Best Practice & Research Clinical Endocrinology & Metabolism 30 (2016) 115–127

Contents lists available at ScienceDirect

Best Practice & Research Clinical Endocrinology & Metabolism

journal homepage: www.elsevier.com/locate/beem

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Somatic and germline mutations in NETs: Implications for their diagnosis and management

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ARTICLE INFO

Article history:
Available online 9 October 2015

Keywords:
genetic
lung NETs
mutation
multiple endocrine neoplasia
neuroendocrine tumour
pancreatic NETs
paraganglioma/phaeocromocytoma
syndromic NETs
sporadic NETs

It is now understood that specific somatic and germline mutations may lead to the development of the neuroendocrine tumours (NETs). NETs usually occur as sporadic isolated tumours, although they also may present as part of complex familial endocrine cancer syndromes, such as multiple endocrine neoplasia type 1 (MEN1) and type 2 (MEN2), Von Hippel-Lindau (VHL) and neurofibromatosis syndromes, tuberous sclerosis, Carney triad and dyad, Reed syndrome and polycythaemia–paraganglioma syndromes. Only in MEN2 syndrome is there a specific genotype–phenotype correlation, although in both sporadic and syndromic NETs some gene mutations are associated with specific clinico-pathological features and prognosis. There have been several advances in our understanding of the NETs leading to earlier detection and targeted therapeutic treatment, but given the poor prognosis associated with metastatic NETs, it will be necessary to find new biomarkers for the prediction of malignant potential and to find novel therapeutic targets for NETs.

Neuroendocrine tumours (NETs) generally occur as sporadic isolated tumours, although they may present as part of complex familial endocrine cancer syndromes. Genes can mutate in either germinal or somatic tissue; these changes are respectively called germinal and somatic mutations. Germinal

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http://dx.doi.org/10.1016/j.beem.2015.09.007
1521-690X/

mutations may be transmitted to the progeny, while somatic mutations are not inherited. Contemporary technology has helped to identify novel mutations and has increased our understanding of neuroendocrine tumorigenesis.

Syndromic forms

Multiple endocrine neoplasia type 1

The multiple endocrine neoplasia type 1 (MEN1) syndrome is an autosomal dominant disorder which occurs in the context of an inactivating mutation of the *MEN1* gene. MEN1 can be diagnosed clinically if a patient has two of these three tumours: duodeno-pancreatic neuroendocrine tumours (dpNETs), anterior pituitary tumours and parathyroid tumours. Familial MEN1 is defined by the presence of at least one MEN1 case plus at least one first-degree relative with one of those three tumours. Apart from these manifestations, others endocrinopathies may be present, including NETs of the thymus (thNETs) and lung, adrenal tumours, lipomas, and multiple skin lesions [1].

Genetics

MEN1 is a tumour suppressor gene and encodes for the protein MENIN [2]. MENIN, which is ubiquitously expressed, interacts with molecules involved in several cellular processes, including transcription regulation, DNA replication, DNA repair and signal transduction. It also targets several genes including homoeobox domain genes, human telomerase, nuclear receptor genes and cyclin-dependent kinase inhibitors [2–6].

More than 1336 different *MEN1* mutations have been identified in MEN1 patients, 203 somatic and 1133 germline to date; truncated and missense mutations have been reported in most of the cases, but larger changes such as deletions may also occur [4].

The majority of the MEN1 related NETs develop after loss of heterozygosity (LOH) on chromosome 11q13 at a tissue level. According to Knudson's 'two-hit hypothesis', biallelic inactivation of MEN1 is required for tumour development [7,8]. The inheritance of a germline MEN1 mutation predisposes an individual to developing a tumour, which arises after a second-hit somatic mutation. Nevertheless, LOH is not observed in about 10% of MEN1-associated tumours. In these cases inactivation of the wild-type allele most commonly occurs as a result of a small deletion, a point mutation or insertion within the coding region, or splice sites of the *MEN1* gene [9].

More than 10% of MEN1 germline mutations arise *de novo* and may be transmitted to the progeny [4]. Patients with MEN1-associated tumours but without *MEN1* mutations may harbour mutations involving other genes or represent *phenocopies*, which may confound the diagnosis of MEN1. Phenocopy refers to the development of disease manifestations which are usually associated with mutations of a gene but instead are due to another aetiology. The involvement of another gene, *CDKN1B*, has been reported by studies of patients who did not have *MEN1* mutations but did have MEN1-associated tumours. Mutations of *CDKN1B*, which codes for the cyclin-dependent kinase inhibitor p27, have been reported in approximately 1.5% of these patients and their families, and this condition is now referred to as MEN4 [10].

Other inherited mutations associated with the MEN1 syndrome, albeit very rare, have been described. Germline mutations of the cyclin-dependent kinase inhibitor genes *CDKN2B* (p15), *CDKN2C* (p18) and *CDKN1A* (p21) may be probable causes of MEN1 in approximately 1, 0.5, and 0.5% of patients, respectively [10,11].

Clinical implications

A clear *MEN1* genotype–phenotype correlation has not been established and combinations of these tumours may be different in members of the same family [12]. In general, primary hyperparathyroidism is the first manifestation of the disease, and there is 95% penetrance of this, in both sexes, by the age of 40 years. However, a recent study showed that patients who develop MEN1-related tumours bearing the CDKN1B V109G polymorphism have a higher frequency to develop aggressive tumours, finding a shorter time interval between birth and the first aggressive tumour and between MEN1 diagnosis and age of the first aggressive tumour [13]. A large-scale French study of 806 MEN1 patients