INTRODUCTION

Prior to 2000 papillary thyroid carcinoma (PTC) was considered by most to be a sporadic disorder without familial predisposition. In contrast to this traditional teaching and as understood early on by Dr. Nadir Farid [1], approximately 5 percent of all PTC are familial. The evidence that supports this familial susceptibility is reviewed here and potential clinical implications are discussed. In addition, PTC may be a relatively infrequent component of other familial tumor syndromes. Although recent findings strongly support a familial PTC predisposition, the final proof will require the identification of the susceptibility genes. There is not yet convincing evidence to suggest that other nonmedullary thyroid carcinomas (follicular thyroid carcinoma, anaplastic thyroid carcinoma, and insular thyroid carcinoma) are familial.

EVIDENCE FOR AN INHERITED SUSCEPTIBILITY TO PTC

It is reasonable to suggest that any malignancy may have a familial predisposition. Cancer is caused by multiple gene mutations that are acquired over time by the cancer progenitor cell. Although these are usually somatic mutations, it would not be surprising if the first gene mutation was inherited (germline mutation). Family members possessing this hypothetical gene mutation would be at increased risk for developing PTC. Such a hypothetical susceptibility gene could persist in the population. It takes years to decades for the thyroid cancer progenitor cell to develop into a malignancy, since it must acquire other necessary gene mutations. Even then the malignancy is slow
growing. If such an inherited gene mutation did not disrupt other essential functions, then those individuals carrying this susceptibility gene mutation would not be at any reproductive disadvantage. By chance alone the gene mutation could persist within a population. Therefore, one can make a theoretical argument that a familial predisposition to PTC may occur.

Epidemiological studies, pedigree analysis, and pathology studies all provide evidence for a familial susceptibility to PTC. Although no single type of study is sufficient to prove a familial susceptibility, taken as a whole, the evidence is strong. This evidence led investigators with access to large kindreds to perform linkage studies that further support a familial predisposition to this disorder. Interestingly, the linkage studies suggest that familial PTC (fPTC) is a heterogeneous disorder caused by more than one susceptibility gene.

Epidemiologic studies have consistently found that first-degree relatives of those with PTC have a 4 to 10 fold increased risk of PTC [2–7]. Most other malignancies in these same studies do not show this familial association. Therefore, it seems unlikely that the observed PTC association is due to an ascertainment bias. Other interpretations of this association include a predisposition caused by an environmental exposure. It seems unlikely that this would be an unusual environmental factor such as radioactive iodine released from nuclear tests, since the association has been observed in multiple studies on different continents and is not limited to populations with the greatest exposure to radiation. This does not exclude the possibility that the susceptibility gene may act by increasing the risk of malignancy as a result of exposure to a more common environmental factor.

A number of large kindreds with fPTC have been described [8–15]. These kindreds are further evidence for a familial predisposition to PTC. Against this interpretation, it can be argued that these kindreds represent the rare association of multiple sporadic thyroid carcinomas, and that the number of affected family members has been exaggerated by ascertainment bias. That is, once two family members have been identified an aggressive search for thyroid carcinoma in other family members may identify microscopic (<1 cm) papillary thyroid carcinomas that have no clinical significance, and, as opposed to large PTC (>1 cm), are relatively common at post mortem examination. However, this is probably not the case, since the PTC within kindreds differs from sporadic PTC in two subtle characteristics. First, fPTC generally presents at a younger age than sporadic disease [16]. Second, there is a greater prevalence of multifocal disease in fPTC than in sporadic PTC [16, 17]. Multifocal disease within the thyroid suggests that a predisposing factor (possibly an inherited genetic susceptibility) is present. Finally, analyses of large kindreds with genetic linkage studies have identified statistically significant associations of PTC with specific chromosomal regions, and these are discussed in the next section. For all these reasons it seems likely the familial association of PTC does not represent the rare association of sporadic PTC, but represents a true familial predisposition.

In summary, the epidemiologic observation of an increased incidence of PTC in first degree relatives of PTC subjects, the presence of large kindreds in which affected
members have a tendency to develop PTC at a relatively young age, and the pathologic finding of multifocality taken together suggest that some cases of PTC are caused by an inherited susceptibility gene mutation. It should be noted that others have interpreted these results to suggest that the familial clustering of PTC indicates that fPTC is a polygenic disease caused by relatively more common but less disruptive gene polymorphisms when the associate by chance in a single kindred [18]. These two hypotheses are not mutually exclusive.

**LINKAGE ANALYSIS AND THE CHROMOSOMAL LOCI OF PUTATIVE fPTC SUSCEPTIBILITY GENES**

Many tumor susceptibility genes are discovered through the genetic analysis of large kindreds. Genetic analysis is particularly useful for identifying tumor susceptibility genes that were of unknown function. The first step in this genetic analysis is to determine the chromosomal location of the tumor susceptibility gene by linkage analysis.

Linkage analysis has been applied to large fPTC kindreds and statistically significant linkage of fPTC to specific chromosomal regions has been identified (Table 1). In linkage studies a statistically significant association is generally agreed to occur when the odds ratio of the probability of affected subjects carrying the same genetic polymorphism and unaffected subjects not carrying this polymorphism is one in one thousand or greater. The results are summarized as a log of the odds ratio or LOD score, so that a LOD score of 3.0 or greater is considered statistically significant. Interestingly the results between studies are discordant suggesting more than one susceptibility gene.

A large kindred with fPTC and benign thyroid nodules with the distinct pathologic finding of eosinophilia (TCO) has been mapped to 19p13.2 with a maximum LOD score of 3.0 [19]. Eosinophilia refers to the staining of the cytosol by eosin, is often caused by a large cytoplasmic population of mitochondria, and in the thyroid these are often referred to as Hurthle cells. Interestingly, other fPTC kindreds also link to this region (19p13), but the fPTC in these kindreds were not associated with eosinophilia [20]. Since the tumors of these fPTC kindreds are pathologically distinct, it is possible that there are two different susceptibility genes at this locus. Alternatively, there may be a single susceptibility gene this locus and an additional modifier gene contributes to the eosinophilia in one kindred.

**Table 1. Familial papillary thyroid carcinoma—summary of linkage analyses**

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Clinical description</th>
<th>Linkage locus</th>
<th>Reference</th>
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<tr>
<td>TCO</td>
<td>Oxysophilic PTC and benign oxysophilic nodules Autosomal Dominant with Partial Penetration</td>
<td>19p13.2</td>
<td>[19]</td>
</tr>
<tr>
<td>PTC at 19p13</td>
<td>PTC without oxysophilia Autosomal dominant</td>
<td>19p13</td>
<td>[20]</td>
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<tr>
<td>FNMTCT</td>
<td>Autosomal Dominant with Partial Penetrance</td>
<td>2q21</td>
<td>[21]</td>
</tr>
<tr>
<td>fPTC/PRN</td>
<td>PTC enriched with PRN Autosomal Dominant with Partial Penetrance</td>
<td>1q21</td>
<td>[22]</td>
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In another group of 80 fPTC kindreds a familial nonmedullary thyroid cancer susceptibility gene referred to as FNMTC has been mapped to the long arm of chromosome 2 (2q21). The maximum multipoint LOD score in all families was 3.07, and this increased to 4.17, when the 17 pedigrees with the follicular variant of PTC were analyzed alone [21]. As with the previous linkage analysis, the susceptibility gene at this locus has not been identified.

Our studies identified the familial association of PTC and papillary renal neoplasia PRN (both adenomas and carcinomas) in a large kindred. This disorder, which is designated fPTC/PRN (OMIM #605642), has been mapped to the long arm of chromosome 1 (1q21) with a multipoint single kindred LOD score of 3.58 [22]. Therefore, this syndrome is both clinically and genetically distinct from other fPTC disorders. There are a number of other neoplasms in this large kindred including benign thyroid adenomas, germ cell neoplasms premenopausal breast carcinomas and renal oncocyoma that occur in subjects that carry the affected allele. Unfortunately there are not enough genetically affected individuals to determine if these non-PTC neoplasms are components of the fPTC/PRN syndrome with low penetrance, or if they are just sporadic events in a large kindred. In this regard, it is of interest that epidemiology studies have identified an increased incidence of premenopausal breast carcinoma in PTC subjects [23]. One interpretation of this finding is that the use of I-131 in thyroid carcinoma subjects predisposes to breast carcinoma. Alternatively, our results support the hypothesis that an inherited susceptibility is responsible for this association. It may be that the fPTC/PRN gene predisposes to other malignancies.

Frequently sporadic tumors and familial tumors may be caused by mutations of the same susceptibility genes. For example, activating RET mutations are inherited in multiple endocrine neoplasia type 2 and develop spontaneously in sporadic medullary thyroid carcinoma. We have reviewed of the gene abnormalities of sporadic PTC to determine if these occur in genes that map to the linkage regions of the familial PTC syndromes. The neurotrophic tyrosine kinase receptor type 1 (NTRK1; TRK; TRKA) that is located at 1q23.1 and RET that is located at 10q11.2 are both rearranged in sporadic PTC. These rearrangements effect illicit expression of these tyrosine kinases in the thyroid follicular cell. Activating BRAF (7q34) mutations also occur in sporadic PTC [24] and activating mutations of hRAS occur in sporadic follicular thyroid neoplasms [25]. Other genes contributing to the pathogenesis of follicular neoplasms include PTEN(10q23.31), PAX8 (2q13), and PPARG1 (3p25). Of these seven genes, PAX8, hRAS and TRK are potential candidates for fPTC based upon their chromosomal location. The sequence analysis of PAX8 in the FNMTIC kindreds that map to 2q21 has not been reported. Completion of the human genome project indicates that TRK is telomeric to the fPTC/PRN locus. Therefore, it is not the fPTC/PRN susceptibility gene. Sequence analysis of hRAS in fPTC/PRN indicates that the known activating mutation of hRAS does not cause this disorder [26]. Interestingly LOH, normally a rare event in PTC, has been observed in about 10 percent of sporadic PTC in the region near 1q21 [27]. This finding suggests that there may be a tumor suppressor gene for
PTC at the fPTC/PRN locus at 1q21. In summary, the genes causing sporadic PTC are not located within the fPTC loci, suggesting that the fPTC genes are distinct from the genes that cause sporadic PTC.

**CLINICAL FEATURES OF fPTC AND IMPLICATIONS FOR PATIENT CARE**

The clinical features of fPTC are beginning to emerge and are compared with the clinical features of sporadic PTC in Table 2. Loh first summarized the clinical features based upon a review of available published kindreds [16]. A more recent study from Japan has reported similar results [17]. Although these results are probably reliable, final confirmation of their accuracy must await the identification of the fPTC susceptibility genes, so that the genetically affected individuals can be unequivocally distinguished from those that are genetically unaffected.

The evaluation of large kindreds suggests that inheritance is autosomal dominant with partial penetrance, although it is possible that modifying genes play an important role. As with sporadic PTC, women are affected more frequently than men. Multifocal disease is more common in fPTC than in sporadic PTC, and the age of onset is somewhat younger in fPTC (mean = 38 y) than in sporadic PTC (mean = 48 y) [16, 28]. However, Uchino did not find an age difference between familial and sporadic PTC [17]. There seems to be a greater incidence of benign thyroid nodules associated with fPTC than with sporadic PTC [17]. There may be other malignancies associated with fPTC. Epidemiologic studies suggest an increased incidence of breast carcinoma in individuals with PTC [23], and one large kindred with fPTC is enriched in PRN and possibly other malignancies [9]. Although it has been, suggested that fPTC may be more aggressive than sporadic PTC [30], the differences on a whole seem to be modest. There are occasional kindreds in which fPTC seems to be more aggressive than sporadic PTC with some subjects dying from this disorder. A more recent study does suggest a greater incidence of recurrent disease with fPTC than with sporadic PTC, but no increased incidence of death [17].

Two known familial tumor syndromes are associated with an increased incidence of PTC [29]. The frequency of PTC in familial adenomatous polyposis (FAP) is about

<table>
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<tr>
<th>Characteristic</th>
<th>Familial PTC</th>
<th>Sporadic PTC</th>
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<tr>
<td>Age of Onset</td>
<td>mean = 38 [16]</td>
<td>mean 45–50 [28]</td>
</tr>
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<td></td>
<td>mean = 49.1</td>
<td>mean 48.5 [17]</td>
</tr>
<tr>
<td>Female:Male Ratio</td>
<td>2:1 [16]</td>
<td>3:1 [16]</td>
</tr>
<tr>
<td>Multifocal PTC</td>
<td>41% [17]</td>
<td>29% [17]</td>
</tr>
<tr>
<td>Recurrence</td>
<td>16% [17]</td>
<td>10% [17]</td>
</tr>
<tr>
<td>Death</td>
<td>rare</td>
<td>rare</td>
</tr>
<tr>
<td>Benign thyroid nodules</td>
<td>42% [17]</td>
<td>30% [17]</td>
</tr>
<tr>
<td>Associated malignancies</td>
<td>papillary renal neoplasia</td>
<td>? breast carcinoma [23]</td>
</tr>
<tr>
<td></td>
<td>(selected kindreds) [29]</td>
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10 times as great as the incidence expected for sporadic PTC. In the Cowden syndrome (multiple hamartoma syndrome) there is an increased incidence breast carcinoma, follicular thyroid carcinoma, and to a lesser degree PTC.

The clinical characteristics of fPTC may modify the evaluation and treatment of fPTC patients. Clinicians should review the family history carefully in subjects with PTC, since it is anticipated that about 5 percent of all PTC subjects will have a familial predisposition to this disorder. FAP and the Cowden syndrome should be excluded. There is no role for prophylactic thyroidectomy as there is in the MEN2 syndromes, since fPTC usually is a relatively slow growing malignancy rate and since asymptomatic carriers cannot be unequivocally identified. Unfortunately, except in the very largest kindreds, genetic studies will not help to identify asymptomatic carriers. We do know that any kindred members with affected first-degree relatives are at 50 percent risk of carrying the susceptibility gene. There is debate as to how aggressively these individuals at risk should be followed. Children do not need to be followed closely, since PTC rarely occurs before puberty. After puberty, yearly neck examinations are a reasonable screening tool. Some clinicians prefer to perform an ultrasound examination of the thyroid in addition to the physical examination. The disadvantage of this approach is that it is likely to identify minor abnormalities that have little clinical significance, but, because of a strong family history, may lead to unnecessary thyroidectomy. For now, the use of ultrasound for screening should be left to the discretion of the individual clinician.

SUMMARY AND CONCLUSIONS

Over the last decade, several lines of evidence have been accumulated that support the existence of fPTC susceptibility genes. Preliminary clinical characteristics of fPTC have been identified, and linkage studies have identified the chromosomal locations of putative fPTC susceptibility genes. A logical clinical approach to fPTC is emerging.

REFERENCES