The C667T mutation makes the protein thermolabile and its enzymatic activity is reduced by half (Frost, 1995). The presence of this mutation in the homozygous state affects folate metabolism and induces a moderate elevation of plasma homocysteine. The C677T mutation of the MTHFR gene has been extensively explored in association studies with stroke; based on strict criteria such as age, stroke subtypes. An association was found between the TT genotype and stroke; it was stronger when the subject is young, with significant OR (Corin 2005, Xiao2009, KT Moe, 2008, Paluku, Nadifi S. et al 2010). Subjects with the TT genotype had higher homocysteine levels and fewer circulating folate than those with CC genotype. (BM McQuillan, 1999; Deloughery TG, 1996, Ma J, 1996, Schwartz SM 1997, L Brattstrom, 1998))

f- Polymorphism insertion/deletion (I/D) ACE gene: The insertion/deletion polymorphism in the angiotensin-converting enzyme gene (ACE) is one of the most common genetic variants studied in relation with atherosclerotic vascular disease. A relative risk of 1.5 to 4 had been reported in association between this polymorphism and ischemic stroke (Cambienet al. 1992). However, other studies have failed to find significant association. This result can be explained by the high frequency of this polymorphism in the population (> 90%). (Catto A, 1996, Dikmen M, 2006, Doi Y, 1997, Pera J, 2006, Tuncer N, 2006, Gao X, 2006; Lin JJ, 2000, Pullicino P, 1996, Ueda S, 1995)

g-The gene for apolipoprotein E (ApoE): The apolipoprotein E gene is one of the most widely studied in vascular and neurodegenerative disease (JE Eichner, 2002). Several meta-analyses reported controversial results between the ApoE4 allele and the risk of ischemic stroke. This association appears to be weak in Asian patients (Xi, 2009) (Benerje, 2007), absent in Italy and Turkey (Cerrato P, 2005, Duzenli S, 2004),). So, the exact role of Apo E4 polymorphism in ischemic stroke is uncertain probably due to the variability of its distribution in populations around the world.

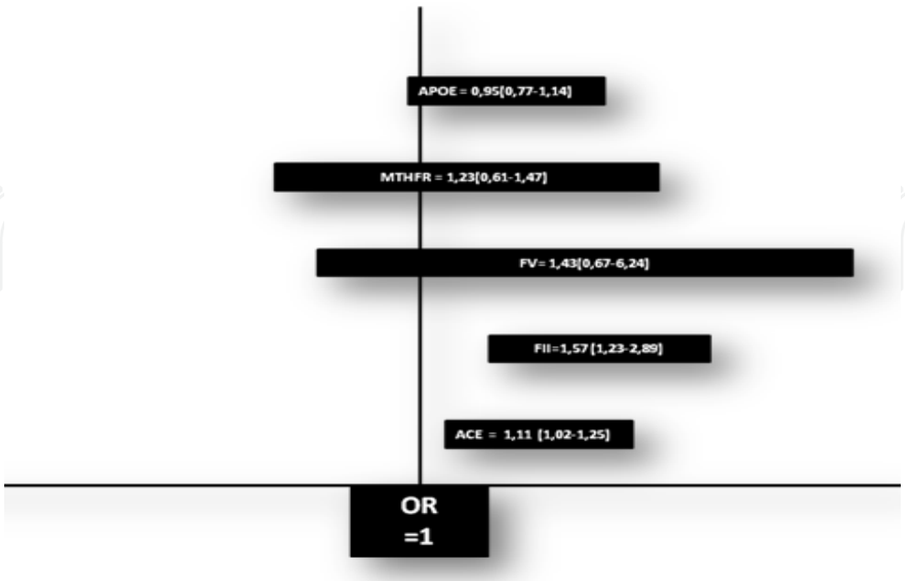


Fig. 5. Panel of 5 Genetic Factors with Degree of Association With Stroke. (Nadifi et al, 2011, Indian Journal of human genetics IJHG57-11)

h-the Phosphodiesterase 4D gene (PDE4D): The PDE4D is the first gene found by linkage in stroke Iceland patients; an association of SNPs of the PDE4D (83T / C) and (-889C / T) was reported, with an increased risk of developing stroke (Nan et al Li1. 2010). Other studies have led to conflicting results. There are few studies limited to a small number of patients. Thus, it is premature to conclude the association of PDE4D gene with stroke and its role in the stroke pathogenesis. In fact, it would be interesting to study larger series of different populations. Therefore, experimental studies on the function of PDE4D will help to unveil the mystery (E Lõhmussaar et al, 2005)

I-5-lipoxygenase-activating protein gene" gene: The locus13q12 ALOX5AP gene is involved in the metabolism of leukotrienes and atherosclerosis. HAPA is the most frequent polymorphism described. It has been associated with increased risk in stroke compared to controls (Helgadottir A, 2004). These results were found only in a Scottish study (Helgadottir A, 200, Meschia JF, 2005).

j-Other candidate genes and pathways have been studied for possible association with ischemic stroke. They are listed in the webtable (www.Genome.org) or discussed in reviews (Table 7). Those genes are involved in inflammation (interleukine 1, interleukin 6, TNF, Toll-like receptor 4, P-selectin and E-selectin, C-reactive protein), and lipid metabolism (apolipoprotein E, paraoxonase III; ApoA1, Apo A5…). (Table 8)

3. Conclusion and outlook

Stroke is an excellent research model for complex multifactorial disease; involving many risk factors (constitutional, environmental and genetic).

Historically, the epidemiological studies were based on a 'candidate gene' approach, defined by the knowledge of pathophysiology (table 9). The advent of Genome-Wide Scan (GWS) had permitted the emergence of new hypothesis in physiological pathways and novel biomarkers. The Genome Wide Association Studies had revolutionized the understanding of disease etiology and risk factors. However, they are still in their beginning and haven't yet incorporated complex statistical data that woul allow us to understand gene-gene (epistatsis) and gene-environment interactions.

These studies could be a major challenge that requires the collaboration of several centers and the elaboration of large clinical and epidemiological databases.

The genetic origin of stroke had been widely studied but many questions are still unsolved. Among them, the cumulative effect of identified mutations, the gene-gene, gene-environmental interactions that modulate the genetic effect represent a big mystery that still needs to be elucidated. The underestimated heritability of the risk factors is probably due to a deficiency in the clinical information and genetic modeling. The influence of all these factors is not only additive, or dominant/recessive, but also interactive. Epidemiological studies had largely explored the genetic mechanisms in a classical approach based on pathophysiology knowledge. But, there are probably other unknown mechanisms that could be explained by « pangenomics hypothesis free ». In this way, many metabolic pathways and novel variants involved in vascular diseases have been identified. Currently, only 12% of SNPs are located in coding regions. The majority of SNP (40% in intergenic regions, 40% in introns) may have a role in regulating the expression of these genes (Hardy et al. 2009, Hindorff et al. 2009]). In addition, gene-environment interactions are largely missed in the

genome-wide approaches. The presence of functional genes is not sufficient to the occurring of a subject phenotype in the absence of environmental stimuli.

Type of factor	Factor	Gene	Polymorphisms	Association
Coagulation system	Factor V Leiden	F5	c.1691G>A	Possible
			c.4070A>G	Uncertain
	Prothrombin	F2	c.20210G>A	Possible
	Fibrinogen	FGA	c.4266A>G	Uncertain
		FGB	c.148C>T	Not demonstrated
			c.455G>A	Not demonstrated
	Factor VII	F7	A1/A2	Not demonstrated
			c.10976G>A	Not demonstrated
			c.323_324insCCTATATCT	Not demonstrated
			c.402G>A	Not demonstrated
			c.401G>T	Not demonstrated
	Factor XIII	F13A1	c.143G>T	Not demonstrated
			p.Pro564Leu	Not demonstrated
	Von Willebrand factor	VWF	Sma I	Uncertain
			c.1423C>T	Not demonstrated
			c.1793C>G	Not demonstrated
	Factor XII	F12	c.46C>T	Uncertain
Fibrinolytic system	Plasminogen activator inhibitor 1	SERPINE1	c.675_676delinsG	Possible
			c.1053 G>T	Not demonstrated
Platelet receptor	GpIIb–IIIa complex	ITGB3	GPIIIa PLA2	Not demonstrated
			GPIIIa c.1691G>A	Not demonstrated
		ITGA2B	GPIIb HPA-3	Not demonstrated
			GPIIb p.Ile843Ser	Not demonstrated
	Gp Ia-IIa Complex	ITGA2	GPIa c.807C>T	Not demonstrated
			GPIa c.873G>A	Not demonstrated
	GpIb/IX/V Complex	GP1BA	HPA2 c.3550C>T	Possible
			VNTR	Not demonstrated
			GPIb (–5) T/C Kozak	Possible
Renin-angiotensin-aldosterone system	ACE	ACE	g.11417_11704del287	Possible
	Angiotensinogen	AGT	p.Met174Thr	Not demonstrated
			p.Met235Thr	Not demonstrated
Homocysteine and eNOS metabolism	eNOS	NOS3	g.3726_3834insGAAGTCTAGACCTGCTGCGGGGGTGAG	Uncertain
			c.894G>T	Uncertain
			c.786T>C	Uncertain
	Hcy	MTHFR	MTHFR c.677C>T	Possible
			MTHFR c.1298A>C	Not demonstrated
		CBS	CBS c.844_845ins68	Not demonstrated
			CBS c.833T>C	Not demonstrated
		MTR	MTR c.275A>G	Not demonstrated
Lipoprotein metabolism	APOE		ε2, ε3, ε4	Possible
		APO ε2, ε3, ε4	p.Cys112Arg	Not demonstrated
			p.Arg158Cys	Not demonstrated
	LPL	LPL	S447X	Not demonstrated
			p.Asp9Asn	Not demonstrated
			c.1127A>G	Not demonstrated
			c. 93C>T	Not demonstrated
	PON1	PON1	p.Gln192Arg	Uncertain
			p.Leu55Met	Uncertain
			c.107C>T	Uncertain
Linkage-association studies	PDE4D	PDE4D	SNP 39-44-56-83-87-89	Uncertain
	5-lipoxygenase-activating-protein	ALOX5AP	HAP A	Uncertain
			SG13S106 - SG13S89	Uncertain

Table 8. Final panel of genetic factors with different degrees of association with stroke. (A. Bersano, et al 2008)

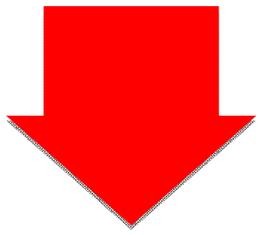
Finally, the understanding of stroke physiopathology and genetics requires developing more efficient tools:

Implementation of an epidemiological case-control study focusing on large populations in different ethnic groups.

Genotyping multiple deleterious polymorphisms in several genes.

In perspective, the development of pharmacogenetics has emerged recently as a promising area of research. For example, warfarine, an oral anticoagulant, is prescribed to millions of patients for cardiovascular problems and that causes many difficulties to determine the effective dose. The polymorphisms in the CYP2C9 and VKORC1 gene influence individual susceptibility response to warfarine. The genotyping of VKORC1 gene showed a strong association and researchers started treatment strategies according to individual patients genotypes.

Functional candidate gene approach
It takes into account their functions in physiological or metabolic pathways.
It starts with a hypothesis and the association between candidate gene and phenotype is sought. This approach involves a study of case-control association of unrelated individuals.
The study of association of a genotype or allele and complex disease with comparison of frequencies in patients and controls.
In SNP association studies in several stroke criticisms were made after many difficulties to reproduce the results published by other researchers (Hirchhorn et al.)
It is essential to apply strict criteria and standardized, as a good selection of genetic polymorphisms in which the candidate gene not only intervene in a pathophysiological pathway, but in which the SNP is real, supported by data on the function.
Finally, it should have large samples for the allele frequencies and odds ratios OR Dichgans and Marcus,



Positional candidate gene approach or positional cloning
is to locate regions of the genome containing susceptibility genes without prior knowledge of its function, except for certain diseases only. When a connection has been well identified, the gene will be cloned and lsa start function can be determined (Risch, N. and Merikangas, KR 1996). Linkage studies are most effective for identifying genes that have a significant effect (Lander, E. 1994).
The analysis of a link between two loci is tested by calculating the LOD score, a statistical analysis that compares the probability that the loci are linked
More than two loci are close to each other, the less likely it is that there is a recombination between the two during meiosis. If they are removed, the alleles of both loci will be sent randomly.
By convention, a LOD score above 3 states the obvious connections, while a LOD score less than -2 indicates no connection, and a score between -2 and 3 can never confirm or reject a bond in a single test.
When linkage analysis is done across the whole genome multipoint LOD score is used. This analysis is not limited only to enumerate all the markers genetically close but calculates allele frequencies of the markers used. This approach by mapping the entire genome suggests significant LOD scores exceeding + 3.3 (Lander, ES 1994).

Table 9. Design of studies on molecular genetics of stroke.

4. Conflicts

None.

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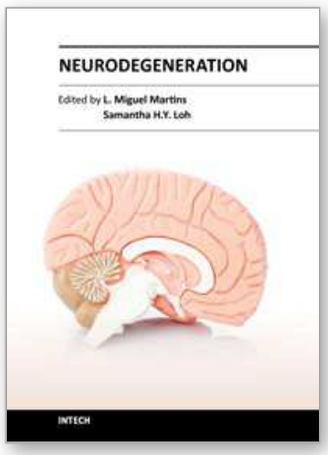

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Currently, the human population is on a collision course for a social and economic burden. As a consequence of changing demographics and an increase in human individuals over the age of 60, age-related neurodegenerative disorders are likely to become more prevalent. It is therefore essential to increase our understanding of such neurodegenerative disorders in order to be more pro-active in managing these diseases processes. The focus of this book is to provide a snapshot of recent advancements in the understanding of basic biological processes that modulate the onset and progression of neurodegenerative processes. This is tackled at the molecular, cellular and whole organism level. We hope that some of the recent discoveries outlined in this book will help to better define the basic biological mechanisms behind neurodegenerative processes and, in the long term, help in the development of novel therapeutic approaches.

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