International Journal of Health Sciences

Available online at www.sciencescholar.us
Vol. 8 No. 1, April 2024, pages: 36-46
e-ISSN: 2550-696X, p-ISSN: 2550-6978
https://doi.org/10.53730/ijhs.v8n1.14719

Apparition of Germline Mutation c.1395-1397del of MUTYH in Algerian Consanguineous Family with Colorectal Cancer

Ziada-Bouchaar Hadia [a], Gharzouli Razika [b], Semmame Ouarda [c], Sedrati Khadidja [d], Boudoukhane Mouna Ibtissem [e], Sifi Karima [f], Abadi Noureddine [g], Satta Dalila [h]

Manuscript submitted: 09 November 2023, Manuscript revised: 18 December 2023, Accepted for publication: 09 January 2024

Corresponding Author [a]

Keywords

Algerian families;
colorectal cancer;
MUTYH-associated polyposis;
MUTYH gene;

Abstract

MUTYH is a glycosylase that removes adenine opposite 8-oxo guanine (OG) during base-excision repair of DNA. Variants of *MUTYH* defective in functional activity lead to MUTYH-associated polyposis (MAP), autosomal recessive predisposition to colorectal cancer (CRC). MAP combines clinical features with other hereditary CRC syndromes and exhibits phenotypic overlap, particularly with Lynch syndrome (LS). To determine the impact of *MUTYH* mutations in colorectal adenomas and cancer susceptibility, this prospective objective screens the *MUTYH* gene in seventeen Eastern Algerian families with clinically suspected LS but without mismatch repair (MMR) mutations. Methods: We examined the presence of the mutations in the probands and their relatives using direct sequencing of the entire coding region of the *MUTYH* gene. Results: The biallelic and monoallelic pathogenic *MUTYH* mutations, c.1395_1397del, were discovered in a consanguineous family with CRC and gastric cancer as a novel finding in our Eastern Algerian population. Conclusion: High rates of consanguinity in the Algerian population increase the risk of CRC caused by biallelic mutations in the *MUTYH* gene. In our families, the LS and MAP phenotypes might coexist. The inclusion of *MUTYH* testing in the diagnostic strategy of LS-suspected patients should make carriers of mutations in this gene, as well as their first-line relatives, aware of their increased risk and encourage them to undergo early screening.

International Journal of Health Sciences © 2024.
This is an open access article under the CC BY-NC-ND license (https://creativecommons.org/licenses/by-nc-nd/4.0/).

[a] University 1, Mentouri Brothers, Constantine, Algeria & University 3, Salah Boubnider, Constantine, Algeria
[b] University 1, Mentouri Brothers, Constantine, Algeria
[c] University 1, Mentouri Brothers, Constantine, Algeria
[d] University 1, Mentouri Brothers, Constantine, Algeria & University 3, Salah Boubnider, Constantine, Algeria
[e] University 1, Mentouri Brothers, Constantine, Algeria
[f] University 3, Salah Boubnider, Constantine, Algeria
[g] University 3, Salah Boubnider, Constantine, Algeria
[h] University 1, Mentouri Brothers, Constantine, Algeria

Contents

1 Introduction

There are two entities of tumour predisposition syndromes with high penetrance, which contribute to approximately 5% to 10% of colorectal cancers (CRC) (Aretz et al., 2006): familial adenomatous polyposis (FAP) (MIM #175100) and hereditary nonpolyposis colorectal cancer (HNPCC or Lynch syndrome, LS) (MIM # 114500). Both these two diseases have autosomal dominant conditions and result from the family history of early onset CRC: typical FAP is characterized by the appearance of hundreds to thousands of colorectal adenomas. In LS, there is usually only a few adenomas, and tumors present high microsatellite instability (MSI-H) (Lynch & de la Chapelle, 2003). The phenotype with fewer (10–100) colorectal adenomas represents a heterogeneous and yet poorly characterized group, between FAP and LS, known as multiple colorectal adenomas (MCA).

On the Genetic profile, the FAP is caused by germline mutations in the tumour suppressor gene *APC*. HNPCC or LS is diagnosed by the detection of a germline mutation in one of the mismatch repair (MMR) genes: *MLH1*, *MSH2*, and *MSH6*. However, in 10-15% of cases clinically suspected of LS, the presence of genealogical criteria of selection (Amsterdam or Bethesda guidelines), MSI-H and abnormal immunohistochemistry (IHC) results in the tumours (clinical criteria) cannot be explained by MMR germline mutation analyses (Morak et al., 2014). The Germline mutations in the human Mut Y homolog (*MUTYH*; MIM# 604933) also known as *MYH* can be probably the cause of these predispositions to colorectal cancer. When the first pathogenic variant of the *MUTYH* gene was described By Al-Tassan (Al-Tassan et al., 2002).

This pathology, called, *MUTYH*-associated polyposis (MAP) (MIM # 608456) is an autosomal recessive inheritance disorder that was also found to correlate with a predisposition to MCA and colorectal carcinomas (Al-Tassan et al., 2002; Raetz & David, 2019). The clinical aspect of MAP gives frequently a spectrum of expression from severe colorectal polyposis to attenuated forms. It can be present at the late age of onset or with few adenomas in CRC, which creates a partial phenotypic overlap with LS and can cause recognition problems (Morak et al., 2014; Sutcliffe et al., 2019). Castillejo and collaborators reported that MAP patients show some phenotypic similarities to LS patients (Castillejo et al., 2014). In this regard, the extracolonic tumour spectrum is similar in both groups and CRC can be diagnosed in the absence of adenomas or associated with a small number of adenomas (Gu et al., 2002).

The *MUTYH* gene is localized on the short arm of chromosome 1(1p32.1- p34.3), contains 16 exons and encodes a DNA glycosylase belonging to the base excision repair pathway (Nielsen et al., 2022). The major function of MUTYH is to prevent 8-oxodG (8-hydroxyguanine), a base lesion brought on by oxidative stress, from having mutagenic effects. To start the base excision repair process, it removes the adenine that was accidentally incorporated into the opposing template, 8-oxodG (8-hydroxyguanine) (Isidro et al., 2004). Base excision repair pathway-mediated resynthesis generates C: 8-oxodG base pairs, which serve as substrates for OGG1-mediated removal of the oxidized purine. Thus the action of MUTYH prevents the formation of G:C to T:A transversion mutations (Ricci et al., 2017; Nielsen et al., 2022). At the protein level, The MUTYH protein structure is made up of many functional domains that are involved in mispair recognition, DNA binding, base flipping, excision, and interaction with other DNA replication and MMR (MSH2, MSH6) protein (Markkanen et al., 2013). MUTYH is physically linked to MSH2/MSH6, and the MSH2/MSH6 complex enhances MUTYH's DNA binding and glycosylase activity by oxo G:A mispairs (Castillejo et al., 2014).

To date, the impact of *MUTYH* mutations has been examined in patients with different phenotypes including FAP, MCA, LS, and sporadic CRC (Nielsen et al., 2022). Two missense mutations p.Tyr179Cys and p.Gly396Asp in the *MUTYH* gene are the most frequently observed in European populations (Grandval et al., 2014). The frequency of mutations in the *MUTYH* gene in Oriental and Arabic populations is much less well documented. Furthermore, the mutational spectrum is clearly distinct (rarity of p.Tyr179Cys and p.Gly396Asp mutations). Because of its autosomal recessive inheritance, MAP is less frequent than LS or FAP. However, this type of genetic predisposition may become more common in Arabic countries, where certain families with many marriages between relatives, exhibit high rates of consanguinity. Here, we present the findings of a comprehensive mutation screening for the *MUTYH* gene in Algerian consanguineous patients from the same family, with clinically suspected LS but no MMR mutation, and we discuss the clinical implications (Nielsen et al., 2011; Sampson & Jones, 2009; Cheadle & Sampson, 2007).

2 Materials and Methods

This study included a series of seventeen families from the Eastern region of Algeria who were suspected of having LS because they fulfilled its clinical criteria (Amsterdam or revised Bethesda guidelines) (Vasen et al., 2013). All probands of these families showed both absences of germline pathogenic mutations and were negative for deletions or duplications *of MLH1*, *MSH2*, *MSH6*, *EPCAM*, and PMS2 genes before this study. Based on the family survey, we discovered a family, F11, in our group that did not have vertical transmission of disease and met Bethesda guidelines. We were attracted by the existence of consanguineous marriages between family members of F11, which made us consider a disorder with recessive inheritance.

Since pathogenic mutations in the *MUTYH* gene occur in patients with the MAP type of some familial colorectal malignancies, we postulated that *MUTYH* is involved in colorectal carcinogenesis in this family. All patients provided their informed consent for the cancer genetics search. Medical histories were obtained through an interview with the proband. Pedigrees were constructed for four generations and data from affected subjects (type, number, and localization of tumors and age at diagnosis) were documented and verified through clinical and pathological records where possible (Nielsen et al., 2009; Vogt et al., 2009; Ali et al., 2008; Mohammed, 2016).

Molecular analysis

Total Genomic DNA was isolated manually from peripheral blood lymphocytes from the probands and members of the families by using standard protocols following the salt extraction procedure (Miller et al., 1988). We investigated the families without mutations in MMR genes, by direct sequencing of the complete coding region of the *MUTYH* gene. All exons were sequenced in both the forward and reverse directions. We used for this, the Big Dye Terminator Chemistry v1.1 and an automated fluorescent sequencer, an ABI Prism 16 Capillary Array Sequencer (Applied Biosystems 3130 XL). The primers were designed using Primer 3Plus (https://www.bioinformatics.nl/cgi-bin/primer3plus/primer3plus.cgi). All germline mutations were confirmed by sequencing at least two independent PCR products.

Bioinformatic tools

The GenBank accession number of the *MUTYH* gene is 604933, available on Online Mendelian Inheritance in Man (OMIM) at https://www.ncbi.nlm.nih.gov/omim/. *MUTYH* reference sequence and exon numbering based on NC_000001.10 and NM_001128425.1.

3 Results and Discussions

In our study, for the first time in Algeria, the biallelic pathogenic *MUTYH* mutation, c.1395_1397del was found in the proband of the family F11 (Fig.1). This 3-bp deletion (1395-7 del GGA) resulted in the removal of a glutamic acid residue, p.Glu466del, within a C-terminal domain which is a highly conserved region of

the *MUTYH*. It has been shown to play a role in 8-oxo-G recognition by biochemical studies (Cheadle & Sampson, 2003).

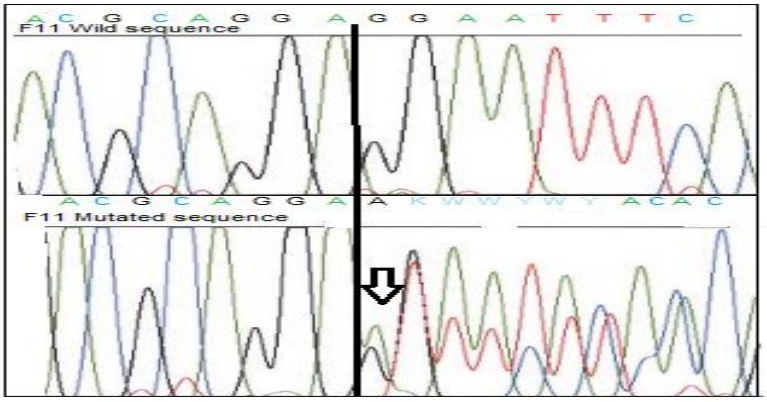


Figure 1. Chromatogram of sequencing of the variant c.1395_1397del on exon 14 in *MUTYH* gene in mutated individuals of family F11

This deletion was discovered in a man F11.1, who was diagnosed with well-differentiated liberkunian type adenocarcinoma in his transverse colon at the age of 46 (excluding familial adenomatous polyposis). Three years later, he developed a recurrence of the left colonic tumour process, which was treated with gastric abdominal wall extension. The index case, F11.1, belongs to an Algerian family from the East. The family pedigree analysis confirms that the family's history is compatible with autosomal recessive inheritance (only the proband or siblings affected by colon cancer). This family has three consanguineous unions, one of which was the proband's parents, who are first cousins (Sakurada et al., 2018; Win et al., 2014; Jones et al., 2009).

Proband F11.1 had five relatives with colon and gastric cancers, according to family history. Two members are of the same generation, and one is a first-degree relative who was diagnosed with colon cancer when he was 60 years old. The common ancestor died of an unidentified cancer at the age of 70. In this family, consanguinity increases the rate of acquiring two copies of the defected recessive alleles from the common ancestor. Therefore, it increases the probability of having homozygosity (Fig.2).

The c.1395_1397del variant of the *MUTYH* gene was found in four members of the same family, F11, among our Algerian patients. Two of them (the proband and one brother) had the biallelic form, while the two remaining members had this mutation in only one allele. The last ones appear to be healthy and disease-free. Their cousin, who came from a first-cousin marriage, was diagnosed with colon cancer at the age of 49. Although he was not tested, he appears to be a homozygous carrier of the same pathogenic variant. When c.1395_1397del of the *MUTYH* gene is homozygous, it co-segregates with cancer in this family (Fig. 2).

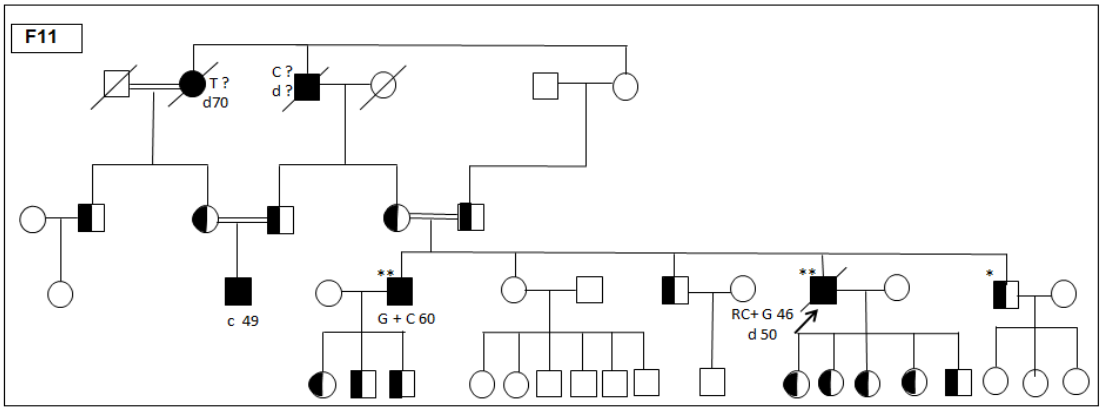


Figure 2. Pedigree of the family F11

Filled symbols, affected subjects; open symbols, unaffected members; symbols with oblique lines, deceased subjects; arrows indicate the probands. The type(s) of cancer(s) and the age(s) at diagnosis, as well as the age of death (d) are listed before the symbols. C colon cancer, G gastric cancer, LC left colon cancer, RC right colon cancer, T tumor of uncertain origin, (**) Carrier of biallelic familial mutation, and (*) Carrier of monoallelic familial mutation.

Discussion

We report in this study screening of the *MUTYH* gene, which is most commonly involved in recessive hereditary predisposition to colorectal cancer, MAP. Here, we investigated 17 unrelated Algerian families with MCA and LS without mutations or defaults in MMR genes (Ziada-Bouchaar et al., 2017). For the first time in Algeria, we found that the germeline mutation c.1395_1397del in exon 14 of *MUTYH* was identified in 5, 88 % of unrelated Algerian families fulfilling LS clinical criteria. Our result agrees with Castillejo's research which revealed the overlapping phenotypes between Lynch and MAP syndromes (Castillejo et al., 2014).

The recurrent pathogenic *MUTYH* mutation, c.1395_1397del, is rare. It has been previously reported in only one of 75 colorectal cancer patients from the United Kingdom (Halford et al., 2003). The same variant has been also described in the Italian population, which suggests that is a sub-polymorphic *MUTYH* mutation in the southern European Caucasian population (Gismondi et al., 2004).

Molecular epidemiology of *MUTYH* alterations demonstrates that the defects of this gene are often represented by the two initials c.536A4G/p.Tyr179Cys and c.1187G4A/p.Gly396Asp (previously c.494A4G/p.Tyr165Cys and c.1145G4A/p.Gly382Asp) missense mutations (Out et al., 2010). These two mutations were found to be the most common (Cleary et al., 2009), accounting for approximately 80% of all reported *MUTYH* variants in Caucasian populations, and is particularly characteristic for Europe (Lv, 2017; Nielsen et al., 2022).

However many countries, including different parts of Europe, have a unique spectrum of regional founder mutations. These mutations have been detected in specific ethnic groups that is Y90X, E466X, and 1187insGG in subjects of, Pakistani, Indian, and Portuguese descent, respectively (Croitoru et al., 2004; Nielsen et al., 2022); p.R245H in Hungary, p.480delE in Italy and p.P405L in the Netherlands (Yanus et al., 2018). In families of North African ancestry, Lefevre and colleagues reported a novel mutation, c.1227_1228dup (Lefevre et al., 2011). This mutation has been described together with another more prevalent one, p.E410GfsX43 in Tunisia (Abdelmaksoud-Dammak et al., 2012).

The increased risk of colorectal cancer and polyposis among biallelic *MUTYH* gene mutation has been confirmed by several groups (Jones et al., 2002; Win et al., 2011). However, the cancer risk associated with germline variants in individuals carrying only one *MUTYH* defective allele is controversial (Lubbe et al., 2009), and based on studies involving few samples (Croitoru et al., 2004; Olschwang et al., 2007).

Jenkins and colleagues discovered an increased risk in monoallelic carriers only in those over the age of 55 in a large study (Jenkins et al., 2006). These findings were recently supported by Patel's study, which included 249 young people with monoallelic *MUTYH* pathogenic mutations but neither a high adenoma rate nor CRCs were found (Patel et al., 2021). This supports our findings that the proband and one sibling are biallelic carriers of the c.1395_1397del, whereas the other two carry the mutation in only one allele and are healthy individuals without any outward signs of disease.

Our patient's follow-up has revealed that patients with biallelic mutations in the *MUTYH* gene developed colon cancer, followed by gastric cancer a few years later, the only extracolonic cancer found. Numerous studies and case reports have reported extracolonic tumours in monoallelic or biallelic *MUTYH* mutation carriers, including gastroduodenal and gastric cancers (Win et al., 2016; Nielsen et al., 2022). While some recent studies found *MUTYH* mutations to be associated with an increased risk of breast cancer (Fonfria et al., 2021; Nunziato et al., 2022), and endometrial cancer (Magrin et al., 2022). Others found no link between *MUTYH* mutations and these cancers (Beiner et al., 2009; Thompson et al., 2022).

Recently, Barreiro's results indicated that *MUTYH* deficiency in heterozygosity can cause cancer via a process known as Loss of Heterozygosity (LOH) of the functional *MUTYH* allele. It has been verified that cancer patients have a greater prevalence of damaging *MUTYH* monoallelic variant carriers than the general population (Barreiro et al., 2021). However, the risks of extracolonic malignancies for carriers with monoallelic mutations have not yet been determined. In our investigation, the individuals with the

c.1395_1397del variant came from a consanguineous union between first cousins; hence, consanguinity increases the probability of having homozygosity of the defective variant in the *MUTYH* gene and the emergence of the cancer risk in this family. The married couple in this case shares 12.5% of the genes (Bener et al., 1996; Kakaje et al., 2020).

Worldwide, there is a variation in the prevalence of consanguineous marriages. When the rate is less than 1% in Europe and North America (Kakaje et al., 2020)**,** the results of a recent study in the Algerian population show a high rate of consanguinity of around 38.33% (Benkou et al., 2020)**.** It is about 36.3% in Syria (Kakaje et al., 2020), and it can reach up to 50% of the general population in Arab countries (Tadmouri et al., 2009), for instance, the rate can reach up to 56% in Saudi Arabia (Warsy et al., 2014), and 68% in Egypt (Mokhtar & Abdel-Fattah, 2001). The risk estimate for consanguinity may be slightly inflated when first-cousin marriages are widespread and encouraged (Thompson & Thompson, 2016)**.**

4 Conclusion

Biallelic mutations in the *MUTYH* gene cause the autosomal recessive condition MAP, which increases the risk of colorectal cancer. A high rate of consanguinity contributes to the homozygosity of defective variants in the *MUTYH* gene and the apparition of the cancer risk in Algerian families. Cancer risks are unknown for people who have inherited a *MUTYH* mutation from only one parent. Because of the degree of consanguinity, a larger study is required to address the issue of potential risk.

The LS phenotype and the MAP phenotype may overlap. Taking into consideration the presence of biallelic *MUTYH* mutations among LS patients, the inclusion of *MUTYH* testing in the diagnostic strategy of LS-suspected patients should make aware carriers of mutations in this gene, as well as their first-line relatives, of this increased risk and encourage them to undergo early screening.

Acknowledgments
We are grateful to the members of the CRC families who agreed to participate in this study and provided blood samples. We would like to express our gratitude to all members of the Oncogenetic Laboratory, Cochin, Paris, for their invaluable collaboration and excellent technical assistance, as well as all members of the Biology and Genetics Laboratory, Medical Oncology Service, University Hospital Center, Constantine, Algeria.

References

Abdelmaksoud-Dammak, R., Miladi-Abdennadher, I., Amouri, A., Tahri, N., Ayadi, L., Khabir, A., ... & Mokdad-Gargouri, R. (2012). High prevalence of the c. 1227_1228dup (p. Glu410GlyfsX43) mutation in Tunisian families affected with MUTYH-associated-polyposis. *Familial cancer*, *11*, 503-508.

Ali, M., Kim, H., Cleary, S., Cupples, C., Gallinger, S., & Bristow, R. (2008). Characterization of mutant MUTYH proteins associated with familial colorectal cancer. *Gastroenterology*, *135*(2), 499-507. https://doi.org/10.1053/j.gastro.2008.04.035

Al-Tassan, N., Chmiel, N. H., Maynard, J., Fleming, N., Livingston, A. L., Williams, G. T., Hodges, A. K., Davies, D. R., David, S. S., Sampson, J. R., & Cheadle, J. P. (2002). Inherited variants of MYH associated with somatic G:C-->T:A mutations in colorectal tumors. *Nature Genetics*, *30*(2).

Aretz, S., Uhlhaas, S., Goergens, H., Siberg, K., Vogel, M., Pagenstecher, C., Mangold, E., Caspari, R., Propping, P., & Friedl, W. (2006). MUTYH-associated polyposis: 70 of 71 patients with biallelic mutations present with an attenuated or atypical phenotype. *International Journal of Cancer*, *119*(4).

Barreiro, R. A. S., Sabbaga, J., Rossi, B. M., Achatz, M. I. W., Camargo, A. A., Asprino, P. F., & Galante, P. A. F. (2021). *Heterozygous deleterious MUTYH variants as a driver for tumorigenesis* (p. 2021.06.09.21258588). medRxiv.

Beiner, M. E., Zhang, W. W., Zhang, S., Gallinger, S., Sun, P., & Narod, S. A. (2009). Mutations of the MYH gene do not substantially contribute to the risk of breast cancer. *Breast Cancer Research and Treatment*, *114*(3).

Bener, A., Abdulrazzaq, Y. M., al-Gazali, L. I., Micallef, R., al-Khayat, A. I., & Gaber, T. (1996). Consanguinity and associated socio-demographic factors in the United Arab Emirates. *Human Heredity*, *46*(5).

Benkou, F., Aouar, A., & Moussouni, A. (2020). Study of the impact of inbreeding on the health profile in the population of Beni Ouarsous (Tlemcen). *Revue d'Anthropologie des Religions*, *16*(1).

Castillejo, A., Vargas, G., Castillejo, M. I., Navarro, M., Barberá, V. M., González, S., ... & Soto, J. L. (2014). Prevalence of germline MUTYH mutations among Lynch-like syndrome patients. *European Journal of Cancer*, *50*(13), 2241-2250. https://doi.org/10.1016/j.ejca.2014.05.022

Cheadle, J. P., & Sampson, J. R. (2003). Exposing the MYtH about base excision repair and human inherited disease. *Human Molecular Genetics*, *12 Spec No 2*, R159-165.

Cheadle, J. P., & Sampson, J. R. (2007). MUTYH-associated polyposis—from defect in base excision repair to clinical genetic testing. *DNA repair*, *6*(3), 274-279. https://doi.org/10.1016/j.dnarep.2006.11.001

Cleary, S. P., Cotterchio, M., Jenkins, M. A., Kim, H., Bristow, R., Green, R., Haile, R., Hopper, J. L., LeMarchand, L., Lindor, N., Parfrey, P., Potter, J., Younghusband, B., & Gallinger, S. (2009). Germline MutY human homologue mutations and colorectal cancer: A multisite case-control study. *Gastroenterology*, *136*(4).

Croitoru, M. E., Cleary, S. P., Di Nicola, N., Manno, M., Selander, T., Aronson, M., Redston, M., Cotterchio, M., Knight, J., Gryfe, R., & Gallinger, S. (2004). Association between biallelic and monoallelic germline MYH gene mutations and colorectal cancer risk. *Journal of the National Cancer Institute*, *96*(21).

Fonfria, M., de Juan Jiménez, I., Tena, I., Chirivella, I., Richart-Aznar, P., Segura, A., Sánchez-Heras, A. B., & Martinez-Dueñas, E. (2021). Prevalence and Clinicopathological Characteristics of Moderate and High-Penetrance Genes in Non-BRCA1/2 Breast Cancer High-Risk Spanish Families. *Journal of Personalized Medicine*, *11*(6).

Gismondi, V., Meta, M., Bonelli, L., Radice, P., Sala, P., Bertario, L., ... & Varesco, L. (2004). Prevalence of the Y165C, G382D and 1395delGGA germline mutations of the MYH gene in Italian patients with adenomatous polyposis coli and colorectal adenomas. *International journal of cancer*, *109*(5), 680-684.

Grandval, P., Fabre, A. J., Gaildrat, P., Baert-Desurmont, S., Blayau, M., Buisine, M. P., ... & Olschwang, S. (2014). Genomic variations integrated database for MUTYH-associated adenomatous polyposis. *Journal of Medical Genetics*.

Gu, Y., Parker, A., Wilson, T. M., Bai, H., Chang, D.-Y., & Lu, A.-L. (2002). Human MutY Homolog, a DNA Glycosylase Involved in Base Excision Repair, Physically and Functionally Interacts with Mismatch Repair Proteins Human MutS Homolog 2/Human MutS Homolog 6*. *Journal of Biological Chemistry*, *277*(13).

Halford, S. E. R., Rowan, A. J., Lipton, L., Sieber, O. M., Pack, K., Thomas, H. J. W., Hodgson, S. V., Bodmer, W. F., & Tomlinson, I. P. M. (2003). Germline mutations but not somatic changes at the MYH locus contribute to the pathogenesis of unselected colorectal cancers. *The American Journal of Pathology*, *162*(5).

Isidro, G., Laranjeira, F., Pires, A., Leite, J., Regateiro, F., Castro e Sousa, F., Soares, J., Castro, C., Giria, J., Brito, M. J., Medeira, A., Teixeira, R., Morna, H., Gaspar, I., Marinho, C., Jorge, R., Brehm, A., Ramos, J. S., & Boavida, M.

G. (2004). Germline MUTYH (MYH) mutations in Portuguese individuals with multiple colorectal adenomas. *Human Mutation*, *24*(4).

Jenkins, M. A., Croitoru, M. E., Monga, N., Cleary, S. P., Cotterchio, M., Hopper, J. L., & Gallinger, S. (2006). Risk of colorectal cancer in monoallelic and biallelic carriers of MYH mutations: a population-based case-family study. *Cancer Epidemiology Biomarkers & Prevention*, *15*(2), 312-314.

Jones, N., Vogt, S., Nielsen, M., Christian, D., Wark, P. A., Eccles, D., ... & Sampson, J. R. (2009). Increased colorectal cancer incidence in obligate carriers of heterozygous mutations in MUTYH. *Gastroenterology*, *137*(2), 489-494. https://doi.org/10.1053/j.gastro.2009.04.047

Jones, S., Emmerson, P., Maynard, J., Best, J. M., Jordan, S., Williams, G. T., Sampson, J. R., & Cheadle, J. P. (2002). Biallelic germline mutations in MYH predispose to multiple colorectal adenoma and somatic G:C-->T:A mutations. *Human Molecular Genetics*, *11*(23).

Kakaje, A., Alhalabi, M. M., Ghareeb, A., Karam, B., Mansour, B., Zahra, B., & Hamdan, O. (2020). Interactions of Consanguinity and Number of Siblings with Childhood Acute Lymphoblastic Leukemia. *BioMed Research International*, *2020*, 7919310.

Lefevre, J. H., Colas, C., Coulet, F., Baert-Desurmont, S., Mongin, C., Tiret, E., Frebourg, T., Soubrier, F., & Parc, Y. (2011). Frequent mutation in North African patients with MUTYH-associated polyposis. *Clinical Genetics*, *80*(4).

Lubbe, S. J., Di Bernardo, M. C., Chandler, I. P., & Houlston, R. S. (2009). Clinical implications of the colorectal cancer risk associated with MUTYH mutation. *Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology*, *27*(24).

Lv, X.-P. (2017). Gastrointestinal tract cancers: Genetics, heritability and germ line mutations (Review). *Oncology Letters*, *13*(3).

Lynch, H. T., & de la Chapelle, A. (2003). Hereditary colorectal cancer. *The New England Journal of Medicine*, *348*(10).

Magrin, L., Fanale, D., Brando, C., Corsini, L. R., Randazzo, U., Di Piazza, M., Gurrera, V., Pedone, E., Bazan Russo, T. D., Vieni, S., Pantuso, G., Russo, A., & Bazan, V. (2022). MUTYH-associated tumor syndrome: The other face of MAP. *Oncogene*, *41*(18).

Markkanen, E., Dorn, J., & Hübscher, U. (2013). MUTYH DNA glycosylase: The rationale for removing undamaged bases from the DNA. *Frontiers in Genetics*, *4*, 18.

Miller, S. A., Dykes, D. D., & Polesky, H. F. (1988). A simple salting out procedure for extracting DNA from human nucleated cells. *Nucleic Acids Research*, *16*(3).

Mohammed, A. D. (2016). The financing health system problem in Algeria. *International Research Journal of Management, IT and Social Sciences*, *3*(7), 53-60.

Mokhtar, M. M., & Abdel-Fattah, M. M. (2001). Consanguinity and advanced maternal age as risk factors for reproductive losses in Alexandria, Egypt. *European Journal of Epidemiology*, *17*(6).

Morak, M., Heidenreich, B., Keller, G., Hampel, H., Laner, A., de la Chapelle, A., & Holinski-Feder, E. (2014). Biallelic MUTYH mutations can mimic Lynch syndrome. *European Journal of Human Genetics: EJHG*, *22*(11).

Nielsen, M., Infante, E., & Brand, R. (2022). MUTYH Polyposis. In M. P. Adam, D. B. Everman, G. M. Mirzaa, R. A. Pagon, S. E. Wallace, L. J. Bean, K. W. Gripp, & A. Amemiya (Eds.), *GeneReviews*®. University of Washington, Seattle.

Nielsen, M., Joerink-Van de Beld, M. C., Jones, N., Vogt, S., Tops, C. M., Vasen, H. F., ... & Hes, F. J. (2009). Analysis of MUTYH genotypes and colorectal phenotypes in patients with MUTYH-associated polyposis. *Gastroenterology*, *136*(2), 471-476. https://doi.org/10.1053/j.gastro.2008.10.056

Nielsen, M., Morreau, H., Vasen, H. F., & Hes, F. J. (2011). MUTYH-associated polyposis (MAP). *Critical reviews in oncology/hematology*, *79*(1), 1-16. https://doi.org/10.1016/j.critrevonc.2010.05.011

Nunziato, M., Di Maggio, F., Pensabene, M., Esposito, M. V., Starnone, F., De Angelis, C., ... & Salvatore, F. (2022). Multi-gene panel testing increases germline predisposing mutations' detection in a cohort of breast/ovarian cancer patients from Southern Italy. *Frontiers in Medicine*, *9*, 894358.

Olschwang, S., Blanché, H., de Moncuit, C., & Thomas, G. (2007). Similar colorectal cancer risk in patients with monoallelic and biallelic mutations in the MYH gene identified in a population with adenomatous polyposis. *Genetic Testing*, *11*(3).

Out, A. A., Tops, C. M., Nielsen, M., Weiss, M. M., Van Minderhout, I. J., Fokkema, I. F., ... & Hes, F. J. (2010). Leiden open variation database of the MUTYH gene. *Human mutation*, *31*(11), 1205-1215.

Patel, R., McGinty, P., Cuthill, V., Hawkins, M., Clark, S. K., & Latchford, A. (2021). Risk of colorectal adenomas and cancer in monoallelic carriers of MUTYH pathogenic variants: A single-centre experience. *International Journal of Colorectal Disease*, *36*, 2199-2204.

Raetz, A. G., & David, S. S. (2019). When you're strange: Unusual features of the MUTYH glycosylase and implications in cancer. *DNA Repair*, *80*, 16–25.

Ricci, M. T., Miccoli, S., Turchetti, D., Bondavalli, D., Viel, A., Quaia, M., ... & Varesco, L. (2017). Type and frequency of MUTYH variants in Italian patients with suspected MAP: a retrospective multicenter study. *Journal of human genetics*, *62*(2), 309-315.

Sakurada, A., Miyanishi, K., Tanaka, S., Sato, M., Sakamoto, H., Kawano, Y., ... & Kato, J. (2018). An intronic single nucleotide polymorphism in the MUTYH gene is associated with increased risk for HCV-induced hepatocellular carcinoma. *Free Radical Biology and Medicine*, *129*, 88-96. https://doi.org/10.1016/j.freeradbiomed.2018.09.010

Sampson, J. R., & Jones, N. (2009). MUTYH-associated polyposis. *Best Practice & Research Clinical Gastroenterology*, *23*(2), 209-218. https://doi.org/10.1016/j.bpg.2009.03.006

Sutcliffe, E. G., Bartenbaker Thompson, A., Stettner, A. R., Marshall, M. L., Roberts, M. E., Susswein, L. R., Wang, Y., Klein, R. T., Hruska, K. S., & Solomon, B. D. (2019). Multi-gene panel testing confirms phenotypic variability in MUTYH-Associated Polyposis. *Familial Cancer*, *18*(2).

Tadmouri, G. O., Nair, P., Obeid, T., Al Ali, M. T., Al Khaja, N., & Hamamy, H. A. (2009). Consanguinity and reproductive health among Arabs. *Reproductive Health*, *6*, 17.

Thompson & Thompson. (2016). Genetics in Medicine. In *Risk Assessment and Genetic Counseling* (Eighth EditionCopyright ©, Vol. 16, pp. 333–348). Elsevier Inc.

Thompson, A. B., Sutcliffe, E. G., Arvai, K., Roberts, M. E., Susswein, L. R., Marshall, M. L., Torene, R., Postula, K. J. V., Hruska, K. S., & Bai, S. (2022). Monoallelic MUTYH pathogenic variants ascertained via multi-gene hereditary cancer panels are not associated with colorectal, endometrial, or breast cancer. *Familial Cancer*, *21*(4).

Vasen, H. F., Blanco, I., Aktan-Collan, K., Gopie, J. P., Alonso, A., Aretz, S., ... & Möslein, G. (2013). Revised guidelines for the clinical management of Lynch syndrome (HNPCC): recommendations by a group of European experts. *Gut*, gutjnl-2012.

Vogt, S., Jones, N., Christian, D., Engel, C., Nielsen, M., Kaufmann, A., ... & Aretz, S. (2009). Expanded extracolonic tumor spectrum in MUTYH-associated polyposis. *Gastroenterology*, *137*(6), 1976-1985. https://doi.org/10.1053/j.gastro.2009.08.052

Warsy, A. S., Al-Jaser, M. H., Albdass, A., Al-Daihan, S., & Alanazi, M. (2014). Is consanguinity prevalence decreasing in Saudis?: A study in two generations. *African health sciences*, *14*(2), 314-321.

Win, A. K., Cleary, S. P., Dowty, J. G., Baron, J. A., Young, J. P., Buchanan, D. D., ... & Jenkins, M. A. (2011). Cancer risks for monoallelic MUTYH mutation carriers with a family history of colorectal cancer. *International journal of cancer*, *129*(9), 2256-2262.

Win, A. K., Dowty, J. G., Cleary, S. P., Kim, H., Buchanan, D. D., Young, J. P., ... & Jenkins, M. A. (2014). Risk of colorectal cancer for carriers of mutations in MUTYH, with and without a family history of cancer. *Gastroenterology*, *146*(5), 1208-1211. https://doi.org/10.1053/j.gastro.2014.01.022

Win, A. K., Reece, J. C., Dowty, J. G., Buchanan, D. D., Clendenning, M., Rosty, C., ... & Jenkins, M. A. (2016). Risk of extracolonic cancers for people with biallelic and monoallelic mutations in MUTYH. *International journal of cancer*, *139*(7), 1557-1563.

Yanus, G. A., Akhapkina, T. A., Ivantsov, A. O., Preobrazhenskaya, E. V., Aleksakhina, S. N., Bizin, I. V., ... & Iyevleva, A. G. (2018). Spectrum of APC and MUTYH germ-line mutations in Russian patients with colorectal malignancies. *Clinical genetics*, *93*(5), 1015-1021.

Ziada-Bouchaar, H., Sifi, K., Filali, T., Hammada, T., Satta, D., & Abadi, N. (2017). First description of mutational analysis of MLH1, MSH2 and MSH6 in Algerian families with suspected Lynch syndrome. *Familial cancer*, *16*(1), 57-66.

Biography of Authors

Ziada-Bouchaar Hadia
Obtained PhD in molecular genetics in 2017. Since 2007 to the present: Teacher-researcher at Brothers Mentouri Constantine 1 University. Member of the Research Laboratory in Biology and Molecular Genetics at Constantine 3 University, in the Oncogenetics unit, and the Research Laboratory in Molecular and Cellular Biology (BMC), Human Pathology Genetics Team. Specialized in the genetics of hereditary colorectal cancers, Lynch Syndrome. Also a member of the Middle East Network on Hereditary Colorectal Cancer (HCCN-ME) association. her areas of interest include bioinformatics, genomics, transcriptomes, and viruses.
Email: ziada.hadia@umc.edu.dz

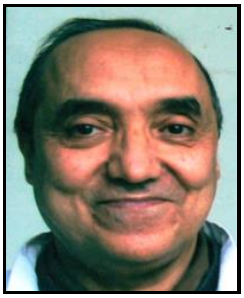
Gharzouli Razika
Teacher researcher at Brothers Mentouri Constantine 1 University, Algeria, in the faculty of natural and life sciences. Team leader in the molecular and cellular biology laboratory. Last diploma obtained: University Accreditation in Molecular and Cellular Biology, Option: Molecular Genetics, February 2018. Scientific areas of interest: Genetics and Molecular Biology, Cancer and neurogenetic diseases.
Email: rgharzouli@umc.edu.dz

Semmame Ouarda
She finished her DES degree in biology, specializing in Biochemistry, and molecular and cellular biology at the University of Constantine, Algeria (June 2003). She graduated with a magister degree in genetics (May 2008), a Doctorate degree (MPhil degree) In genetics of human pathologies (January 2017), and a PhD degree from the University of Constantine 1, Algeria (November 2023). From November 2009 to the present day she worked as a Professor-Researcher in the Department of Animal Biology, Faculty of Natural and Life Sciences at the University of Constantine 1, Algeria
Email: semmame.ouarda@umc.edu.dz

Sedrati Khadidja
Holder of a higher education diploma in molecular and cellular biology with a genetics option in 2003, she began her post-graduation with a master's degree in the genetics of human pathologies to finish with a doctor of science degree in 2017 in the same option. Member of two research laboratories; the genetics and molecular biology laboratory (University of Constantine 3 Algeria) and the molecular and cellular biology laboratory (University of Constantine 1 Algeria). Since 2009, teacher-researcher at the Faculty of Science of Nature and Life at the University of the Brothers Mentouri Constantine 1 University Algeria.
Email: khadidja.sedrati@umc.edu.dz

Boudoukhane Mouna Ibtissem
She finished her magister degree in human genetics and graduated with her PhD in genetic susceptibility to lung cancer from Abou Bakr Belkaid University Tlemcen. She's currently a teacher-researcher at the University of Brothers Mentouri Constantine 1. Since 2020 She has been a pedagogic responsible for licensing genetic options in the biology animal department.
Email: ibtissemmouna.boudokhane@umc.edu.dz

Sifi Karima
She is a Professor of Biochemistry and Molecular Genetics in the Department of Medicine at the Faculty of Medicine, Salah Boubnider University, Constantine 3, Constantine, Algeria. She is also a Ph.D. and MD. She has published a number of papers in scientific journals. Her research focuses on neurogenetics and constitutional and somatic oncogenetics. She also teaches Medical genetics and molecular biology.
Email: Karima.sifi@univ-constantine3.dz



Abadi Noureddine
Medical doctor since 1980, then Assistant Professor in Biochemistry in 1986 at the Constantine University Hospital Center, and a full Professor since 2004. He held the position of director of the laboratory of biology and molecular genetics from 2000 to 2022 at Constantine 3 University. He served as the Head of the "Special Biochemistry" unit since 1995 at Constantine University Hospital (CHU) and as the interim Head of the Biochemistry Department from 2015 to 2017 at CHU Constantine.
Email: Nouredine.abadi@univ-constantine3.dz

Satta Dalila
Professor in the Department of Genetics, and until 2022, the chief of the Laboratory of Molecular and Cellular Biology at the University Constantine 1, Algeria. Her research focuses on gene mutations through targeted analyses or panels of genes involved in human pathologies. Her lines of research include: 1- Genetic study of reproductive disorders and pathologies of the reproductive system (testicular and ovarian cancer) 2- molecular exploration of genetic and epigenetic abnormalities in cancer pathology, 3- Neurogenetic: the primary objective is to identify the genetic factors that increase a person's risk of developing a mental illness and their response to medications used in psychiatry.
Email: dsatta741@gmail.com