

# Familial neuroendocrine tumor syndromes: From genetics to clinical practice

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**Abstract** Thanks to recent developments in molecular biology and cancer genetics, genetic testing has become widely available and useful in several kinds of familial tumor syndrome. However, the impact of genetic testing on medical management is not always straightforward. Clinicians have to consider the psychological impact and ethical complexities of communicating hereditary cancer risk information to families. This review notes some points on genetic counseling before and after genetic testing for familial neuroendocrine tumor syndromes.

**Keywords** Presymptomatic testing · Genetic counseling · Distress · Survivor's guilt

## Genetics of neuroendocrine tumors

The definition of the “neuroendocrine tumor” seems to some extent ambiguous. The website of the National Cancer Institute describes the neuroendocrine tumor (NET) as “a tumor derived from cells that release a hormone in response to a signal from the nervous system. Some representative examples of neuroendocrine tumors are carcinoid tumors, islet cell tumors, medullary thyroid carcinoma, and pheochromocytoma. These tumors secrete hormones in excess, caus-

ing a variety of symptoms.” Meanwhile, some researchers define the NET as a tumor which produces hormones and expresses specific markers such as neuron-specific enolase (NSE), chromogranin and synaptophysin. In either case, the NET is characterized not by its location but by its cellular features.

NETs are rare disorders and sporadic in most cases. But familial NETs are also known and the genes responsible for those syndromes have been isolated. This review notes some points on genetic counseling before and after genetic testing for familial cancer syndromes.

## Application of genetic information to clinical practice

Unlike other laboratory tests, genetic testing has some characteristic features. Clinicians have to be aware of this fact and the impact of genetic testing on patients and family members.

### Specific features of genetic testing

Many genes responsible for familial NETs have been isolated and the opportunities of genetic testing for those genes in clinical practice are increasing. Advances in genetic science have largely changed the diagnosis and management of familial tumor syndromes. It seems that genetic testing has become one of the everyday items in laboratory tests. However, it should be noted that genetic testing has a number of particular features compared with other laboratory tests.

### *Unchangeability*

Unlike other laboratory test results, the genetic information of each individual does not change from conception to death (and even after death). This is why the ultimate privacy

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regarding each individual's genetic information must be regarded as sacrosanct. Such information could be exploited for discrimination or stigmatization unless appropriately managed by specialists. To recognize the utility and possible hazards of genetic information and to learn the way to appropriately handle such information is very important for all clinicians.

#### *Predictability*

In the case of an existing disease, other laboratory tests can also to some extent predict the patient's clinical course and prognosis. On the other hand, genetic information can predict the future occurrence of the disease with high reliability in a currently healthy individual, particularly in the case of an adult-onset disease with high penetrance. This is capable of causing significant psychological distress, grief, anger and so on. It is very important for clinicians to understand the psychological impact of genetic testing and to know how to deal with that issue.

#### *Sharing among relatives*

First-degree relatives (parents, offspring, siblings) share 50% of the genetic information of each other. Once a deleterious mutation is found in one member of the family, other members of the family have the chance of carrying the same mutation; the probability of actually having the mutation depends on the distance of each individual from a proband. This means that genetic information in one individual can be utilized for the health care of other family members, by early (presymptomatic) diagnosis and early intervention. However, it is also the case that once the genetic status of one individual is clarified, family members can be forced to become involved in issues of genetic disease whether they wish to or not.

#### *Benefits of genetic testing for familial tumors*

##### *More accurate information on natural history and prognosis*

Unless a positive family history is already known, it is not easy to determine whether any tumor occurring in a patient is based on genetic predisposition or not. In general, hereditary tumors tend to occur at an earlier age than the same tumor without genetic predisposition (e.g., the average age of the onset of hyperparathyroidism in MEN1 patients is about 20 years, while sporadic hyperparathyroidism occurs predominantly in middle-aged to elderly women). However, there is a certain overlap between sporadic cases and familial cases, and it is difficult to distinguish them from each other simply with clinical presentation and/or pathological examination.

Genetic testing can clarify the presence of a genetic background on the occurrence of the tumor in the patient, which enables a more accurate and reliable prediction of the natural history and/or prognosis of the tumor. As an example, in patients with paraganglioma, genetic testing for *SDHX* genes may be informative in predicting the prognosis. A high percentage of malignant transformation is known in patients with *SDHB* mutation compared with patients without an *SDHB* mutation or patients with an *SDHD* mutation [1].

##### *More specified management*

Clarification of the genetic background of the tumor enables a more specified clinical management based on the prediction of the natural history of the tumor. Surgical procedure and follow-up strategies can be modified with genetic information. For example, the standard surgical approach for sporadic primary hyperparathyroidism is removal of the adenoma, while total parathyroidectomy with autotransplantation is the most widely selected procedure for patients with MEN1-associated primary hyperparathyroidism [2]. For patients with MEN1, partial thymectomy could also be considered at the time of surgery [3]. For medullary thyroid cancer, partial thyroidectomy is usually chosen for sporadic cases, but total thyroidectomy with extensive lymph node resection is required if genetic testing has revealed *RET* mutation [4].

##### *Information on the risk of family members and next generations*

If a deleterious mutation is found in a patient, the genetic status of family members and their risk of having the same tumor can be clarified. Identification of the mutation before development of clinical symptoms is expected to improve the future prognosis of such individuals by offering an efficient surveillance program or in some diseases, the option for prophylactic surgery. Also, determination of the genetic status makes it possible to provide precise information on the risk of the children of the patient for future development of the same disease. Knowing their own genetic status may also affect patients' self-image and family planning [5].

##### *Opportunity to be aware of/join a patient support group*

Since familial NET syndromes are rare, most patients are not familiar with the disease they have been diagnosed as having. They have never seen other patients with the same disease. Patients want as much information as they can obtain but that may be insufficient because their attending physicians are not necessarily familiar with that disease, making patients feel a sense of isolation. Patients' alliances or self

support groups have been established for many of hereditary diseases and those organizations function to strengthen their solidarity and share the latest information on the disease. They also deliver messages from the patients to the administration or the government. Following the establishing of their diagnosis, patients may want to contact such support groups, and physicians and genetic counselors can help patients to do so [6]. Joining a patients' alliance may help patients to reduce the feeling of isolation and to obtain more information on their disease. Their attitude toward disease or even views on life may be affected through personal exchanges in the alliance.

#### *Reduce psychological distress*

Members of a family with hereditary tumor syndromes experience a variety of forms of emotional distress; anxiety and fear about developing cancer, anger and frustration about the uncertainty of their future, fear of death, and so on. Genetic testing may reduce the uncertainty of the future of the client, and thus may reduce psychological distress even if the result of the test is positive. A negative result will naturally bring relief to a client, guarantees that the client can terminate periodical screening and offers assurance that the client's offspring will not inherit the deleterious mutation. To offer appropriate genetic counseling is crucial to ensure that clients understand and accept the result, and allow effective health management for clients based on the information developed from the testing.

#### *Positive behavioral changes*

Patients may start to consider their health status and try to do what their physicians recommend in a more positive way. Identification of genetic status may facilitate the patients' willingness to have periodic surveillance compared to when their genetic status is ambiguous.

#### *Possible hazards of genetic testing*

##### *Inconclusive results*

Many clients expect that their genetic status will become clear by genetic testing, but that is not always the case. If the deleterious mutation has already been identified in the family, a negative result automatically indicates that the client did not inherit the mutation, thus risk of developing a specific cancer is not high (the same as the general population). On the other hand, if the mutation has not yet been identified in the family or the client is the first patient in the family with the mutation, interpretation of the test result has to be done with caution.

- *When mutation is found in the gene examined.* If this mutation has been reported as a deleterious mutation, interpretation of the result is straightforward. In general, non-sense mutation or frame-shift mutation is highly likely to be causative mutation. If the identified mutation is a missense mutation, the conclusion that the mutation may be pathologic should be drawn with caution since it could be a benign polymorphism. In such case, linkage between this mutation and occurrence of the tumor has to be examined in the family, and prevalence of this mutation in the general population may also be examined. If there is only one patient in a family and a missense mutation is found in that patient, the significance of the mutation cannot be determined unless laboratory study of the mutant gene product reveals functional impairment.
- *When mutation is not found in the gene examined.* The client may not have mutation in the gene, but may have a mutation in another area which is usually not examined (promoter region and introns). Alternatively, the client may have a large deletion of the gene which cannot be detected by simple sequence analysis. In von Hippel-Lindau disease, about 30% of patients have a deletional mutation in the *VHL* gene, which can be detected by gene dosage analysis [7].

The significance of negative results differs from disease to disease. For example, a negative result of *RET* gene mutation analysis in a patient with medullary thyroid cancer can almost totally rule out the possibility of MEN2. On the other hand, for a disease in which the mutation detection rate is low, such as familial isolated hyperparathyroidism, a negative result cannot rule out the possibility of genetic predisposition [8].

#### *Psychological distress*

Disclosure of the result of genetic testing causes a variety of emotional responses. Clients who are informed of a positive result typically experience sadness, disappointment, shock, anger, anxiety, fear of becoming a burden, fear of dying, grief, negative body image and so on. Clients who are informed of a negative result experience relief and joy, but they can also experience some psychological distress. There are a few studies which have described the psychological responses after disclosure of genetic testing for NET syndromes. Grosfeld et al. examined the psychological impact of genetic testing for MEN2 [9]. An unfavorable test outcome (*RET* mutation positive) resulted in anxiety and depression but also relief. Carriers were preoccupied with disease-related complaints. A favorable test (*RET* mutation negative) led, in most applicants and partners, to both relief and worry. Some non-carriers felt guilty and isolated from their families.

*Case 1.* Two sisters aged 22 and 20 visited genetic counseling. They were at risk of von Hippel-Lindau disease. Their father and paternal grandmother suffered from von Hippel-Lindau disease and the *VHL* gene mutation was detected in the father. These sisters requested presymptomatic genetic testing. After genetic counseling and suitable informed consent, the testing was carried out. The result was that the younger sister was negative and the older was positive. Soon after the disclosure of the result, the younger sister became very depressed and she was unable to go to college for several months.

She may have felt “survivor’s guilt” and suffered from non-carrier syndrome [10]. She may also have felt that she was isolated from affected or mutation-positive family members. Counselors have to pay attention even to individuals with a preferable result after presymptomatic genetic testing.

#### *Conflict within family members*

Autonomy is the cornerstone of genetic testing. However, difference in views and expectations toward genetic testing can create significant conflicts among family members. Such conflicts can interrupt their close relationships and worsen psychological distress.

*Case 2.* A 37-year-old woman visited a hospital because of secondary amenorrhea. Examination revealed primary hyperparathyroidism and prolactinoma, and she was diagnosed as having MEN1. Her brothers, sisters, and some nieces worried that they might also be affected with MEN1 in the future and asked her to undergo a genetic testing for the *MEN1* gene. She understood that her relatives wanted her test result for their presymptomatic testing, but she was not willing to take the test because she did not have children and the test result would not alter her future surveillance plan.

### **Genetic testing and genetic counseling**

What is genetic counseling?

Genetic counseling is defined by the National Society of Genetic Counselors’ Definition Task Force [11] as “the process of helping people understand and adapt to the medical, psychological and familial implications of genetic contributions to disease. This process integrates the following:

- Interpretation of family and medical histories to assess the chance of disease occurrence or recurrence.
- Education about inheritance, testing, management, prevention, resources and research.
- Counseling to promote informed choices and adaptation to the risk or condition.”

#### Process of genetic counseling

Ideally, genetic counseling should be carried out over several sessions to cover the following issues.

#### *Determination of the autonomy*

At the first visit, counselor has to assess the autonomy of the client, in other words, why the client requested genetic counseling. Some clients may have come to genetic counseling with high motivation and with their own goals for genetic counseling, while other clients may be rather reluctant and are to some extent uncomfortable about undergoing genetic counseling. For example, the client does not want to assess their risk of cancer but they may have been under pressure from their relatives to have genetic testing.

#### *Taking the family history*

Taking the family history is the core element of genetic counseling. Careful and extensive family history taking sometimes draws the correct diagnosis and assesses the risk of the client by itself. Although accuracy of the family history greatly influences the value of a pedigree, clients do not always remember the medical history of relatives and may misunderstand the diagnosis. Asking permission to review the medical records of relatives may be necessary. Since the family history represents very private information regarding the client and family members, management and secure storage requires a high level of attention.

#### *Risk assessment*

Genetic counselors analyze the family history and estimate the risk of the client to inherit a deleterious mutation in a gene that has caused specific tumors in their family. Since most familial cancer syndromes are inherited in an autosomal dominant manner, the risk of the client is calculated on the basis of the genetic distance of the client from the identified patients in the family and penetrance of the disease. The age of the client is also an important element to estimate the risk since many tumors in familial tumor syndromes occur in a certain age group (usually younger than sporadic tumors), and so the risk of developing a tumor declines as the age of the client increases.

#### *Options for testing and screening/surveillance*

During the first visit of a genetic counseling regimen for a familial tumor syndrome, the genetic counselor usually discusses the availability of genetic testing in case it might be useful for clients. Alternatively, the counselor may find that the cancer status of the client’s family is not likely to be

hereditary and genetic testing is not applicable, despite the client's wishes to undergo a test. During genetic counseling, the counselor has to discuss with clients what can be clarified and what cannot be clarified by genetic testing. It is important to ask clients about their likely reaction should the test result be positive, negative, or inconclusive. Simulating reactions after disclosure of the test result will enable clients to reconsider the significance of genetic testing and may reduce psychological distress after disclosure of the test result, regardless of the outcome.

Unless clients are sure that they really want genetic testing with a full understanding of its significance and limitation, and they are emotionally prepared to take the test and receive the result, it may be appropriate for the counselor to propose that the clients to go home and to decide whether or not to undergo genetic testing having carefully considered all topics discussed. The counselor should encourage clients to discuss their plans and concerns with family members. Some clients may decide not to undergo genetic testing and rather to continue periodical screening.

#### *Genetic testing and informed consent*

In many cases, because of the situations described above, drawing of blood for genetic testing is performed at the second visit. Before drawing blood, benefits, possible risks and limitations of the testing should be reviewed again and the psychological status of clients should be briefly examined by the counselor. At the same time, the person to whom the test result will be disclosed and those who should have access to the result should be clarified.

#### *Disclosure of test results*

The result of genetic testing is normally disclosed at the third visit, with the interval between sampling and disclosure depending on laboratory requirements. Before disclosure of the result, the counselor should again confirm that the client wants to receive the result of the genetic testing, because the client may have changed their mind. The result should be delivered as quickly as possible. After disclosure, implications of the result and an appropriate follow-up plan for clients are discussed. During discussion, the counselor has to carefully observe client's emotional status. A calm atmosphere and clear speaking on the part of the counselor are desirable.

#### *Follow-up*

A series of genetic counseling meetings does not end with the disclosure of the results or completion to provide information. The psychological impact of genetic testing can last for a long period and the attitude and self image of clients

may change after a certain period of time, so the counselor should keep contact with the client by telephone or e-mail to continue support. Setting of an additional counseling session or sessions may be appropriate for some clients.

#### Specific considerations

##### *Genetic testing for children*

With a few exceptions, tumors occur after adolescence in patients with familial NETs. For those diseases, the benefits and risks of testing children for a mutation have been carefully considered.

Many individuals who have cancer predisposing mutations want to know whether their children have inherited the mutation. Genetic testing of children for adult-onset disease may reduce parental anxiety and remove worry about cancer risk from children once they are found not to inherit the deleterious mutation. On the other hand, knowing their genetic status may affect the self-esteem and emotional well-being of children and could disrupt familial equilibrium and cause stigmatization by parents. Also, the right of autonomy of children cannot be protected and the privacy of their genetic information cannot be fully assured.

*Case 3.* A 35-year-old man had been suffering from paraganglioma and mutation of the *SDHB* gene has been already detected. He had two children aged 6 and 3 years. He visited genetic counseling and asked for presymptomatic genetic testing for his children.

Is it ethical to take up his request and test the *SDHB* gene of the children? If the disease this client suffers is MEN2, presymptomatic testing of *RET* gene mutation for children would be appropriate because carrier detection of MEN2 would enable the possibility of prophylactic thyroidectomy for children who have tested positive and that would significantly improve the prognosis [12]. What about presymptomatic testing for adult-onset diseases such as familial paraganglioma? Testing of *SDHB* mutation for children will not provide any prophylactic options or specific surveillance program even if the result is positive. In general, testing of children should be offered at the earliest age when health benefits accrue, but not before this time. Accepting the parents' request and performing genetic testing too early provides no medical benefits but rather lead to stigmatization. If no benefits exist, the counselor should advise parents to restrain their desire to know the genetic status of their children. When the children themselves express their willingness and request genetic testing, such a request has to be respected, but the autonomy of the children has to be carefully estimated. They could be under pressure to take a test from their parents or other relatives.

### Duty to warn family members

**Case 4.** A 40-year-old woman visited a hospital because of hypertension. Examination revealed she had right adrenal pheochromocytoma. During examination, a thyroid mass was incidentally noticed by an attending physician and that was found to be medullary thyroid cancer. MEN2A was suspected and genetic testing confirmed she had an activating mutation in the *RET* gene. Because she had two younger brothers and a daughter, the counselor and an attending physician suggested that she should pass on the test result to family members and advise them to take a test. Although she had agreed to do so before testing, following the test she said that she was not going to tell the result to anyone, not even to her husband.

In this case, the client is absolutely obliged to explain her disease and the result of the genetic testing to other family members even though it means sacrificing her privacy. This is a kind of burden for her. She needs support and suggestions from the counselor how to explain everything to her family members and practical advice on how to deal with emotional distress. The counselor has to consider methods to help this patient reduce her distress and pass on information about the disease and her genetic testing, so that the future health of her family members can be protected.

### Conclusions

Cancer genetic counseling is a field which has recently emerged in clinical medicine. All clinicians should be aware of the psychological impact and ethical complexities of hereditary tumor syndromes and to learn how to communicate in a supportive manner with affected patients and their family members. References [13 to 15] are recommended to read to know more about genetic counseling for familial tumor syndromes [13–15].

### References

1. Favier J, Briere JJ, Strompf L, Amar L, Filali M, Jeunemaitre X, Rustin P, Gimenez-Roqueplo AP (2005) PGL.NET Network. Hereditary paraganglioma/pheochromocytoma and inherited succinate dehydrogenase deficiency. *Horm Res* 63:171–179

2. Carling T, Udelsmann R (2005) Parathyroid surgery in familial hyperparathyroid disorders. *J Intern Med* 257:27–37
3. Lambert LA, Shapiro SE, Lee JE, Perrier ND, Truong M, Wallace MJ, Hoff AO, Gagel RF, Evans DB (2005) Surgical treatment of hyperparathyroidism in patients with multiple endocrine neoplasia type 1. *Arch Surg* 140:374–382
4. Pacini F, Romei C, Miccoli P, Elisei R, Molinaro E, Mancusi F, Iacconi P, Basolo F, Martino E, Pinchera A (1995) Early treatment of hereditary medullary thyroid carcinoma after attribution of multiple endocrine neoplasia type 2 gene carrier status by screening for *ret* gene mutations. *Surgery* 118:1031–1035
5. Loader S, Shields C, Rowley PT (2005) Impact of genetic counseling and DNA testing on individuals with colorectal cancer with a positive family history: a population-based study. *Genet Test* 9:313–319
6. Lips CJ, Hoppener JW, Van Nesselrooij BP, Van der Luijt RB (2005) Counselling in multiple endocrine neoplasia syndromes: from individual experience to general guidelines. *J Intern Med* 257:69–77
7. Hattori K, Teranishi J, Stolle C, Yoshida M, Kondo K, Kishida T, Kanno H, Baba M, Kubota Y, Yao M (2006) Detection of germline deletions using real-time quantitative polymerase chain reaction in Japanese patients with von Hippel-Lindau disease. *Cancer Sci* 97:400–405.
8. Simonds WF, Robbins CM, Agarwal SK, Hendy GN, Carpten JD, Marx SJ (2004) Familial isolated hyperparathyroidism is rarely caused by germline mutation in *HRPT2*, the gene for the hyperparathyroidism-jaw tumor syndrome. *J Clin Endocrinol Metab* 89:96–102
9. Grosfeld FJ, Lips CJ, Ten Kroode HF, Beemer FA, Van Spijker HG, Brouwers-Smalbraak GJ (1996) Psychosocial consequences of DNA analysis for MEN type 2. *Oncology* 10:141–146
10. Wiggins S, Whyte P, Huggins M, Adam S, Theilmann J, Bloch M, Sheps SB, Schechter MT, Hayden MR (1992) The psychological consequences of predictive testing for Huntington's disease. Canadian collaborative study of predictive testing. *N Engl J Med* 327:1401–1405
11. National Society of Genetic Counselors' Definition Task Force; Resta R, Biesecker BB, Bennett RL, Blum S, Hahn SE, Strecker MN, Williams JL (2006) A new definition of Genetic Counseling: National society of genetic counselors' task force report. *J Genet Couns* 15:77–83.
12. Brandi ML, Gagel RF, Angeli A, Bilezikian JP, Beck-Peccoz P, Bordi C, Conte-Devolx B, Falchetti A, Gheri RG, Libroia A, Lips CJ, Lombardi G, Mannelli M, Pacini F, Ponder BA, Raue F, Skogseid B, Tamburrano G, Thakker RV, Thompson NW, Tomassetti P, Tonelli F, Wells SA Jr, Marx SJ (2001) Guidelines for diagnosis and therapy of MEN type 1 and type 2. *J Clin Endocrinol Metab* 86:5658–5671
13. Batenaude AF (2004) Genetic testing for cancer. Psychological approaches for helping patients and families. Washington, DC: American Psychological Association.
14. Schneider K (2002) Counseling about cancer. Strategies for genetic counseling, 2nd ed. Wiley-Liss, New York.
15. Review of ethical issues in medical genetics. World Health Organization Home Page. <http://www.who.int/genomics/publications/>