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Genetic screening for multiple endocrine neoplasia syndrome type 1 (MEN-1): when and how

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Abstract

Multiple endocrine neoplasia syndrome type 1 (MEN1) syndrome has benefited from the identification of the gene whose mutations account for the genetic susceptibility to develop endocrine tumors. Asymptomatic *MEN1* mutant carriers need to be clearly recognized because the gene-related mutations confer a high risk of multiple primary cancers, occur at younger ages, and affect multiple family members who inherit the cancer-predisposing genetic mutation.

Introduction and context

Multiple endocrine neoplasia syndrome type 1 (MEN1) syndrome is characterized by the occurrence of varying combinations of more than 20 endocrine and non-endocrine tumors. Endocrine tumors are represented mainly by the 'classic' P-triad originally described by Wermer: parathyroid, pituitary, and pancreatic tumors [1-4]. Tables 1 and 2 describe the endocrine and non-endocrine tumors associated with MEN1.

Familial and simplex MEN1 forms

The familial form of MEN1 syndrome occurs with a significantly higher frequency (90% of cases) than the simplex form, where only one individual is affected within a family with no history of the disease (10% of cases). Familial MEN1 is defined in an individual who has at least one first-degree relative with one or more main endocrine tumors or involvement of only one organ and a MEN1 disease-causing germline mutation. MEN1 syndrome is inherited in an autosomal dominant manner, and each child of an affected individual has a 50% chance of inheriting the mutation [5].

Clinical definition of MEN1

MEN1 syndrome can be defined by the presence of two 'classic' endocrine tumors (parathyroid, pituitary, or tumors of the gastro-entero-pancreatic tract) in an affected subject. In Figure 1, an algorithmic summary of the possible diagnostic scenario is presented.

Chromosomal location of the **MEN1** *gene and related tumorigenesis*

The *MEN1* gene was originally located on chromosome 11q13 [6-8]. The related tumorigenesis was according to Knudson's 'two hits' hypothesis [9], strongly suggesting a gene inactivation.

MEN1 *gene and its mutations*

The *MEN1* gene spans 9 kb and consists of 10 exons with a 1830-bp/1845-bp coding region encoding a novel 610/615-amino acid protein (two isoforms [10]), referred to as menin [11-13]. More than 1000 different germline *MEN1* mutations, without evidence of hot-spot regions, have been described [14-18], mainly predicting absent or truncated menin. Approximately 1-3% of *MEN1* germline mutations consist of large deletions detectable by Southern blot analysis or other gene dosage procedures (i.e., based on polymerase chain reaction) [15-18]. Polymorphic variants have also been described [18]. Neither the finding of a tumor suppressor mechanism nor the identification of binding partners has established the ultimate pathways of menin action in normal tissues or in tumors [16].

Table 1. Multiple endocrine neoplasia syndrome type 1 (MEN1)-related endocrine tumors and their prevalence (40 years)

Tumor type	Tumor subtype	Prevalence in MEN1 syndrome
Parathyroid[a]	Not applicable	100% by age 50 years
Anterior pituitary (~10-60% of cases have anterior pituitary tumors)		
	Prolactinoma (PRL-oma)	Most common anterior pituitary tumor
	Growth hormone-secreting	5%
	Growth hormone/ Prolactin-secreting	5%
	TSH-secreting	Rare
	ACTH-secreting	2%
Well-differentiated endocrine tumors		
	Gastrinoma[b]	40%
	Insulinoma	10%
	Glucagonoma	2%
	VIPoma	2%
Carcinoid		
	Bronchial Thymic[c]	10%
Adrenocortical (~20-40% of cases have adrenocortical tumors)		
	Cortisol-secreting	Rare
	Aldosterone-secreting	Rare
	Pheochromocytoma	<1%

[a]Parathyroid tumors represent the main MEN1-associated endocrinopathy whose onset, in 90% of individuals, is between the ages of 20 and 25 years with hypercalcemia evident by the age of 50 years. [b]The MEN1 gastrinomas, located mainly at the duodenal level, are frequently multiple and usually malignant, and half of them have metastasized before diagnosis. [c]Thymic carcinoids of MEN1 syndrome tend to be aggressive and are highly lethal, particularly in male smokers [16]. Adrenocortical tumors are rarely associated with primary hypercortisolism or hyperaldosteronism. Among the non-endocrine tumors, facial angiofibromas, collagenomas, lipomas, meningiomas, ependymomas, and leiomyomas have been described in MEN1 subjects [16]. ACTH, adrenocorticotropic hormone; PRL-oma, prolactin-secreting adenoma; TSH, thyroid-stimulating hormone; VIPoma, vasoactive intestinal peptide-producing tumor.

When and how to perform the genetic screening

A DNA test of the *MEN1* gene detects mutations in 80-90% of probands with familial MEN1 and in 65% of individuals with simplex MEN1 [18] (Table 3).

Genetic counseling in MEN1

Genetic counseling has a central role in the management of MEN1 patients and their closely related family members. MEN1 genetically predisposed subjects may benefit greatly from early identification by DNA analysis, especially at a presymptomatic stage [15,17]. Once a pathogenic *MEN1* mutation has been identified in a proband, referral to a clinical geneticist is advised. Since it is recommended that adequate genetic counseling be given prior to DNA testing, presymptomatic testing in families with an identified *MEN1* mutation should be performed within the context of genetic counseling [19] (Tables 3 and 4).

Table 2. Multiple endocrine neoplasia syndrome type 1 (MEN1)-related non-endocrine tumors and their prevalence (40 years)

Tumor type	Tumor subtype	Prevalence in MEN1 syndrome
Cutaneous tumors	Lipomas	30%
	Facial angiofibromas	85%
	Collagenomas	70%
Central nervous system	Meningiomas	5%
	Ependymomas	1%
Other	Leyomiomas	10%

Individuals at risk

Subjects in whom the germline mutation has not been identified are at risk if they have inherited the *MEN1* mutation from one affected parent or if they are the relatives of subjects clinically defined as suffering from MEN1.

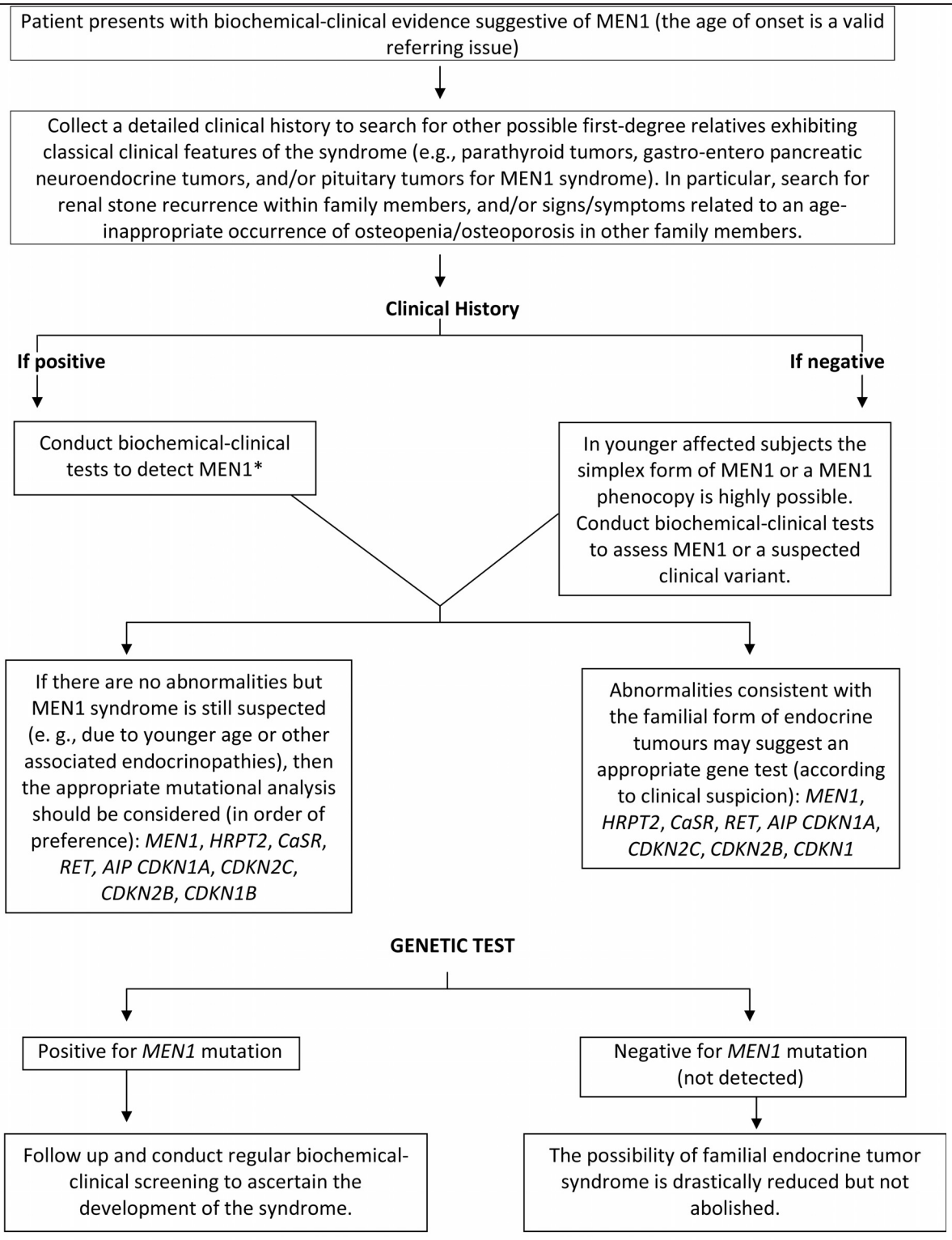
Testing of relatives at risk

Genetic testing should be offered to at-risk members of a family in which a germline *MEN1* mutation has been identified in an affected relative [18]. If molecular genetic testing is not possible or is not informative, individuals with a 50% risk (first-degree relatives of an individual with MEN1 syndrome) should undergo routine evaluation (Table 4). A DNA test for MEN1 may be offered to children within their first decade because tumors such as insulinoma and pituitary adenomas have developed in some children by the age of 5 years [2,20,21] (Table 4). Unfortunately, the great diversity and the lack of both mutational hot-spots and genotype-phenotype correlation make mutational screening time-consuming, arduous, and expensive [14]. Currently, a DNA test identifying an individual as a mutant gene carrier does not usually lead to immediate medical or surgical treatment, but it does suggest that precocious and frequent clinical screening should be carried out. Since we are still unable to predict tumor penetrance and malignancy individually, lifelong follow-up of *MEN1* carriers is strongly recommended to prevent tumor morbidity.

Risk to family members

Approximately 90% of MEN1 individuals have an affected parent. However, the family history may appear negative because of (a) failure to recognize the disorder in family members, (b) early death of the parent before the onset of symptoms, or (c) late onset of the disease in the affected parent [17]. The risk to the siblings of the proband depends on the genetic status of the proband's parents. If a parent of the proband is affected or has a disease-causing

Figure 1. Algorithmic summary of the diagnostic protocols



*when a germline *MEN1* mutation has already been detected in affected familial member, a DNA-based test should be performed before the biochemical-clinical testing.

MEN1, multiple endocrine neoplasia syndrome type 1.

Table 3. General features of multiple endocrine neoplasia syndrome type 1 (*MEN1*) predictive testing

- Diagnostic testing is appropriate in symptomatic individuals of any age.
- Confirming a diagnosis may alter medical management for the individual.
- It is medically indicated since early diagnosis allows interventions that reduce morbidity or mortality.
- Even in the absence of medical indications, predictive testing can influence life planning decisions.
- Molecular genetic testing of an affected family member may be required to determine the disease-causing mutation(s) present in the family.
- Genetic testing should be offered to at-risk members of a family in which a germline *MEN1* mutation has been identified in an affected relative. Identifying carriers allows reproductive choices.
- A DNA test in MEN1 may be offered to children within the first decade because tumors such as insulinoma and pituitary adenomas have developed in some children by the age of 5 years.
- Genetic counseling and education should accompany carrier testing because of the potential for personal and social concerns.
- Many laboratories will not proceed with predictive testing without proof of informed consent and genetic counseling.
- Identification of the specific gene mutation in an affected relative or establishment of linkage within the family should precede predictive testing.
- Because predictive testing can have psychological ramifications, careful patient assessment, counseling, and follow-up are important.
- Predictive testing of asymptomatic children at risk for an adult-onset or later-onset disorder is strongly discouraged when no medical intervention is available (American Society of Human Genetics/ American College of Medical Genetics Policy Statement - 1995) [38].
- If molecular genetic testing is not possible or is not informative, individuals at 50% risk (first-degree relatives of an individual with MEN1 syndrome) should undergo routine biochemical-clinical evaluation.
- Currently, a DNA test identifying an individual as a *MEN1* mutant gene carrier does not usually lead to immediate medical or surgical treatment, but it suggests precocious and frequent clinical screening.

Table 4. Considerations when a multiple endocrine neoplasia syndrome type 1 (*MEN1*) genetic test has to be ordered

The choosing of an adequate laboratory
Pretest counseling and appropriate informed consent
Sample logistics and supporting documentation
Test result interpretation and follow-up program

mutation, the risk to the siblings is 50%. If the disease-causing mutation found in the proband cannot be detected in the DNA of either parent, two possible explanations exist: (a) germline mosaicism in a parent or (b) a *de novo* mutation in the proband [17]. Each child of an individual with MEN1 has a 50% chance of inheriting the mutation. The risk to other family members depends on the status of the proband's parents. If a parent is found to be affected or to have a disease-causing mutation or both, his or her family members are at risk [17].

Families with an apparent de novo *mutation*

When neither parent of a proband with MEN1 has the disease-causing mutation or clinical evidence of the disorder, it is likely that the proband has a *de novo* mutation (approximately 10%). However, explanations such as alternate paternity or maternity (i.e., with assisted reproduction), undisclosed adoption, or secretiveness within the family could also be considered [17].

Testing of at-risk asymptomatic individuals

When a disease-causing germline mutation has been identified in an affected family member, the genetic testing of at-risk asymptomatic individuals is appropriate for surveillance. When a known disease-causing mutation is not identified, linkage or haplotype analysis can be considered in families with more than one affected family member from different generations. Early detection of at-risk individuals affects medical management, and testing of asymptomatic individuals during childhood is beneficial [17].

Prenatal testing

Prenatal testing for MEN1 syndrome is not commonly requested, partly due to the lack of a universal consensus on performing such a diagnosis in MEN1. The disease-causing allele of an affected family member must be identified or linkage established in the family before prenatal testing can be performed [17].

Detection of MEN1 *gene mutations*

The advantages of DNA analysis are that (a) it requires a single blood sample and (b) it does not need to be repeated since the analysis is independent of the age of the individual and provides an objective result. Approximately 45% of germline mutations detected by sequence analysis are small deletions, and approximately 15% are small insertions [5]. The likelihood of detecting a *MEN1* mutation is higher in individuals with more main P-triad tumors, especially from families with hyperparathyroidism and pancreatic islet tumors [22-24]. *MEN1* genetic screening should also be offered to patients with primary hyperparathyroidism or gastrinomas after thorough investigation into the family history [25]. Simplex MEN1 cases are less likely to test positive than familial cases, in part because some of these simplex cases may be caused by somatic mosaicism [24]. Individuals who have a single MEN1-related tumor and no family history of MEN1 syndrome rarely have germline *MEN1* mutations [22].

Recent advances

Intronic *MEN1* mutations, such as SpaGVs (splicing-affecting genomic variants), have been recently reported. They are likely to be of significance in the 10% of MEN1 patients who do not have coding region mutations [26,27]. A new intron 3 mutation associated with PRL-oma (prolactin-secreting adenoma), decreased familial penetrance, and variable effects on MEN1 mRNA and menin have recently been described [28]. The MLPA

(multiplex ligation-dependent probe amplification) assay may detect large deletions (4%) as germline mutation in *MEN1* [29]. Through polymorphism analyses, gene dose assays, and nucleotide sequencing, a large germline deletion (approximately 29-kb pairs), spanning the whole *MEN1* gene, has been identified in one patient with a positive family history for MEN1 whose germline *MEN1* mutation was undetectable by conventional sequencing analysis [30]. Moreover, genetically diagnosed patients already harbor manifestations at the time of diagnosis, confirming that screening for a *MEN1* mutation should be done at an early age [31].

It is very important to consider that germline mutations in other genes may cause a MEN1-like disorder in *MEN1* mutation-negative families, namely the *AIP* gene [32] and the four cyclin-dependent kinase inhibitor genes *CDKN1A*/p15, *CDKN2C*/p18, *CDKN2B*/p21, and *CDKN1B*/p27 [33-35]. Interestingly, several of the proteins encoded by these genes play a role within the same molecular pathway as the menin protein. Although germline mutations in these genes appear to be rare (probably explaining only a small fraction of the *MEN1* mutation-negative families), it may still be important to consider analysis of these genes in such families.

Implications for clinical practice

MEN1 mutant gene carriers must be followed by periodic clinical tumor surveillance as well as surveillance of recurrence after treatment or progression of the disease. The knowledge about carrier status enables early diagnosis and intervention [2,17]. A prospective clinical study on *MEN1* mutant gene carriers revealed that biochemical evidence of neoplasia could be identified an average of 10 years before the clinical evidence of the disease, allowing early surgery. Thus, genetically positive individuals should undergo a focused surveillance for early identification of potentially malignant neuroendocrine tumors accounting for morbidity and/or mortality related to MEN1 [18].

Importantly, a very recent study having as the primary endpoint the evaluation of the occurrence of non-functioning pancreatic tumors (PETs) in asymptomatic *MEN1* children carriers revealed the presence of non-functioning PETs, providing the opportunity to perform clinical surveillance to unravel their growth [36]. Thus, according to Triponez *et al.* [37], the possibility of precociously identifying asymptomatic MEN1 children carriers, as well as young adults with MEN1, may be helpful for the early identification of non-functioning PETs that otherwise may not be biochemically identified.

Gene testing decreased the morbidity and mortality associated with MEN1

A multicenter study of more than 250 *MEN1* gene carriers revealed that, as a result of differential tumor detection, *MEN1* carriers born during the second half of the 20th century tend to have their tumors diagnosed earlier than carriers of the same age born in the first half [31], a known general phenomen (anticipation phenomenon) observed in several other inherited tumors.

Conclusions

The identification of many molecular partners interacting with menin has increased our knowledge of its pathophysiology. However, more studies are necessary to clarify the MEN1-dependent tumorigenesis and the role that menin has in the development of endocrine and non-endocrine tumors. In the near future, there are prospects for novel treatments based on DNA, RNA, or even other small molecules. A better understanding of the intricate molecular pathway networks related to menin will be helpful for designing novel therapeutic strategies.

Abbreviations

MEN1, multiple endocrine neoplasia syndrome type 1; PET, pancreatic tumor.

Competing interests

The author declares that he has no competing interests.

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