hMSH2 and hMLH1 in young colon cancer patients and controls. Am J Hum Genet 63:749-759
Ford D, Easton DF, Peto J (1995) Estimates of the gene frequency of BRCA1 and its contribution to breast and ovarian cancer incidence. Am J Hum Genet 57:1457-1462
Greger V, Passarge E, Horsthemke B (1990) Somatic mosaicism in a patient with bilateral retinoblastoma. Am J Hum Genet 46:1187-1193
Hackman P, Tannergard P, Osei-Mensa S, Chen J, Kane MF, Kolodner R, Lambert B, et al (1997) A compound heterozygote for two MLH1 missense mutations. Nat Genet 17: 135-136
Hall JG (1988) Somatic mosaicism: observations related to clinical genetics. Am J Hum Genet 43:355-363
Huang J, Papadopoulos N, McKinley AJ, Farrington SM, Curtis LJ, Wyllie AH, Zheng S, et al (1996) APC mutations in colorectal tumors with mismatch repair deficiency. Proc Natl Acad Sci USA 93:9049-9054
Kinzler KW, Vogelstein B (1996) Lessons from hereditary colorectal cancer. Cell 87:159-170
Kovar H, Auinger A, Jug G, Muller T, Pillwein K (1992) p53 Mosaicism with an exon 8 germline mutation in the founder of a cancer-prone pedigree. Oncogene 7:2169-2173
Lázaro C, Gaona A, Lynch M, Kruyer H, Ravella A, Estivill X (1995) Molecular characterization of the breakpoints of a 12-kb deletion in the *NF1* gene in a family showing germline mosaicism. Am J Hum Genet 57:1044-1049
Lohmann DR, Gerick M, Brandt B, Oelschläger U, Lorenz B, Passarge E, Horsthemke B (1997) Constitutional RB1-gene mutations in patients with isolated unilateral retinoblastoma. Am J Hum Genet 61:282-294
Lynch HT, Ruma TA, Albano WA (1982) Phenotypic variation in hereditary adenomatosis: unusual tumor spectrum. Dis Colon Rectum 25:235-238
Mandl M, Kadmon M, Sengteller M, Caspari R, Propping P, Friedl W (1994) A somatic mutation in the adenomatous polyposis coil (APC) gene in peripheral blood cells—implications for predictive diagnosis. Hum Mol Genet 3:1009-1011
Mullen P, Miller WR, Mackay J, Fitzpatrick DR, Langdon SP, Warner JP (1997) BRCA1 5382insC mutation in sporadic and familial breast and ovarian carcinoma in Scotland. Br J Cancer 75:1377-1380
Novelli MR, Williamson JA, Tomlinson IM, Elia G, Hodgson SV, Talbot IC, Bodmer WF, et al (1996) Polyclonal origin of colonic adenomas in an XO/XY patient with FAP. Science 272:1187-1190
Parsons R, Li G-M, Longley M, Modrich P, Liu B, Berk T, Hamilton SR, et al (1995) Mismatch repair deficiency in phenotypically normal human cells. Science 268:738-740
Prosser J, Condie A, Wright M, Horn JM, Fantes JA, Wyllie AH, Dunlop MG (1994) APC mutation analysis by chemical cleavage of mismatch and a protein truncation assay in familial adenomatous polyposis. Br J Cancer 70:841-846
Sharrock A, Bunyan DJ, Pond MC, Murray A, Eccles D, Jacobs P (1997) FRAXA instability in a family with HNPCC. J Med Genet Suppl 34:S55
Wooster R, Cleton-Jansen A-M, Collins N, Mangion J, Cornelis RS, Cooper CS, Gusterson BA, et al (1994) Instability of short tandem repeats (microsatellites) in human cancers. Nat Genet 6:152-156
Yates JRW, van Bakel I, Sepp T, Payne SJ, Webb DW, Nevin NC (1997) Female germline mosaicism in tuberous sclerosis confirmed by molecular genetic analysis. Hum Mol Genet 6:2265-2269

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0002-9297/99/6402-0038$02.00

Am. J. Hum. Genet. 64:658–659, 1999

HPS Gene Mutations in Hermansky-Pudlak Syndrome

To the Editor:

We recently reported a series of mutations of the *HPS* gene in non–Puerto Rican patients with Hermansky-Pudlak syndrome (MIM 203300) (Oh et al. 1998). One of these mutations was designated incorrectly in some places in the article; a frameshift in codon Q397 was incorrectly designated "E397" in the text (this mutation is now designated "c1189delC," in the new nomenclature; Antonarakis 1998). In addition, subsequent to publication we determined that patient 20 is homozygous for a novel frameshift due to a single-base deletion in codon G96, designated "c288delT," with the first-cousin parents both being heterozygous for this mutation. Thus, *HPS* gene mutations have now been identified in all patients and families who show apparent linkage to 10q23. With our original description of the gene (Oh et al. 1996) and the recent report of Shotelersuk et al. (1998), this brings the number of reported *HPS* gene mutations to 11 and further underscores the lack of missense mutations identified in patients with this disorder.

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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 Hermansky-Pudlak syndrome [MIM 203300])

References

Antonarakis SE (1998) Recommendations for a nomenclature system for human gene mutations. Nomenclature Working Group. Hum Mutat 11:1–3

Oh J, Bailin T, Fukai K, Feng GH, Ho L, Mao J-I, Frenk E, et al (1996) Positional cloning of a gene for Hermansky-Pudlak syndrome, a disorder of cytoplasmic organelles. Nat Genet 14:300–306

Oh J, Ho L, Ala-Mello S, Amato D, Armstrong L, Bellucci S, Carakushansky G, et al (1998) Mutation analysis of patients with Hermansky-Pudlak syndrome: a frameshift hot spot in the *HPS* gene and apparent locus heterogeneity. Am J Hum Genet 62:593–598

Shotelersuk V, Hazelwood S, Larson D, Iwata F, Kaiser-Kupfer MI, Kuehl E, Bernardini I, et al (1998) Three new mutations in a gene causing Hermansky-Pudlak syndrome: clinical correlations. Mol Genet Metab 64:99–107

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0002-9297/99/6402-0039$02.00

Am. J. Hum. Genet. 64:659–667, 1999

A Novel 22q11.2 Microdeletion in DiGeorge Syndrome

To the Editor:

DiGeorge syndrome (DGS; MIM 188400) is a multiple-malformation syndrome characterized by aplasia or hypoplasia of the thymus; immunodeficiency, aplasia, or hypoplasia of the parathyroid glands; conotruncal cardiac defects; and typical facial anomalies(DiGeorge 1965; Conley et al. 1979). Despite causal heterogeneity (Lammer and Opitz 1986), ~90% of patients with DGS have hemizygosity of an ~1.5–3-Mb region within 22q11.2 (Driscoll et al. 1990; Scambler et al. 1991; Driscoll et al. 1992*a*). Because of phenotypic overlap, the same deletion was demonstrated in the majority of patients with velo-cardio-facial syndrome (VCFS; MIM 192430) (Driscoll et al. 1992*b;* Carlson et al. 1997*b*), which was initially characterized by hypernasal speech caused by cleft palate, cardiac anomalies, learning disabilities, and typical facial appearance (Shprintzen et al. 1978, 1981). In addition, 22q11.2 deletions were observed in cases fitting within the spectrum of Cayler syndrome (MIM 125520) (Giannotti et al. 1994), Takao conotruncal anomaly face syndrome (contained in MIM 188400) (Burn et al. 1993), Noonan syndrome (MIM 163915) (Wilson et al. 1993), Kousseff syndrome (MIM 245210) (Nickel et al. 1994), and Opitz GBBB syndrome (MIM 145410) (McDonald-McGinn et al. 1995). Meanwhile, it became evident that deletion 22q11.2 is associated with a phenotypic spectrum that may present as one of the aforementioned syndromes or any condition in between them that has considerable inter- and intrafamilial variability (De Silva et al. 1995; Leana-Cox et al. 1996; Devriendt et al. 1997; Ryan et al. 1997). Therefore, 22q11.2 microdeletion is one of the most common genetic defects, with an estimated incidence of >1 in 5,000 (Wilson et al. 1994; Tezenas Du Montcel et al. 1996). According to Carlson et al. (1997*b*), 90% of patients with deletions have a common 3-Mb deletion, 8.5% have a proximal 1.5-Mb deletion, and 3% have unique nested proximal deletions, which may define a proximal shortest region of overlap within the commonly deleted 3-Mb region. Because of two patients with small deletions in the distal part of the 3-Mb deletion, a distal shortest region of overlap within the deleted region may also be defined (Kurahashi et al. 1997; O'Donnell et al. 1997). However, there is no obvious correlation between the site or size of the deletion and the severity of the clinical manifestations, and position effects have been taken into consideration (Carlson et al. 1997*b;* Kurahashi et al. 1997; O'Donnell et al. 1997). We describe here a novel 22q11.2 microdeletion in a family with mild to severe phenotype. This deletion is adjacent to but does not overlap with the known deletions. Nevertheless, it shows similar clinical characteristics and may therefore give a clue to the mechanisms and genes involved in phenotype determination in 22q11.2 deletions.

Patient III:3 was primarily investigated in the context of a study of incidence and significance of 22q11.2 hemizygosity in patients with interrupted aortic arch (Rauch et al. 1998*b*). Within that study, she was the only patient with symptoms of the DGS/VCFS spectrum who did not have the 22q11.2 deletion and, therefore, prompted further analysis. Phenotype assessment of the patient, her parents, and her sibs was performed before molecular studies and included dysmorphologic analysis of lymphocyte subpopulations by flow cytometry on an Orthoscan, by means of fluorochrome-labeled antibodies against CD3, CD4, CD8, and CD19; and surface immunoglobulin (according to Becton-Dickinson). Diphtheria toxoid and tetanus toxoid were measured after vaccination, by means of a commercially available enzyme-linked immunosorbent assay (ELISA) (ABICAP; Abion). Parathyroid hormone levels were determined by chemoluminescence-ELISA (Nichols) of the patient's sera. Cardiac status was established by echocardiography and angiography in the patient and by echocardiography only in the patient's parents and sibs. Flexible transnasal pharyngoscopy was performed in the patient's sister and mother, to exclude velopharyngeal insufficiency.