formally exclude that a second disease susceptibility gene is located on 6q25. Investigation of these regions in other independent families with the same phenotype will be important in order to provide a definite confirmation of our findings.

The present study cannot determine the precise mechanism by which this locus contributes to the phenotype, particularly given the presence of several non-penetrant carriers. Chance alone may be at work, or the locus may be necessary but not sufficient to cause disease in the absence of modifying loci elsewhere in the genome. It is possible also that there are two or more linked susceptibility loci within this large interval in 6p.

Several genes that affect LR axis development have been identified in the mouse.⁴ Where human homologues have been identified, none maps to 6p, and none of the remaining murine genes maps to regions homologous to 6p.¹⁴ A search for candidate genes among those transcripts localised to the critical region shows several that might be involved, but no immediately compelling candidates. Identification of the susceptibility gene (or genes) in this interval awaits further understanding of the genetic pathway in model systems or the future discovery of suitable candidate genes in this region of the human genome.

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Electronic database information: Online Mendelian Inheritance in Man (OMIM), <http://www.ncbi.nlm.nih.gov/omim/> (for asplenia with cardiovascular anomalies (MIM 208530), situs inversus viscerum (MIM 270100), heterotaxy, visceral, X linked (MIM 306955), laterality defects, autosomal dominant (MIM 601086)). Center for Medical Genetics, Screening Sets of Markers, version 6, <http://www.marshmed.org/genetics/sets/scrset6.txt>

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Founder effect in multiple endocrine neoplasia type 1 (MEN 1) in Finland

EDITOR—Multiple endocrine neoplasia type 1 (MEN 1, OMIM 131100) is transmitted as an autosomal dominant trait with an equal sex distribution and close to full penetrance. Hyperparathyroidism occurs in over 90% of the cases and is invariably associated with multiglandular disease. In addition, the patients may develop tumours of the endocrine pancreas, the anterior pituitary, and the adrenal cortex, as well as lipomas and carcinoids.¹ The *MEN1* tumour suppressor gene at 11q13 was cloned by positional cloning and the protein, menin, has been found to bind specifically to JunD leading to inhibition of JunD activated transcription.²⁻⁵ Following the initial description of the disease gene, over 200 *MEN1* germline mutations scattered throughout the entire gene have been reported. The majority of these mutations are unique and no clear cut genotype-phenotype correlation has been established so far.^{3 4 6-13} To date, only a few reports of a founder effect

in MEN 1 families have been published.^{10 14 15} In all the cases, the evidence for a founder chromosome was based on the presence of a shared disease haplotype and a *MEN1* mutation, in combination with a common geographical origin of the families involved.

To date, more than 30 rare single gene diseases, mostly autosomal recessive, have been identified in the Finnish population.^{16 17} The clustering of mutations in the Finnish population can be explained by the mechanisms of isolation, genetic drift, and founder effect. The relatively small founder population, the geographical isolation, and the internal migration movement in the 1500s led to the formation of numerous founder populations. The Finnish population has been widely used in linkage disequilibrium studies for mapping disease gene loci. By combining genetic and clinical investigations with careful genealogical studies, several founder chromosomes for various genetic diseases have been established.¹⁷⁻¹⁹

A total of 22 MEN 1 families and four isolated MEN 1 cases have been identified in Finland, 20 of them in the northern part of the country. The diagnosis of MEN 1 was based on the findings of tumours in two or more of the

Figure 1 Diagrammatic representation of the mutations found in the *MEN1* gene in the Finnish population. Each triangle represents one mutation found in one *MEN1* family. Hatched areas are not translated.

principal *MEN1* related glands (that is, the parathyroid glands, the endocrine pancreas-duodenum, and the

anterior pituitary). In familial *MEN1*, one or more affected relatives also had clinical, radiological, or surgical evidence of *MEN1* related tumours. Isolated *MEN1* was considered in a subject with clinical features of *MEN1* without a known family history of the disease. Informed consent for the mutation screening and genotyping studies was obtained from the participating patients, and the study was approved by the local ethical committee. Some of the families have been published previously,²⁰ as well as some of the results from *MEN1* mutation screening.⁹

Mutation analysis on 26 subjects representing each of the 22 familial and four isolated cases was performed using single strand conformation analysis (SSCA) and direct DNA sequencing, as previously described.^{4, 21} For all familial cases where a mutation was detected, its presence in additional family members was tested and confirmed by sequencing or restriction cleavage. Two or more affected members from each of the 22 families were genotyped for five microsatellite markers (D11S1883, D11S4946, D11S4940, D11S4937, and D11S449) spanning the *MEN1* region in 11q13. The pedigrees with the two prevailing mutations were further analysed by genealogical studies. The names, dates, and places of birth of ancestors were traced using the Finnish church records, which frequently cover birth and family information back to the years 1650-1700.

The mutation screening of the *MEN1* gene showed six different germline mutations in 17 familial (77%) and one isolated (25%) cases. The mutations G42A (GGC→GCC)

Figure 2 Pedigrees of the families with the 1466del12 mutation. Black symbols indicate clinically affected *MEN1* mutation carriers. The affected haplotype is outlined by a box. The common ancestor was found for eight of the nine 1466del12 families.

and 359del4 (GTCT) were located in exon 2, D418N (GAC→AAC) in exon 9, and 1466del12 (GCAGAAGGT-GCG), 1657insC, and R527X (CGA→TGA) in exon 10 (fig 1). As expected, most of the mutations were frameshift (359del4, 1657insC), nonsense mutations (R527X), and deletions (1466del12), which are likely to cause truncation of the *MEN1* gene product, menin, resulting in the loss of its function. The two missense mutations detected, G42A and D418N, are also expected to be pathogenic since they have not been detected in 100 normal subjects. The mutations 1466del12, 1657insC, and R527X were found recurrently in nine, four, and two probands, respectively (fig 1). Four of the mutations identified in this study (359del4, D418N, 1657insC, and R527X) have previously been reported in familial or isolated MEN 1 patients of non-Finnish origin.^{7-12 14} The regions of the *MEN1* gene where these recurrent mutations have occurred consist of CpG, short DNA repeats, or single nucleotide repeat motifs, which have been reported to be prone to mutations in the *MEN1* gene.¹⁴ The codons 83-84, 210-211, and 514-516 appear to be "warm"spots for *MEN1* mutations.^{7 14} The mutations G42A and 1466del12 have not been reported in other populations.

MEN1 mutations were not detected in five familial and three isolated cases. In these cases, the mutation could be a large deletion located in regulatory or untranscribed regions of the *MEN1* gene, which would be undetectable by the method used. The introns except for the intron/exon boundaries were excluded in the mutation analysis. It has been reported that even 20% of the *MEN1* mutations involve intron sequences.¹² *MEN1* mutations have been found less frequently in isolated than in familial cases, suggesting that some of the isolated cases may have a different genetic aetiology or that two endocrine tumours occur coincidentally in the same patient.^{6 7 9 10 13}

Although the majority of the Finnish population live in the southern part of the country, most of the MEN 1 cases (20/26) were clustered in a limited geographical area in the north of the country. This can be partly explained by clustering of the mutations, a phenomenon, which has been described in many Finnish genetic diseases.¹⁶ Haplotype

analysis showed that the nine families with the 1466del12 mutation shared the same haplotype (6-3-3-7) for the region covered by D11S4946 - D11S4940 - D11S4937 - D11S449 (fig 2). By careful genealogical study, eight families were found to be descended from an identifiable founder couple (fig 2). The couple were born in 1705 and 1709 in a small village where most of the descendants still live. The resulting pedigree consists of eight generations, when counted from the present day patients. It is possible that the *MEN1* mutation has occurred beyond the last eight generations, because the connection of the ninth family to this pedigree has not been found even though it shares the same affected haplotype with the other eight families. The mutation analysis showed 1466del12 in the two Finnish families sharing the disease linked haplotype in the previous linkage disequilibrium study.²² The age of the 1466del12 mutation and the large family sizes, usually seen in northern Finland, suggest that more mutation carriers than presently known could exist in northern Finland.

The families with the 1657insC mutation also shared a common haplotype (3-5-3-3-8) with all the five markers (fig 3). Two patients with the same haplotype on both chromosomes do not indicate homozygosity of the mutation, but a common haplotype in the Finnish population. All the four families could be traced back to a couple born in 1844 and 1846, respectively, four generations from the youngest living patients (fig 3). Two families sharing the common disease linked haplotype in our previous linkage disequilibrium study²² were found to have the 1657insC mutation.

In the two families with the R527X mutation, the disease was clearly linked to different haplotypes, showing that the mutations had occurred independently.

All the 22 families and four isolated cases with MEN 1 fulfilled the criteria for the MEN 1 syndrome with at least two MEN 1 related endocrine organs affected. The main clinical manifestations of the patients with the identified *MEN1* mutation are detailed in table 1. In total, 65 affected *MEN1* mutation carriers and 10 clinically unaffected *MEN1* mutation carriers were found in these families. Primary hyperparathyroidism (pHPT) was the most common

Figure 3 Pedigrees of the families with the 1657insC mutation. Black symbols indicate clinically affected *MEN1* mutation carriers and hatched symbols indicate unaffected (or with unknown clinical status) mutation carriers. The affected haplotype is outlined by a box. The common ancestor was found for all the four families with the 1657insC mutation.

Table 1 Clinical manifestations in 18 Finnish MEN1 families with identified MEN1 gene mutation

	MEN1 mutation						Total
	1466del12	1657insC	R527X	D418N	359del4	G42A*	
No of families	9	4	2	1	1	1	18
Affected mutation carriers	31	20	5	5	3	1	65
Main MEN1 lesions							
Primary HPT	30	20	5	4	3	1	63
GEP tumour	21	9	3	3	0	0	36
Pituitary tumour	6	7	2	2	0	1	18
Other associated tumours							
Adrenal hyperplasia	10	4	0	1	0	0	15
Lipoma	8	3	1	0	0	0	12
Carcinoid	1	3	0	0	0	0	4

*Isolated case.

manifestation and was seen in 63 patients (97%). The second most frequent clinical finding was gastroenteropancreatic tumour (55%), followed by pituitary tumours (28%) and benign adrenal hyperplasia (23%), as well as lipomas (18%) and carcinoids (6%).

GEP tumours were more common in the 1466del12 families (68%) than in the 1657insC families (45%), while the occurrence of the pituitary adenomas was the reverse. The differences in the occurrences of the clinical findings might be explained by the varied age and sex of the MEN 1 patients in different families. Families with the prolactinoma variant of MEN 1 families have been reported as a phenotypic variant of MEN 1; however, the mutations were different in these families.⁶ Several families with isolated hyperparathyroidism have been reported and in some families with at least three affected subjects a mutation of the *MEN1* gene (E255K, Q260P, L267P, G305D, Y353X, 1350del3) has been detected.^{13 21 23-26} pHPT is usually the first symptom of the MEN 1 syndrome and some of the patients in the isolated hyperparathyroidism families may develop MEN 1 syndrome at later ages.

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Familial non-medullary thyroid cancer in Iceland

EDITOR—Incidence of thyroid carcinoma in Iceland is high¹ and papillary carcinoma comprises 80% of all thyroid malignancies in the country.² It is well known that medullary thyroid carcinoma aggregates in families and the genetic component in the aetiology has been established.³ Familial occurrence of non-medullary thyroid carcinoma is rare, but it has been increasingly recognised in recent years.⁴⁻⁶ There has been increasing awareness that this may constitute a distinct disease subgroup rather than chance occurrence, as reflected by the review of case series by Loh.⁷ Familial papillary microcarcinoma has also been suggested as a new clinical entity.^{8,9} In an earlier paper, we reported on the occurrence of papillary thyroid carcinoma (373 probands) in first degree relatives of all patients diagnosed between 1955 and 1984 in Iceland.¹⁰ This study showed a non-significant trend to familiarity. In the present study, the population includes second and third degree relatives in addition to first degree relatives and we now include all non-medullary thyroid carcinoma patients.

Information on thyroid cancer cases was obtained from the Icelandic Cancer Registry. All cases (n=712) of non-medullary thyroid carcinoma diagnosed in Iceland between 1955 and 1994 form the basis of this study. This includes 147 thyroid cancers found incidentally at necropsy and 565 thyroid cancers diagnosed clinically. The information on first, second, and third degree relatives was obtained from the Genetical Committee of the University of Iceland. This committee has a computerised family tracing resource based on the 1910 census and birth records for 1840-1910. This resource is linked with the national register and death records for later periods. Permission was obtained from the Data Protection Commission to link files from the Cancer Registry with records from the Genetical Committee. The 712 families contributed to the man year calculations on which expected numbers are based. For nine probands of foreign origin, there were no relatives in the study population.

All cases were histologically verified. The histopathology was re-examined by one of the authors (JGJ). Included in the file were all differentiated thyroid cancers. These include papillary and follicular thyroid cancers, as well as anaplastic cancers, as these tumours are derived from the follicular epithelial cells. Thyroid carcinomas showing Hürtle cell differentiation were classified either as follicular or papillary histological type. Medullary cancers and lymphomas of the thyroid were excluded from the study.

The study risk period started in January 1955 or at birth (for persons born after 1 January 1955) and ended on 31 December 1997 or at death if death occurred earlier. Incidence rates of thyroid cancer stratified according to gender, five year age intervals, and five year calendar intervals from

1955 to 1997 were used. Incidence rates of thyroid cancer before 1955 were not available.

Years at risk stratified in the same manner for each degree of relatedness were calculated using the program PERSON-YEARS (PYRS) from the World Health Organization.¹¹ Expected numbers of cases were calculated as the sums of products of incidence and years at risk. Relative risk (RR) was calculated as the ratio between observed and expected numbers. Pooled relative risk was calculated as the weighted sum of relative risk over the degrees of relatedness 1, 2, and 3 with the weights 1, 1/2, and 1/4, respectively; p values less than 0.05 were considered significant.

Table 1 summarises the study population. Altogether, there were 57 391 relatives in the pedigrees. Of these, 49 949 (25 396 males and 24 553 females) were alive on or after 1 January 1955, thus contributing to the man year calculations. Table 1 describes the distribution of probands and relatives. There were 712 thyroid cancer cases as probands. Among relatives, thyroid cancer occurred 249 times.

Table 2 classifies the probands according to family history, histology, and sex. There were 184 probands with one or more relatives affected. In six pedigrees, three affected relatives were found. There is only a small difference in histology between familial and sporadic cases. Papillary cancer is somewhat more common in the familial group (81%) than in the sporadic group (76%) in males. This difference was not found among females.

Table 3A shows the relative risk of thyroid cancer for relatives of all thyroid cancer patients. Figures are shown separately for first, second, and third degree relatives and

Table 1 Probands with number of male and female relatives and number of relatives with thyroid cancer

	Study population		Thyroid cancer No of relatives
	No in pedigree	No alive in 1955	
Probands			
Males	206		
Females	506		
Total	712		
Relatives			
Males	29 400	25 396	84
Females	27 991	24 553	165
Total	57 391	49 949	249

Table 2 Number of probands with and without relatives affected with non-medullary thyroid cancer according to histology and sex

	Males	Females
Probands with affected relatives		
Papillary	46	102
Follicular	7	19
Anaplastic	4	6
Total	57	127
Probands with no affected relatives		
Papillary	113	303
Follicular	29	47
Anaplastic	7	29
Total	149	379