significant genetic modifier of *BRCA* penetrance for breast, but not ovarian, cancer. Of interest, in this context, are observations from animal studies in which the *Min* mouse, carrying a germ-line mutation in the murine homologue of *APC*, is susceptible to mammary gland tumorigenesis, in addition to that of the gastrointestinal tract (Bilger et al. 1996). These data also support the concept that genetic modifiers of *BRCA* penetrance are likely to exert differential effects on breast and ovarian tumorigenesis, as was found for the effect of rare *HRAS1* alleles on ovarian, but not breast, cancer risk (Phelan et al. 1996). As for many other genetic disorders, penetrance of dominant cancer-susceptibility alleles is likely to depend on complex interactions between multiple genetic and environmental modifying factors; furthermore, those genetic factors that are found to affect *BRCA* penetrance are not likely to be generalizable to both breast and ovarian cancer risk.

Acknowledgments

This work was supported by National Institutes of Health grant R01-CA71840. The authors are also grateful to Drs. William J. Hoskins and Patrick I. Borgen for their support of this laboratory.

Diane L. Maresco, Patricia H. Arnold, Yukio Sonoda, Mark G. Federici, Faina Bogomolniy, Esther Rhei, and Jeff Boyd
Gynecology and Breast Research Laboratory
Departments of Surgery and Human Genetics
Memorial Sloan-Kettering Cancer Center
New York

References

Abrahamson J, Moslehi R, Vesprini D, Karlan B, Fishman D, Smotkin D, Ben David Y, et al (1998) No association of the I1307K *APC* allele with ovarian cancer risk in Ashkenazi Jews. Cancer Res 58:2919–2922

Bilger A, Shoemaker AR, Gould KA, Dove WF (1996) Manipulation of the mouse germline in the study of Min-induced neoplasia. Sem Cancer Biol 7:249–260

Boyd J (1998) Molecular genetics of hereditary ovarian cancer. Oncology (Huntingt) 12:399–406

Easton DF, Ford D, Bishop DT, Breast Cancer Linkage Consortium (1995) Breast and ovarian cancer incidence in *BRCA1*-mutation carriers. Am J Hum Genet 56:265–271

Ford D, Easton DF, Stratton M, Narod S, Goldgar D, Devilee P, Bishop DT, et al (1998) Genetic heterogeneity and penetrance analysis of the *BRCA1* and *BRCA2* genes in breast cancer families. Am J Hum Genet 62:676–689

Gryfe R, Di Nicola N, Gallinger S, Redston M (1998) Somatic instability of the *APC I1307K* allele in colorectal neoplasia. Cancer Res 58:4040–4043

Kinzler KW, Vogelstein B (1996) Lessons from hereditary colorectal cancer. Cell 87:159–170

Laken SJ, Petersen GM, Gruber SB, Oddoux C, Ostrer H, Giardiello FM, Hamilton SR, et al (1997) Familial colorectal cancer in Ashkenazim due to a hypermutable tract in *APC*. Nat Genet 17:79–83

Narod SA, Goldgar D, Cannon-Albright L, Weber B, Moslehi R, Ives E, Lenoir G, et al (1995) Risk modifiers in carriers of *BRCA1* mutations. Int J Cancer 64:394–398

Narod SA, Risch H, Moslehi R, Dorum A, Neuhausen S, Olsson H, Provencher D, et al (1998) Oral contraceptives and the risk of hereditary ovarian cancer. N Engl J Med 339: 424–428

Petrukhin L, Dangel J, Vanderveer L, Costalas J, Bellacosa A, Grana G, Daly M, et al (1997) The I1307K APC mutation does not predispose to colorectal cancer in Jewish Ashkenazi breast and breast-ovarian cancer kindreds. Cancer Res 57: 5480–5484

Phelan CM, Rebbeck TR, Weber BL, Devilee P, Ruttledge MH, Lynch HT, Lenoir GM, et al (1996) Ovarian cancer risk in *BRCA1* carriers is modified by the *HRAS1* variable number of tandem repeat (VNTR) locus. Nat Genet 12:309–311

Redston M, Nathanson KL, Yuan ZQ, Neuhausen SL, Satagopan J, Wong N, Yang D, et al (1998) The *APC* I1307K allele and breast cancer risk. Nat Genet 20:13–14

Rhei E, Bogomolniy F, Federici MG, Maresco DL, Offit K, Robson ME, Saigo PE, et al (1998) Molecular genetic characterization of *BRCA1*- and *BRCA2*-linked hereditary ovarian cancers. Cancer Res 58:3193–3196

Struewing JP, Hartge P, Wacholder S, Baker SM, Berlin M, McAdams M, Timmerman MM, et al (1997) The risk of cancer associated with specific mutations of *BRCA1* and *BRCA2* among Ashkenazi Jews. N Engl J Med 336: 1401–1408

Woodage T, King SM, Wacholder S, Hartge P, Struewing JP, McAdams M, Laken SJ, et al (1998) The APC I1307K allele and cancer risk in a community-based study of Ashkenazi Jews. Nat Genet 20:62–65

Address for correspondence and reprints: Dr. Jeff Boyd, Department of Surgery, Box 201, Memorial Sloan-Kettering Cancer Center, 1275 York Avenue, New York, NY 10021. E-mail: boydj@mskcc.org

0002-9297/99/6404-0038$02.00

Am. J. Hum. Genet. 64:1230–1233, 1999

Germ-Line *NF2* Mutations and Disease Severity in Neurofibromatosis Type 2 Patients with Retinal Abnormalities

To the Editor:

Neurofibromatosis type 2 (NF2; MIM 101000) is a clinically variable disease caused by mutations in the *NF2* tumor-suppressor gene. Common manifestations include nervous system tumors and ocular abnormalities such as presenile lens opacities and retinal abnormalities

Table 1

Identified Germ-Line *NF2* Mutations and Disease Severity in NF2 Patients with Retinal Abnormalities

Patient	Exon	Sequence Change	Codon Change	Consequence	Family History	Retinal Hamartoma	Epiretinal Membrane	Disease Severity
German:								
Identified mutations:								
130	3	331 C→T	Gln 111 to stop	Nonsense	Sporadic	Yes	Yes	Severe
161	7	+5 g→c		Splice donor site	Sporadic	No	Yes	Severe
1088	8	701 T→G	234 Leu to Arg	Missense	Sporadic	Yes	No	Severe
16	11	1047-1053 del TGAACGC		Frameshift	Sporadic	No	Yes	Severe
26	14	1574+1 g→c		Splice donor site	Sporadic	Yes	No	Mild
Unidentified mutations:								
1008					Sporadic	Yes	No	Mild
1013					Sporadic	Yes	No	Mild
1014					Familial	No	Yes	Severe
1021					Sporadic	Yes	Yes	Severe
U.S.:								
CH101					Sporadic	Yes	No	Severe
CH102					Familial	Yes	No	Mild
CH103					Familial	Yes	No	Severe
CH104					Sporadic	Yes	Yes	Severe
CH105					Sporadic	Yes	No	Severe
CH106					Sporadic	Yes	Yes	Mild
CH107					Familial	Yes	No	Mild
CH108					Sporadic	Yes	No	Severe
CH109					Sporadic	Yes	Yes	Severe

NOTE.—Disease severity was as defined by Parry et al. (1994): mild disease = vestibular schwannoma (VS) and <2 non-VS intracranial tumors, or age at onset ≥20 years; severe disease = VS and ≥2 non-VS intracranial tumors, or rare spinal tumor and age at onset <20 years. G17693 had severe disease, but the affected parent had a late age at onset. Patients 130, 161, 16, and 26: Kluwe et al. (1996, 1998); patients 1088, 1008, 1013, 1014, and 1021: Dr. Lan Kluwe (private communication); and patients CH101–CH109: Dr. Mark Borchert (private communication).

(Evans et al. 1992; Parry et al. 1994; Ragge et al. 1995; Mautner et al. 1996). In general, germ-line *NF2* nonsense and frameshift mutations are associated with severe disease, missense mutations with mild disease, and splice-site mutations with variable disease severity (Kluwe et al. 1996, 1998; Parry et al. 1996; Ruttledge et al. 1996; Evans et al. 1998). Several studies indicate that ocular genotype-phenotype correlations might exist. Four patients studied in a three-generation NF2 family had combined pigment epithelial and retinal hamartomas (CPERH) (Bouzas et al. 1992; Parry et al. 1996). Retinal hamartomas have been found only in NF2 patients with severe disease (Parry et al. 1994, 1996). In reviewing phenotypes of 21 NF2 families with identified germ-line mutations, Parry et al. (1996) noted that patients with retinal abnormalities had only nonsense mutations and hypothesized that this was a genotype-phenotype correlation. The purpose of the present study was to examine the relationship among the germ-line *NF2* mutation type, retinal abnormalities, and disease severity.

We studied 18 unrelated NF2 patients with retinal abnormalities at the Allgemeines Krankenhaus Ochsenzoll, Hamburg (nine patients), and the House Ear Institute and Children's Hospital, Los Angeles (nine patients). All patients provided informed consent and met the NF2 clinical diagnostic criteria (Gutmann et al. 1997). Disease severity was as defined by Parry et al. (1994). Retinal lesions were initially classified as retinal hamartomas, epiretinal membranes, or CPERH (Ragge et al. 1995; Mautner et al. 1996) and then confirmed by a second neuro-ophthalmologist who was masked as to the original diagnosis (patient numbers 1013 and CH102 were examined by only one neuro-ophthalmologist). For the German patients, germ-line *NF2* mutations were analyzed by scanning the *NF2* coding region (17 known exons and adjacent splice junctions), 60 bp of the 5′ UTR, and 98 bp of the 3′ UTR, by using SSCP or temperature-gradient gel electrophoresis, followed by direct sequencing (Jacoby et al. 1994; Kluwe et al. 1996, 1998).

Ten of 18 patients had retinal hamartomas only, 3 had epiretinal membranes only, and 5 had both retinal hamartomas and epiretinal membranes. No CPERHs were found. Six of 18 patients had mild disease, including 6 (40%) of 15 with retinal hamartomas. The germ-line mutations that were identified in five (55.6%) of nine German patients occurred in exons 3–14 and included nonsense, frameshift, splice donor site, and missense mutations (table 1). Retinal abnormalities were not asso-

ciated with mutation location: in the present study and in Parry et al. (1996), 4 (40%) of 10 index cases with retinal abnormalities had identified mutations in exons 1–7, compared with 7 (43.8%) of 16 index cases without retinal abnormalities. Of particular interest, patient CH101 was followed up with at least semiannual neuro-ophthalmic examinations for 13 years. By age 15 years, he had lost all useful vision in his right eye because of exposure keratitis and orbital meningioma. His vision remained 20/20 in his left eye until age 22, when he complained of difficulty in reading. His vision had decreased to 20/70, and fundus examination revealed a new retinal hamartoma in the macula of the left eye.

Parry et al. (1996) hypothesized that there was a genotype-phenotype correlation between nonsense mutations and retinal abnormalities, because retinal abnormalities occurred only in nine patients from five families with nonsense mutations. The biological basis of this hypothesis is unclear, because both nonsense and frameshift mutations are predicted to truncate the NF2 protein. Because Parry et al. (1996) identified only two frameshift mutations, but nonsense mutations are common, the association of nonsense mutations with retinal abnormalities may have been due to chance, in a small number of families. In the present study we found that NF2 patients with retinal lesions had various germ-line *NF2* mutation types. Our mutation-detection efficiency rate (55.6%) is within the range of previous studies; the four patients with unidentified mutations may have had mutations in the 5′ or 3′ UTRs, intronic mutations, or large deletions.

Parry et al. (1994, 1996) found that all NF2 patients with retinal hamartomas had severe disease, but our results do not support an exclusive association of NF2 retinal hamartomas with severe disease. Only 60% of patients with retinal hamartomas had severe disease, which is similar to the 50%–75% proportion noted in other studies for patients without retinal hamartomas (Parry et al. 1994, 1996; Ragge et al. 1995). NF2 disease severity and retinal lesions can vary within families (Bouzas et al. 1992; Baser et al. 1996*a;* Kluwe et al. 1996; Parry et al. 1996; Scoles et al. 1996), and phenotypic variability between MZ twins with NF2 suggests an influence of gene-environment interactions or stochastic processes such as the timing of the loss of the second *NF2* allele (Baser et al. 1996*b*).

NF2 retinal lesions are clinically variable and have been named according to similar-appearing lesions that include (in other conditions) retinal hamartomas, epiretinal membranes, and CPERH. Ragge et al. (1995) suggested that NF2 retinal hamartomas may be useful for presymptomatic diagnosis in at-risk children and adolescents. However, patient CH101 in the present study demonstrates that these lesions are not always present at birth or early childhood, although this patient may have had a subclinical hamartoma prior to detection. Retinal hamartomas in tuberous sclerosis also occasionally grow or arise later in life (Zimmer-Galler and Robertson 1995). Epiretinal membranes in children should raise concern for NF2 (Kaye et al. 1992; Meyers et al. 1995; Ragge et al. 1995). Because epiretinal membranes can result from numerous pathologic processes and occur idiopathically, the cell type of the thin layer of cells associated with these membranes also varies, and it is premature to assume that the pathologic process or cell type in NF2 epiretinal membranes is always the same. Lesions similar to CPERH occurred in four members of an NF2 family (Bouzas et al. 1992), but the germ-line mutation was one that also occurs in patients without retinal abnormalities (1021 C→T, Arg 341 to stop) (Sainz et al. 1995; Parry et al. 1996), which does not support a genotype-phenotype correlation.

In summary, retinal hamartomas are not exclusively associated with severe NF2, and neither the type nor the location of the germ-line *NF2* mutation is the sole determinant of NF2 retinal abnormalities, which can be variably expressed in NF2 families. We recommend caution in evaluating genotype-phenotype correlations for NF2 retinal lesions, as they are clinically variable and pathogenetically undefined conditions.

Acknowledgments

We thank the NF2 patients and their families for participating, Dr. Mark Borchert for a review of fundus photographs and manuscript contributions, Dr. Dilys Parry for manuscript review, and the many other clinicians and researchers who contributed. This work was supported in part by Hamburger Stiftung zur Förderung der Krebsbekämpfung 116, 117, and Wilhelm-Sander-Stiftung 93052.2 (L. K., V.-F. M.).

Michael E. Baser,[1] Lan Kluwe,[2] and Victor-F. Mautner[3]

[1]*Los Angeles;* [2]*Neurosurgery Department, University Hospital Eppendorf, Germany; and* [3]*Department of Neurology, Allgemeines Krankenhaus Ochsenzoll, Hamburg, Germany*

Electronic-Database Information

Accession number and URL for data in this article are as follows:

Online Mendelian Inheritance in Man (OMIM), http://www.ncbi.nlm.nih.gov/Omim (for NF2 [MIM 101000]).

References

Baser ME, Mautner VF, Ragge NK, Nechiporuk A, Riccardi VM, Klein J, Sainz J, et al (1996*a*) Presymptomatic diagnosis of neurofibromatosis 2 using linked genetic markers, neu-

roimaging, and ocular examinations. Neurology 47:1269–1277
Baser ME, Ragge NK, Riccardi VM, Janus T, Ganz B, Pulst S (1996*b*) Phenotypic variability in monozygotic twins with neurofibromatosis 2. Am J Med Genet 64:563–567
Bouzas EA, Parry DM, Eldridge R, Kaiser-Kupfer MI (1992) Familial occurrence of combined pigment epithelial and retinal hamartomas associated with neurofibromatosis 2. Retina 12:103–107
Evans DGR, Huson SM, Donnai D, Neary W, Blair V, Newton V, Harris R (1992) A clinical study of type 2 neurofibromatosis. Q J Med 84:603–618
Evans DGR, Trueman L, Wallace A, Strachan T (1998) Genotype/phenotype correlations in type 2 neurofibromatosis (NF2): evidence for more severe disease caused by truncating mutations. J Med Genet 35:450–455
Gutmann DH, Aylsworth A, Carey JC, Korf B, Marks J, Pyeritz RE, Rubenstein A, et al (1997) The diagnostic evaluation and multidisciplinary management of neurofibromatosis 1 and neurofibromtaosis 2. JAMA 278:51–57
Jacoby LB, MacCollin M, Louis DN, Mohney T, Rubio MP, Pulaski K, Trofatter JA, et al (1994) Exon scanning for mutation of the *NF2* gene in schwannomas. Hum Mol Genet 3:413–419
Kaye LD, Rothner AD, Beauchamp GR, Meyers SM, Estes ML (1992) Ocular findings associated with neurofibromatosis type II. Ophthalmology 99:1424–1429
Kluwe L, Beyer S, Baser ME, Hazim W, Haase W, Fünsterer C, Mautner VF (1996) Identification of *NF2* germ-line mutations and comparison with NF2 phenotypes. Hum Genet 98:534–538
Kluwe L, MacCollin M, Tatagiba M, Thomas S, Hazim W, Haase W, Mautner V-F (1998) Phenotypic variability associated with 14 splice-site mutations in the NF2 gene. Am J Med Genet 77:228–233
Mautner V, Lindenau M, Baser ME, Hazim W, Tatagiba M, Haase W, Samii M, et al (1996) The neuroimaging and clinical spectrum of neurofibromatosis 2. Neurosurgery 38:880–886
Meyers SM, Gutman FA, Kaye LD, Rothner AD (1995) Retinal changes associated with neurofibromatosis 2. Trans Am Ophthalmol Soc 93:245–252
Parry DM, Eldridge R, Kaiser-Kupfer MI, Bouzas EA, Pikus A, Patronas N (1994) Neurofibromatosis 2 (NF2): clinical characteristics of 63 affected individuals and clinical evidence for heterogeneity. Am J Med Genet 52:450–461
Parry DM, MacCollin MM, Kaiser-Kupfer MI, Pulaski K, Nicholson HS, Bolesta M, Eldridge R, et al (1996) Germline mutations in the neurofibromatosis 2 gene: correlations with disease severity and retinal abnormalities. Am J Hum Genet 59:529–539
Ragge NK, Baser ME, Klein J, Nechiporuk A, Sainz J, Pulst SM, Riccardi VM (1995) Ocular abnormalities in neurofibromatosis 2. Am J Ophthalmol 120:634–641
Ruttledge MH, Andermann AA, Phelan CM, Claudio JO, Han F, Chretien N, Rangaratnam S, et al (1996) Type of mutation in the neurofibromatosis type 2 gene (*NF2*) frequently determines severity of disease. Am J Hum Genet 59:331–342
Sainz J, Figueroa K, Baser ME, Mautner VF, Pulst SM (1995) High frequency of nonsense mutations in the NF2 gene caused by C to T transitions in five CGA codons. Hum Mol Genet 4:137–139
Scoles DR, Baser ME, Pulst SM (1996) A missense mutation in the neurofibromatosis 2 gene occurs in patients with mild and severe phenotypes. Neurology 47:544–546
Zimmer-Galler IE, Robertson DM (1995) Long-term observation of retinal lesions in tuberous sclerosis. Am J Ophthalmol 119:318–324

Address for correspondence and reprints: Dr. Michael Baser, 11746 Bellagio Road, #308, Los Angeles, CA 90049. E-mail: baser@earthlink.net

0002-9297/99/6404-0039$02.00

Am. J. Hum. Genet. 64:1233–1238, 1999

Gaucher Disease: The N370S Mutation in Ashkenazi Jewish and Spanish Patients has a Common Origin and Arose Several Thousand Years Ago

To the Editor:

The identification of highly polymorphic markers, which are widely distributed throughout the human genome, has allowed the mapping of several disease genes. These markers have been used to analyze the origin, in time and place, of the most prevalent mutations for different diseases, such as cystic fibrosis (Morral et al. 1994), idiopathic torsion dystonia (Risch et al. 1995), hereditary colon cancer (Moisio et al. 1996), factor XI deficiency (Peretz et al. 1997), and myotonic dystrophy (Tishkoff et al. 1998). We present the analysis of the origin of N370S, the most common Gaucher disease (GD) mutation among Ashkenazi Jewish and Spanish patients. The results show that both patient populations share the same ancestral haplotype and that this mutation arose several thousand years ago.

GD (MIM 230800), caused by mutations in the glucocerebrosidase (*GBA*) gene, is the most prevalent lysosomal storage disease. It is inherited as an autosomal recessive trait, which is particularly frequent in the Ashkenazi Jewish population, with a disease incidence of ~1/850 (Beutler and Grabowski 1995). It is also found in other populations, albeit with lower frequency, with a range of 1/40,000–1/60,000 (Grabowski 1993). Among Ashkenazi Jewish patients with GD, ~70% of the alleles carry the N370S (1226A→G) mutation (Beutler et al. 1992*a*; Horowitz et al. 1993; Sibille et al. 1993). It appears that approximately two-thirds of the individuals homozygous for this mutation escape detection because of the very mild clinical manifestation; thus, the N370S frequency in the Ashkenazi Jewish population is higher, ~90% of all GD mutations (Beutler et al. 1993; Grabowski 1997). This mutation is also frequent