*Am. J. Hum. Genet. 63:468–473, 1998*

# Founder Effect at PGL1 in Hereditary Head and Neck Paraganglioma Families from The Netherlands

Evert M. van Schothorst,[1,*] Jeroen C. Jansen,[2,*] Edward Grooters,[2] Duncan E. M. Prins,[3] Joris J. Wiersinga,[4,5] Andel G. L. van der Mey,[2] G.-J. B. van Ommen,[1] Peter Devilee,[1,3] and Cees J. Cornelisse[3]

Departments of [1]Human Genetics, [2]Otorhinolaryngology, and [3]Pathology, Leiden University Medical Center, and Departments of [4]Biology and [5]History, Leiden University, Leiden, The Netherlands

## Summary

**PGL1, a gene responsible for hereditary paragangliomas of the head and neck, recently was mapped to a 2-cM interval on chromosome 11q22-q23, by linkage and haplotype-sharing analysis of a large multibranch Dutch family. We determined the disease-linked haplotype, as defined by 13 markers encompassing a large interval on 11q21-q23, in 10 additional families ascertained from the same geographical locale. Alleles were identical for six contiguous markers, spanning a genetic distance of 6 cM and containing PGL1. Despite this strong indication of a common ancestor, no kinships between the families could be demonstrated through genealogical surveys going back to 1800 A.D. We conclude that a single ancestral mutation is responsible for most, if not all, hereditary paragangliomas, in this region of The Netherlands, and that strong founder effects may exist at the PGL1 locus.**

## Introduction

Paragangliomas are rare, usually benign tumors of the extra-adrenal paraganglion tissue associated with the autonomous nervous system (Parry et al. 1982). Most paragangliomas occur in the head and neck region, where they may lead to cranial nerve deficit. Characteristically, the tumor progresses slowly, and, although the age at onset is variable, most patients develop symptoms after puberty. Familial nonchromaffin paragangliomas of the head and neck (HN-paragangliomas; MIM 168000) are inherited as an autosomal dominant disease with reduced penetrance (Van Baars et al. 1982; McCaffrey et al. 1994). Affected offspring are observed only after paternal transmission, which is considered to be evidence that the underlying gene defect is subject to genomic imprinting (Van der Mey et al. 1989).

Linkage analysis of a single large Dutch pedigree mapped the gene, termed "PGL1," to 11q22-q23 (Heutink et al. 1992). This result was replicated in additional families (Heutink et al. 1994) and was confirmed in North American families (Baysal et al. 1997*a;* Milunsky et al. 1997), but the detected recombination events did not map the gene to an interval more precise than ~10 cM. We recently identified a common ancestor, born in 1776, of three families originating from the same geographical region, including the family in which the original linkage was found. A 2-cM haplotype, presumably containing PGL1, was shared among all patients in the two most recent generations of these families (Van Schothorst et al. 1996). Although a second locus has been implicated to reside on 11q13 in one other Dutch paraganglioma family (Mariman et al. 1995), all informative families analyzed to date have revealed linkage evidence for only the distal PGL1 locus on 11q22-q23 (Heutink et al. 1994; Baysal et al. 1997*a;* Milunsky et al. 1997).

Recently, another 10 families with HN-paragangliomas were ascertained from the same geographical region as that from which the large PGL1-linked family originated. Assuming that such conspicuous geographical clustering of a rare disorder might reflect a founder effect, which could be exploited for further gene localization, we performed a genealogical survey and determined the disease-linked haplotypes for all 10 families. Although no family relationships could be demonstrated by genealogy, haplotype analysis provided strong evidence for a common founder in this population.

## Subjects and Methods

### *Family Ascertainment*

Since 1950, 183 patients with HN-paragangliomas have been referred to our Ear, Nose, and Throat De-

Received October 8, 1997; accepted for publication May 29, 1998; electronically published June 29, 1998.

Address for correspondence and reprints: Dr. Peter Devilee, Department of Human Genetics, Leiden University Medical Center, Wassenaarseweg 72, 2333AL Leiden, The Netherlands. E-mail: devilee@ruly46.Medfac.Leidenuniv.nl

* These authors contributed equally to this work.



0002-9297/98/6302-0022$02.00

partment. Queries were sent to those patients with a recorded family history of HN-paragangliomas, enabling us to ascertain 27 pedigrees with a total of at least 142 patients. Three families (FGT1, FGT8, and FGT9) originating from the central western region of The Netherlands could be traced to a common ancestor (Van Schothorst et al. 1996), and the resulting single kindred was renamed "FGT189." Fourteen other families originated from the same province as that of family FGT189, and we obtained DNA samples in order to reconstruct the disease haplotype from 10 of these families. FGT3, FGT11, and FGT18 have been partially described elsewhere (Van der Mey et al. 1989; Hart and Maartense 1992; Heutink et al. 1994), and the other families are reported here for the first time.

### *Disease Ascertainment*

Diagnosis of HN-paragangliomas was based on clinical signs and, for most patients, was confirmed by histological or radiological investigation. Twelve probable affected progenitors were identified by evaluation of their medical history. Ten of these putative patients, of whom two died during surgical intervention, are known to have had lateral neck masses. The other two are known to have had ear complaints leading to bleeding or loss of facial nerve function.

### *Genealogy Analysis*

Familial ancestries were traced back starting from the oldest known common ancestor of affected family members and included both the paternal and maternal lines. Civil registration data on generations beyond the year 1800 could not be retrieved. Three ancestral lines were not completed: in family FGT27, data on one generation in the maternal line were not available; in family FGT32, an in-married spouse, born in approximately 1850, could not be traced; in FGT20, the genealogical search was thwarted by the existence of an adopted ancestor.

### *DNA Isolation and PCR Analysis*

Blood samples were collected, and genomic DNA was isolated from peripheral blood lymphocytes (Miller et al. 1988). PCR and gel-electrophoresis conditions for the visualization of microsatellite polymorphisms were as described elsewhere (Van Schothorst et al. 1996). All primer sequences for these markers are retrievable from the Genome Database, and all oligonucleotides were manufactured by Isogen.

### *Haplotype Analysis*

For haplotype analysis, we used a marker order described by Van Schothorst et al. (1996). The genetic map (Litt et al. 1995; Dib et al. 1996) was complemented with data obtained by physical mapping of the region between markers D11S897 and D11S4111 (Baysal et al. 1997*b*). The markers selected covered a genetic distance of ~50 cM. Allele lengths were determined by use of an M13 sequence as a reference. Allele frequencies in the control population were determined for 41 in-married spouses, of whom 20 were from family FGT189 and 21 from families with familial atypical multiple-mole melanoma (FAMMM) syndrome. These FAMMM-syndrome families originated from the same area as FGT189 (Gruis et al. 1995). Allele lengths and frequencies thus determined were not appreciably different from those reported in the Genome Database.

## Results

### *Clinical Description and Inheritance Patterns in 10 HN-Paraganglioma Families*

A total of 63 HN-paraganglioma patients, of whom 42 had complete medical records, were identified in the 10 families reported here (table 1). The carotid bifurcation was the most frequently affected site (57% of all HN-paragangliomas). Multiple paragangliomas occurred in 66% of the patients, as expected for inherited cases (McCaffrey et al. 1994). Three patients, from different families, had developed a paraganglioma of the adrenal gland (pheochromocytoma). In family FGT11, primary hypothyroidism occurred in a father and his daughter, who both also had HN-paragangliomas. No affected offspring of female carriers were observed, and all affected family members received the disease gene from their father, which is consistent with the hypothesis of genomic imprinting of PGL1 (Van der Mey et al. 1989). Remarkably, 42 patients received the gene from their grandfather, whereas only 2 patients received it from their grandmother (for 19 patients, the transmitting grandparent could not be determined [data not shown]).

### *Haplotype Analysis*

Blood samples were obtained from 136 family members, including 33 patients (table 1). DNA was genotyped at 13 markers encompassing an ~50-cM interval on 11q13-q24. Previously, we had identified a three-marker haplotype of ~2 cM, defined by markers D11S1792, D11S1327, and D11S908, which was conserved among all the patients from a large multibranch family, FGT189 (summarized in fig. 1). However, a much larger haplotype, of ~10 cM, defined by markers between D11S876 and D11S4092, was shared among the patients from branches C–K, and this sharing extended beyond marker CD3D in branches E–H. We compared this so-called E/H-haplotype with the disease-linked haplotypes of the 10 families included in this study (table 2). None of the families contained recombinants between the disease and any marker mapping between

**Table 1**

**Clinical Data from 10 HN-Paraganglioma Kindreds**

| | No. of Patients | | | | No. of Tumors[c] | | | |
|---|---|---|---|---|---|---|---|---|
| Family | Total[a] | Verified[b] | Genotyped | Kinship of Patients | CBT | VBT | JTT | PH |
| FGT3 | 13 | 8 | 4 | Cousins, father-sibs | 6 | 4 | 7 | 0 |
| FGT5 | 5 | 4 | 3 | Cousins, sibs, father-son | 5 | 2 | 0 | 0 |
| FGT11 | 2 | 2 | 2 | Father-daughter | 1 | 0 | 2 | 0 |
| FGT17 | 7 | 4 | 2 | Cousins, sibs | 3 | 0 | 2 | 1 |
| FGT18 | 18 | 13 | 10 | Cousins, father-sibs | 15 | 2 | 0 | 0 |
| FGT20 | 3 | 2 | 2 | Sibs | 4 | 3 | 1 | 1 |
| FGT25 | 7 | 5 | 5 | Cousins, father-sibs | 4 | 1 | 1 | 0 |
| FGT27 | 4 | 1 | 2 | Father-sibs | 1 | 0 | 0 | 1 |
| FGT29 | 2 | 1 | 2 | Father-daughter | 1 | 0 | 1 | 0 |
| FGT32 | 2 | 2 | 1 | Cousins | 2 | 3 | 3 | 0 |
| Total | 63 | 42 | 33 | | 42 | 15 | 17 | 3 |

[a] Total number identified anamnestically.
[b] As documented by medical records.
[c] CBT = carotid body tumor; VBT = vagale body tumor; JTT = jugulo-tympanicum tumor; and PH = pheochromocytoma.

D11S1647 and D11S908. These markers previously had been shown to be recombinant in two other independently ascertained families (Van Schothorst et al. 1996; Baysal et al. 1997*a*). All patients shared a haplotype defined by six markers and bracketed by D11S927 and D11S908. This haplotype was not observed among 41 unrelated individuals (82 chromosomes) from the same geographical region, supporting the hypothesis that all patients in these 11 families are genetically identical by descent. Notably, several families—namely, FGT11, FGT18, and FGT20—appear to share with family FGT189 a very large region that includes all but the most distant markers tested (table 2).

### *Genealogy*

Records on 72 ancestors of the 10 families were retrievable. These ancestors were born between 1770 A.D. and 1830 A.D. and originated from several rural areas of the central western region of The Netherlands, all within a radius of ~40 km. Despite this strong geographical clustering, none of the families studied were proved to be interrelated.

## Discussion

HN-paragangliomas usually follow a slow, benign natural course and generally occur at age >18 years (Parry et al. 1982; Van Baars et al. 1982; Van Gils et al. 1992). As a result, they are not expected to impede reproductive fitness. By analyzing pooled data from Dutch pathologic laboratories, we estimated an annual rate of 0.11/100,000 (Oosterwijk et al. 1996). Lack et al. (1977) found 69 paragangliomas among 600,000 surgical cases seen at the Sloan-Kettering Memorial Cancer Center, during 1937–75. If a relevant-population size of 1–2 million is assumed, this would suggest a comparable incidence rate. However, because of the late onset and benign course of the disease, an unknown proportion of the patients will not be hospitalized, leading to an underestimation of disease incidence (Van Gils et al. 1992). For similar reasons, the proportion of familial cases will be underestimated. This proportion has been reported to be 5%–10% (Grufferman et al. 1980; Parry et al. 1982), but in The Netherlands we are seeing a more conspicuous occurrence of familial cases (J. C. Jansen, unpublished data). Therefore, a founder effect is not unexpected, in particular because this also has been observed for a variety of other hereditary diseases in The Netherlands (Buyle et al. 1993; Houwen et al. 1994; Gruis et al. 1995; Taschner et al. 1995; Freimer et al. 1996; Peelen et al. 1997).

Recently, we described a 2-cM haplotype shared by all patients in the most recent two generations of the large multibranch family FGT189 (Van Schothorst et al. 1996). However, conservation of this haplotype extended over much larger regions in a subset of the patients (the E/H-haplotype; fig. 1). We have shown in this study that parts of this particular haplotype are conserved in another 10 families originating from within a radius of ~40 km from the town in which FGT189 originated. The minimal region shared with the E/H-haplotype covers ~6 cM and encompasses the previously identified 2-cM haplotype presumably containing the PGL1 locus. This haplotype was not detected in 82 chromosomes from unrelated individuals from the same region. Under Hardy-Weinberg equilibrium, the population frequency of this haplotype would be 0.04%, making it highly unlikely that this haplotype is linked by chance to PGL1 in 11 families. Since we included 10 of the 14 HN-paraganglioma families ascertained from

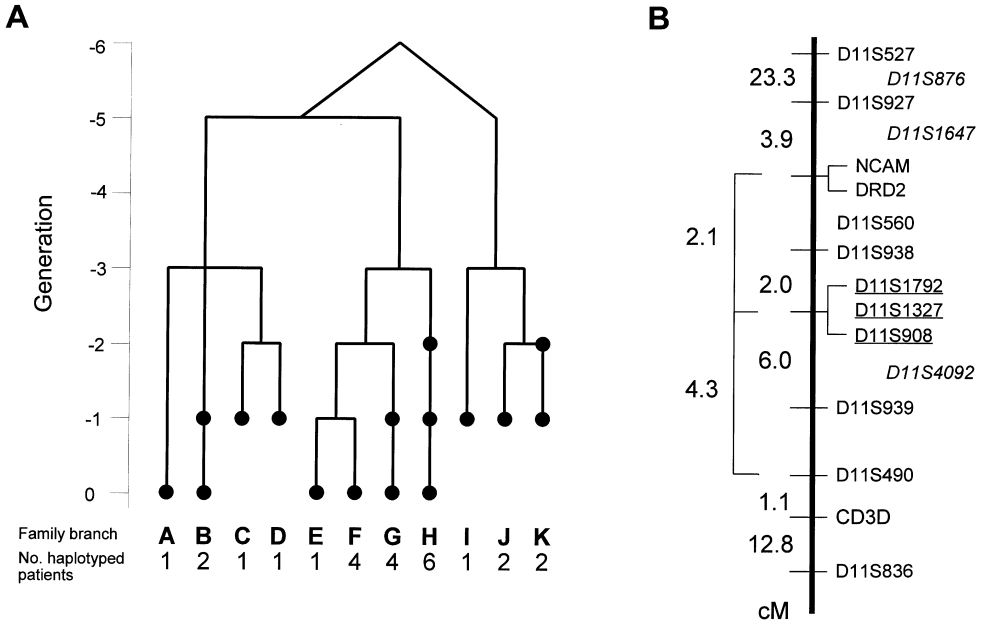


**Figure 1** *A*, Abbreviated version of the pedigree structure of extended family FGT189, described in detail in the study by Van Schothorst et al. (1996). The family was arbitrarily subdivided into branches A–K. Blackened circles represent sibships in which at least one patient has been verified by review of medical records. The number of haplotyped patients is indicated below each branch. *B*, Genetic map of markers used in this study. Distances are in centimorgans (cM). The underlined markers showed allele sharing in all patients of family FGT189. The markers in italics are provided for orientation.

this region, these data therefore strongly indicate that a single ancestral mutation in PGL1 is responsible for most paragangliomas occurring in the central western region of The Netherlands. The genealogies of these 10 families do not link any of them to FGT189, suggesting that this mutation must be $\geqslant$200 years old.

In view of the age of this PGLl mutation, it is remarkable that several families (FGT11, FGT18, and FGT20) share a region of >15 cM with the E/H-haplotype of FGT189. The genetic distance between the haplotyped patients from families FGT11, FGT18, and FGT20 and those from branches E–H of family FGT189 must be $\geqslant$16 meioses (fig. 1*A*). We have suggested a deficit of recombination events involving the disease-linked haplotype, in paraganglioma families (Van Schothorst et al. 1996), but this hypothesis lacks statistical support, so far. In fact, such events must have occurred more recently in branches A and B of family FGT189, since the haplotype sharing between these branches is only ~2 cM. Moreover, a more than twofold excess of female versus male recombination has been reported for this region of chromosome 11 (Litt et al. 1995). Thus, the size of the conserved haplotype might be explained in part by the overrepresentation of male transmission in our families. Also, strong haplotype conservation has been reported for families with FAMMM syndrome from the same geographical area (Gruis et al. 1995), as well as for other founder populations (Peltonen and Uusitalo 1997), and therefore might not be uncommon. Nevertheless, because of the finding that genomic imprinting may interfere with sex-specific recombination rates (Paldi et al. 1995; Robinson and Lalande 1995), it is tempting to speculate that the PGL1 mutation that is responsible for HN-paragangliomas also affects recombination rates in this region of chromosome 11.

The overrepresentation of paternal and grandpaternal transmission that we have noted here might be explained by an ascertainment bias, owing to the fact that HN-paragangliomas develop only after paternal transmission (Van der Mey et al. 1989). Even though PGL1-carrying females would have the same chance, on average, of having affected grandchildren as PGL1-carrying males, their affected grandchildren are less likely to be recognized as hereditary cases, because they inherit the gene from their nonpenetrant father. This would imply that an unknown proportion of allegedly sporadic paraganglioma cases are in fact hereditary.

Another interesting feature of this founder mutation in PGL1 is its apparent ability to predispose to pheochromocytomas (paraganglioma of the adrenal gland). We detected five cases of this rare tumor in the 11 families studied here (table 1; also see Van Gils et al. 1992), which confirms suggestions, reported elsewhere, of an association with HN-paragangliomas (Sato et al. 1974;

**Table 2**

**Disease Haplotypes of 10 HN-Paraganglioma Families, Compared with the E/H-Haplotype of Family FGT189**

| Marker | Size of Linked Allele in Family[a] (bp) | | | | | | | | | | | Frequency[b] (%) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | FGT189 | FGT11 | FGT18 | FGT20 | FGT32 | FGT25 | FGT3 | FGT17 | FGT5 | FGT26 | FGT27 | |
| D11S527 | 159 | 159 | 147 | 157 | 151 | 159 | 157 + 151 | 155/159 | 165 | 147/157 | 161/155 | 16 |
| D11S927 | 135 | 135 | 135 | 135 | 135 | 135 | 135 | 135 | 135 | 135 | 141/137 | 18 |
| NCAM | 126 | 126 | 126 | 126 | 126 | 126 | 126 | 126 | 126 | 126 | 126 | 7 |
| DRD2 | 82 | 82 | 82 | 82 | 82 | 82 | 82 | 82 | 82 | 82 | 82 | 52 |
| D11S560 | 87 | 87 | 87 | 87 | 87 | 87 | 87 | ND | 75/87 | ND | 77/87 | 4 |
| D11S938 | 212 | 212 | 212 | 212 | 212 | 212 | 212 | 212 | 212 | 212 | 212 | 58 |
| D11S1792 | 269 | 269 | 269 | 269 | 269 | 269 | 269 | 269 | 269 | 269 | 269 | 76 |
| D11S1327 | 250 | 250 | 250 | 250 | 250 | 250 | 250 | 250 | 250 | 250 | 250 | 64 |
| D11S908 | 147 | 147 | 147 | 147 | 147 | 147 | 147 | 147 | 149 | 149 | 151 | 38 |
| D11S939 | 247 | 247 | 247 | 247 | 247 | 241 | 241 | 241 | 241 | 249 | 247 | 45 |
| D11S490 | 159 | 159 | 159 | 159 | 161 | 149 | 167 | 159 | 159 | 149 | 159 | 32 |
| CD3D | 89 | 89 | 89 | 89 | 89 | 85 | 93 + 91 | 89/93 | 89 | ND | 89 | 27 |
| D11S836 | 70 | 72 | 72 | 74 | 74 | 72 | 74 + 66 | 74 | 74 | 74/70 | 74 | 8 |

[a] Families are ordered according to decreasing overlap of the haplotype linked with that of family FGT189. Two allele lengths separated by a plus sign (+) indicate a recombination event in that family; and two allele lengths separated by a slash (/) indicate that the phase is unknown. ND = not determined.

[b] Frequency of alleles that define the linked E/H-haplotype (see text) in FGT189, as observed in the control population.

Bogdasarian and Lotz 1979). Thus, PGL1 might be another factor in the already heterogeneous genetic basis of familial pheochromocytomas (Woodward et al. 1997).

Our finding of a strong founder effect at PGL1 contrasts with the haplotype analysis of North American HN-paraganglioma families, in which no obvious, large regions of allele sharing were apparent (Baysal et al. 1997*a*). This likely is due to the heterogeneous ethnic background of the families in that study. The founder effect reported here can now be exploited further for the purpose of gene mapping, by analysis of haplotype sharing across a densely spaced polymorphic marker map covering the culprit 11q23 region and its immediately flanking regions in additional hereditary HN-paraganglioma patients of Dutch origin.

## Acknowledgments

The authors wish to thank all the families for their participation in this study and C. W. R. J. Cremers (Department of Otolaryngology, Nijmegen University Hospital, Nijmegen, The Netherlands) for providing diagnostic data for several patients. This work was supported by the Dutch Organization for Scientific Research (grant NWO 900-716-815) and the Dutch Cancer Society (grant KWF 93-537).

## Electronic-Database Information

Accession numbers and URLs for data in this article are as follows:

Genome Database, http://www.gdb.org/
Online Mendelian Inheritance in Man (OMIM), http://www.ncbi.nlm.nih.gov/Omim (for familial nonchromaffin HN-paragangliomas [MIM 168000])

## References

Baysal BE, Farr JE, Rubinstein WS, Galus RA, Johnson KA, Aston CE, Myers EN, et al (1997*a*) Fine mapping of an imprinted gene for familial nonchromaffin paragangliomas, on chromosome 11q23. Am J Hum Genet 60:121–132

Baysal BE, Van Schothorst EM, Farr JE, James MR, Devilee P, Richard CW III (1997*b*) A high resolution STS, EST, and gene-based physical map of the hereditary paraganglioma region on chromosome 11q23. Genomics 44:214–221

Bogdasarian R, Lotz P (1979) Multiple simultaneous paragangliomas of the head and neck in association with multiple retroperitoneal pheochromocytomas. Otolaryngol Head Neck Surg 87:648–652

Buyle S, Reyniers E, Vits L, De Boulle K, Handig I, Wuyts FL, Deelen W, et al (1993) Founder effect in a Belgian-Dutch fragile X population. Hum Genet 92:269–272

Dib C, Fauré S, Fizames C, Samson D, Drouot N, Vignal A, Millasseau P, et al (1996) A comprehensive genetic map of the human genome based on 5,264 microsatellites. Nature 380:152–154

Freimer NB, Reus VI, Escamilla MA, McInnes LA, Spesny M, Leon P, Service SK, et al (1996) Genetic mapping using haplotype, association and linkage methods suggests a locus for severe bipolar disorder (BPI) at 18q22-q23. Nat Genet 12: 436–441

Grufferman S, Gillman M, Pasternak L, Peterson C, Young W (1980) Familial carotid body tumors: case report and epidemiologic review. Cancer 46:2116–2122

Gruis NA, Sandkuijl LA, Van der Velden PA, Bergman W, Frants RR (1995) CDKN2 explains part of the clinical phenotype in Dutch familial atypical multiple-mole melanoma (FAMMM) syndrome families. Melanoma Res 5:169–177

Hart W, Maartense E (1992) Hypothyroidism and chemodectoma in father and daughter: a new syndrome or a coincidence? Clin Endocrinol (Oxf) 36:295–296

Heutink P, Van der Mey A, Sandkuijl L, Van Gils A, Bardoel A, Breedveld G, Van Vliet M, et al (1992) A gene subject to genomic imprinting and responsible for hereditary paragangliomas maps to chromosome 11q23-qter. Hum Mol Genet 1:7–10

Heutink P, Van Schothorst E, Van der Mey A, Bardoel A, Breedveld G, Pertijs J, Sandkuijl L, et al (1994) Further localization of the gene for hereditary paragangliomas and evidence for linkage in unrelated families. Eur J Hum Genet 2:148–158

Houwen R, Baharloo S, Blankenship K, Raeymaekers P, Juyn J, Sandkuijl L, Freimer N (1994) Genome screening by searching for shared segments: mapping a gene for benign recurrent intrahepatic cholestasis. Nat Genet 8:380–386

Lack EE, Cubilla AL, Woodruff JM, Farr HW (1977) Paragangliomas of the head and neck region: a clinical study in 69 patients. Cancer 39:397–409

Litt M, Kramer P, Kort E, Fain P, Cox S, Root D, White R, et al (1995) The CEPH consortium linkage map of human chromosome 11. Genomics 27:101–112

Mariman E, Van Beersum S, Cremers C, Struycken P, Ropers H (1995) Fine mapping of a putatively imprinted gene for familial non-chromaffin paragangliomas to chromosome 11q131: evidence for genetic heterogeneity. Hum Genet 95: 56–62

McCaffrey T, Meyer F, Michels V, Piepgras D, Marion M (1994) Familial paragangliomas of the head and neck. Arch Otolaryngol Head Neck Surg 120:1211–1216

Miller SA, Dykes DD, Polesky HF (1988) A simple salting out procedure for extracting DNA from human nucleated cells. Nucleic Acids Res 16:1215

Milunsky J, Destefano AL, Huang XL, Baldwin CT, Michels VV, Jako G, Milunsky A (1997) Familial paragangliomas: linkage to chromosome 11q23 and clinical implications. Am J Med Genet 72:66–70

Oosterwijk JC, Jansen JC, Van Schothorst EM, Oosterhof AW, Devilee P, Bakker E, Zoeteweij MW, et al (1996) First experiences with genetic counseling based on predictive DNA diagnosis in hereditary glomus tumours (paragangliomas). J Med Genet 33:379–383

Paldi A, Gyapay G, Jami J (1995) Imprinted chromosomal regions of the human genome display sex-specific meiotic recombination frequencies. Curr Biol 5:1030–1035

Parry D, Li F, Strong L, Carney J, Schottenfeld D, Reimer R, Grufferman S (1982) Carotid body tumors in humans: genetics and epidemiology. J Natl Cancer Inst 68:573–578

Peelen T, van Vliet M, Petrij-Bosch A, Mieremet R, Szabo C, van den Ouweland AMW, Hogervorst F, et al (1997) A high proportion of novel mutations in BRCA1 with strong founder effects among Dutch and Belgian hereditary breast and ovarian cancer families. Am J Hum Genet 60:1041–1049

Peltonen L, Uusitalo A (1997) Rare disease genes: lessons and challenges. Genome Res 7:765–767

Robinson W, Lalande M (1995) Sex-specific meiotic recombination in the Prader-Willi/Angelman syndrome imprinted region. Hum Mol Genet 4:801–806

Sato T, Saito H, Yoshinga K, Shibota Y, Sasano N (1974) Concurrence of carotid body tumor and pheochromocytoma. Cancer 34:1787–1795

Taschner PE, de Vos N, Post JG, Meijers-Heijboer EJ, Hofman I, Loonen MC, Pinckers AJ, et al (1995) Carrier detection of Batten disease (juvenile neuronal ceroid-lipofuscinosis). Am J Med Genet 57:333–337

Van Baars F, Cremers C, Van den Broek P, Geerts S, Veldman J (1982) Genetic aspects of nonchromaffin paraganglioma. Hum Genet 60:305–309

Van der Mey A, Maaswinkel-Mooy P, Cornelisse C, Schmidt P, Van de Kamp J (1989) Genomic imprinting in hereditary glomus tumours: evidence for new genetic theory. Lancet 2: 1291–1294

Van Gils A, Van der Mey A, Hoogma R, Sandkuijl L, Maaswinkel-Mooy P, Falke T, Pauwels E (1992) MRI screening of kindred at risk of developing paragangliomas: support for genomic imprinting in hereditary glomus tumours. Br J Cancer 65:903–907

Van Schothorst EM, Jansen JC, Bardoel A, Van der Mey AGL, James MJ, Sobol H, Weissenbach J, et al (1996) Confinement of PGL, an imprinted gene causing hereditary paragangliomas, to a 2 cM interval on 11q22-q23 and exclusion of DRD2 and NCAM as candidate genes. Eur J Hum Genet 4:267–273

Woodward ER, Eng C, McMahon R, Voutilainen R, Affara NA, Ponder BA, Maher ER (1997) Genetic predisposition to phaeochromocytoma: analysis of candidate genes GDNF, RET and VHL. Hum Mol Genet 6:1051–1056