

## Review Article

## Genetics of Glioblastoma in Moroccan population: Review of literature

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## ABSTRACT

Glioblastoma is the most aggressive malignant type of central nervous system tumors. The literature review revealed that the most common genetic abnormalities in primary and secondary glioblastomas are IDH1 / 2 mutations, p53 mutations, and overexpression of EGFR.

To our knowledge, this is the first Moroccan study to provide a global picture of genetic studies performed on Moroccan patients to describe genetic markers and their frequency in our population.

An in-depth research in ScienceDirect and Pubmed on glioblastoma articles treated in Morocco, this research is based on the following keywords: glioblastoma in Morocco, primary glioblastoma in Morocco, secondary glioblastoma in Morocco.

We found only three research articles on genomic alteration of IDH1 / 2, p53 and EGFR expression. The frequency of these gene mutations in our population was similar to those reported from other populations.

Additional molecular studies need to be performed on other genes to describe other genetic markers in the Moroccan population.

## Introduction

The glioma accounting for about 45% of brain tumors, is the most common neoplasm of the central nervous system, representing 81% of malignant brain tumors in all of the world (Ostrom et al., 2014). It is classified according to the World Health Organization (WHO), according to their cell of origin, these include astrocytic tumors (astrocytoma grade I–IV), oligodendrogliomas (WHO grade II–III) and oligoastrocytomas (WHO grade II–III).

The glioblastoma multiforme (GBM) is one of the most malignant brain tumors in humans, accounting for 60% of all brain tumors in adult (Rock et al., 2012). The primary glioblastoma (*de novo*) is the most frequently and progress rapidly in elderly patients (> 45 years), contrariwise the secondary glioblastoma develops from the anaplastic astrocytoma or low-grade diffuse astrocytoma in younger patients (< 45 years) (Ohgaki and Kleihues, 2013).

The overall incidence is less than of 10/100 000 and It occurs more in males than in females (Hanif et al., 2017). The cancer registry in Morocco has no data on the incidence of the central nervous system. On the other hand, GBM is associated with a poor prognosis. Despite aggressive surgery, radiation, and chemotherapies with temozolomide, the average life of survival still ~ 1 year (Dong et al., 2014). The progress in the treatment modalities, it remains incurable. Among the most frequently observed genetic abnormalities in glioblastoma multiforme are overexpression and amplification of epidermal growth factor

receptor (EGFR) with or without activating mutation and loss of PTEN expression, IDH 1/2 and p53 genes mutation, and the loss of the arm 10q (Ines Crespo et al., 2015). The consequences of altering the signaling pathways of these genes, cause uncontrolled cell proliferation, enhanced cell survival and decrease apoptosis (Jian Chen, Renée M. McKay, 2012).

The IDHs enzymes (IDH1, IDH2, and IDH3) play role in the citric acid cycle, convert isocitrate to  $\alpha$ -ketoglutarate with the conversion of NAD<sup>+</sup> to NADH (Hanumantha Rao Madala et al., 2018). All mutation identified to date in the IDH1 gene are missense at R132 and at analogous (R172) in IDH2 (Ohgaki and Kleihues, 2013). The studies demonstrated that these mutations are frequent in secondary (> 80%) than in primary (< 5%) (Ohgaki and Kleihues, 2013).

The p53 gene has a five conserved region and encodes for a transcription factor protein (393 amino-acid), plays role in apoptosis, cell regulation, and DNA reparation (Vogelstein et al., 2000). The P53 mutations are higher in secondary (> 90%) than in primary (< 35%) (Nagpal et al., 2006). Loss of the p53 gene in GBM is due to mutations in exons 5 and exon 8 or homozygous/heterozygous deletion of chromosome 17 (Nagpal et al., 2006). The mutations affected exon 8 of the p53 gene are missense at R273H (818 G > A), and nonsense at R306X (916 C > T). The other mutation in exon 5 localized at Q136X (406C > T) (Hilmani et al., 2013).

The EGFR gene is located on chromosome 7p12, codes for a tyrosine kinase membrane receptor that is bound to the EGF ligand. This binding

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activates the dimerization and autophosphorylation receptor of the cytoplasmic domain (Yamanashi et al., 2012). In Glioblastoma, mutations of EGFR affect exons 18-19-20 and 21 (Arif et al., 2015). The EGFR signaling pathways participate in cell cycle activation, cell survival, proliferation, angiogenesis, motility, adhesion and metastasis of tumor cells (Wee and Wang, 2017).

The aim of this study was to conduct a literature review of the literature on glioblastoma genetic studies conducted in Moroccan patients and to identify the characteristics of our population.

**Methods**

A comprehensive literature search was conducted via ScienceDirect and PubMed (the latest research update was held on May 15, 2018) to find research articles related to glioblastoma in Morocco, using the following search terms: Glioblastoma Morocco, Primary glioblastoma Morocco, secondary glioblastoma Morocco. No language restrictions were imposed in either database.

The following criteria were used for our review: research articles dealing with the genetics of glioblastoma in Morocco, including primary and secondary glioblastoma. The major reason for exclusion of studies was as follow: reviews, epidemiological articles or poster and studies without genetic assay or have not been done on the Moroccan population (Fig. 1).

**Results**

*Results of the literature search*

After extensive research in Pubmed and ScienceDirect, we founded 90 results. we selected 3 research articles based on the title and relationship with the genetic glioblastoma of Moroccan patients.

*Results of selected articles*

The Table 1 shows the results of the three studies carried out in Morocco to determine the genetic characteristics of the Moroccan population.

It was reported in these selected articles, after sequencing of 65 and 62 patients in two different studies performed by Senhaji et al, the IDH 1 gene mutation (codons 132) was found in 12.36% and 36.75% of patients with glioblastoma (Senhaji et al., 2017; Senhaji et al., 2016).

On the other hand, the study of Hilmani et al reported that there is no IDH 1 gene mutation among 34 patients with primary glioblastoma (Hilmani et al., 2013).

For the mutation at IDH level 2 (codons 172), the sequencing of 65 and 62 patients with GBM, did not revealed any mutation in these patients, the same results were found in primary glioblastoma samples by the Hilmani team (Hilmani et al., 2013).

The exons from 4 to 10 of the p53 gene were screened by sequencing in 34 cases with primary glioblastoma; the analysis revealed a mutation only in exons 5 and 8 with a frequency of 8.82% (Hilmani et al., 2013) (Fig. 2).

Analysis of EGFR expression (exon 20) in 34 GBM patients revealed overexpression of this gene in 26.15% of the samples (Senhaji et al., 2017).

**Discussion**

Numerous alterations have been associated with genetic glioblastomas, such as the IDH1 / 2 mutation, the loss of 10q heterozygosity, the p53 mutation, the MDM2 overexpression and the p16<sup>ink4a</sup> deletion (Fig. 1), but the mechanism leading to the development of glioblastoma still unclear. Here we study different genetic alteration studies in Moroccan patients with glioblastoma, after selection of articles, only the genes IDH1 / 2, p53 and EGFR were studied.

The IDH1 and IDH2 use NADP + as a cofactor to catalyze the reversible decarboxylation of isocitrate to α-ketoglutarate (α-KG), the latter itself playing an antioxidant role (Hanumantha Rao Madala et al., 2018). This reaction results from the production of NADPH in the process. NADPH plays an important role in the reproduction of oxidative glutathione (SU MIN LEE et al., 2002). IDH 1 is more expressed in cytosol and peroxisome. In contrast, the IDH2 is in the mitochondria (Horbinski, 2013). These enzymes play a vital role in the response to oxidative stress. It has been reported that, the IDH mutations promote cell proliferation and blocks cell differentiation (Cambuzzi, 2017). Molecular analysis by sequencing of the IDH1 gene, codon 132, showed a frequency of 12.36% and 36.75% in Moroccan population (Senhaji et al., 2017; Senhaji et al., 2016). This finding is similar to those reported from other populations in different continents; for example, 10% in America, 20% in the Netherlands and 25% in India. Nonetheless, the outcome of the studies conducted among Moroccans disagree with others performed in Germany (3%), France (5.6%) and China (56%). (Bleeker et al., 2008; Agarwal et al., 2013; Killela et al., 2014; Combs

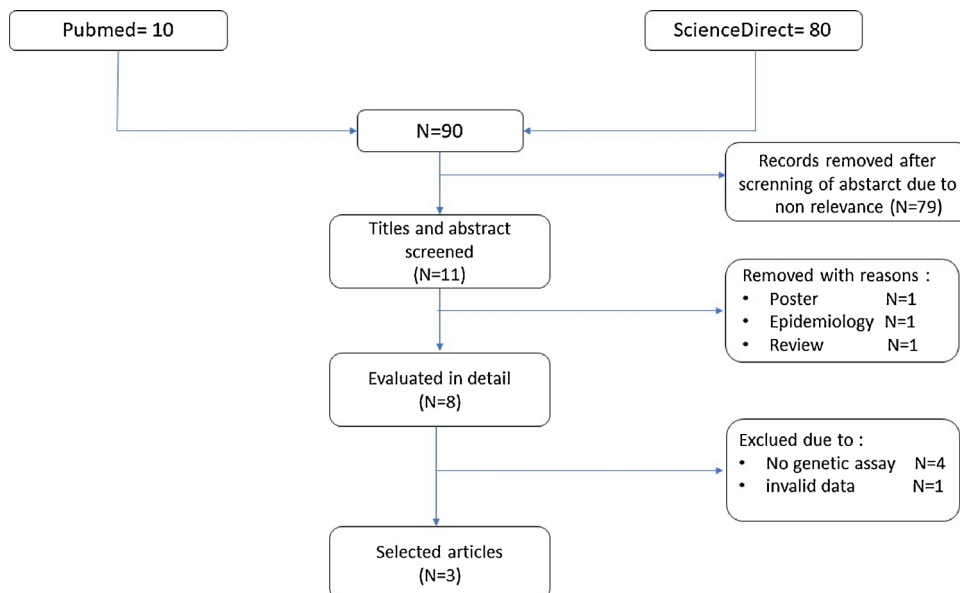
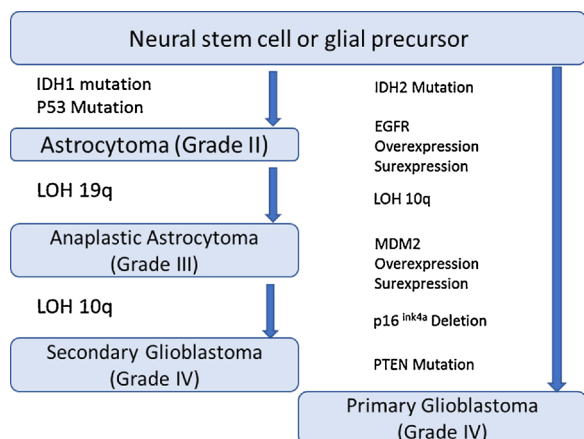


Fig. 1. Flow diagram of the study selection process.

**Table 1**  
Frequency of IDH1, IDH2 and TP53 mutations in glioblastomas from selected studies.

Article	n	IDH1 Codons 132			IDH2 Codons 172			P53 Exons 5 & 8			EGFR Exon 20		
		GBM	pGBM	sGBM	GBM	pGBM	sGBM	GBM	pGBM	sGBM	GBM	pGBM	sGBM
Senhaji et al. (2017)	65	12.36%	ND	ND	0 %	ND	ND	ND	ND	ND	26.15%	ND	ND
Senhaji et al. (2016)	62	36.75%	ND	ND	0 %	ND	ND	ND	ND	ND	ND	ND	ND
Hilmani et al. (2013)	34	ND	0%	ND	ND	0%	ND	ND	8,82%	ND	ND	ND	ND

GBM glioblastomas, pGBM primary glioblastomas, sGBM secondary glioblastomas and ND not determined.



**Fig. 2.** Genetic alteration in primary and secondary glioblastoma (Osborne et al., 2001).

et al.,2011; Sanson et al., 2009; Zhou et al., 2012).

No mutations were observed in the IDH2 gene (172 codons), this result confirmed that this mutation was a secondary glioblastoma marker (Ohgaki and Kleihues, 2013).

The p53 is a transcription factor that plays a crucial role in apoptosis, DNA repair, participates and in the regulation of cell growth (Vogelstein et al., 2000). The p53 is not a hallmark of tumor types (Nørøxe et al., 2016), while the expression of p53 was higher in secondary GBM (> 90%) than in primary (35%) (Kunihiko Watanabe et al., 1997). The sequencing of the p53 gene (exons 5 and 8) in a sample of the Moroccan population with primary glioblastoma revealed a low frequency of mutation (8.82%) compared to the Italian (21.2%) and American (23%) (Hai Yan et al., 2009; Shoji Shiraishi et al., 2002 and Mellai et al.,2011).

The EGFR is a tyrosine kinase family, including HER1 also known as EGFR, HER2, HER3 and HER4 (XU et al., 2017). It's a proto-oncogene and anti-apoptotic protein that stimulating cell proliferation (Wee and Wang, 2017). The EGFR is localized on chromosome 17q22 and divided into 28 exons (Davies et al., 1980). The expression analysis of the EGFR gene, exon 20, which codes for the tyrosine kinase region showed that the amplification of this gene was 26.15% in the Moroccan population (Senhaji et al., 2017). These results are similar to those of the Tunisian population (24%) and discordant with other continents: in Italy (44%), in Spain (53%) and in Portugal (53%) populations (Trabelsi et al., 2017; Franceschi et al., 2015; Benito et al., 2010; Viana-pereira et al., 2008).

**Conclusion**

In this review, including the only three articles dealing with glioblastoma showed that the frequency of IDH1 (R132), IDH2 (R172) and EGFR gene expression (Exon 20) in the Moroccan population coincide and agree with other populations, as described in the discussion. On the contrary, the frequency of the p53 gene (exons 5 and 8) is low compared to the Italian and Japanese populations.

To our knowledge, this is the first Moroccan study on the frequency of altered genes in patients with glioblastoma, based on the studies conducted in this population. Other molecular studies must be conducted on a large number of patients and describe other genetic markers, their impact on the diagnosis, survival and treatment of the Moroccan population.

**Conflict of interest**

The authors declare no conflict of interest.

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