Am. J. Hum. Genet. 56:224–230, 1995

X-Linked Progressive Mixed Deafness: A New Microdeletion That Involves a More Proximal Region in Xq21

C. Piussan,[1] A. Hanauer,[3] N. Dahl,[3] M. Mathieu,[1] C. Kolski,[2] V. Biancalana,[3] S. Heyberger,[3] and V. Strunski[2]

[1]Unité de Génétique Clinique, Service de Pédiatrie I, and [2]Service d'ORL, CHU d'Amiens, Amiens; and [3]LGME/CNRS, INSERM, Institut de Chimie Biologique, Strasbourg

Summary

We report a large two-generation pedigree with seven affected males segregating for an X-linked mixed conductive sensorineural deafness. The patients present with atypical Mondini-like dysplasia, dilated petrous facial canal, dilatation of the internal auditory meatus fully connected with enlarged cochlear canals, and, in one patient, a wide bulbous posterior labyrinth. Obligatory carrier females are mildly affected. Molecular characterization of this family revealed a deletion of locus DXS169, in Xq21.1. Loci DXS72 and DXS26, which, respectively, flank DXS169 proximally and distally, were intact. Since a gene responsible for X-linked progressive mixed deafness with perilymphatic gusher (DFN3) has previously been assigned by deletion mapping to a slightly more distal interval between DXS26 and DXS121, this study indicates either two different deafness genes or the involvement of a very large region in Xq21.

Introduction

Mutations of defective genes located on the X chromosome are an infrequent cause of congenital or early-onset deafness. Some determine more extensive syndromes such as Alport syndrome, MPS type II or Hunter syndrome, oto-palato-digital syndrome, Norrie disease, Juberg-Marsidi syndrome, as well as ocular albinism, partial cutaneous albinism, or rare X-linked hypogonadisms (Brunner et al. 1988). In addition to these syndromic causes, several nonsyndromic forms of deafness have been reported, whose inheritance is either autosomal dominant (Chan et al. 1991), autosomal recessive, or X linked. In addition, four different isolated bilateral X-linked forms of deafness have been delineated on the basis of their audiological characteristics (Koningsmark and Gorlin 1976): DFN1 is characterized by the early onset of pure sensorineural hearing loss; DFN2 results in a profound congenital sensorineural deafness; and another gene is probably responsible for a milder and less severe deafness, while yet another mutation, DFN3, results in a mixed sensorineural and conductive hearing loss, as first described by Nance et al. (1971). Whether these different forms of deafness are caused by genes at different loci on the X chromosome or are allelic mutations remains to be resolved. However, a first suggestion of genetic heterogeneity in X-linked sensorineural deafness has been provided by Reardon et al. (1992). As a whole, profound childhood deafness occurs in 1/1,000 newborns (Fraser 1965), of which nonsyndromic X-linked deafness may account for ~1.7%. Half of these, in turn, may well reflect DFN3 gene mutations responsible for an X-linked progressive mixed sensorineural hearing loss (Nance et al. 1971).

Anatomically, many attempts have been made to classify deafness types according to the presence or absence of specific malformations of the inner and middle ear: (1) combined defects involving the organ of Corti and the bony labyrinth, either of the complete Michel type or partial defects of the type described by Mondini as early as 1791 (Mondini 1791); (2) isolated defect of organ of Corti (Sheibe type); and (3) combined anomaly of organ of Corti and the cochlear and/or vestibular nerves, or bulbar nuclei. Many autosomal forms of deafness are known that are associated with either specific disorders or craniofacial malformations (Jardin and Vignaud 1988; Johnsen et al. 1989; Dumas et al. 1991; Ostri et al. 1991). Among X-linked forms of deafness, craniofacial malformations are also seen in the oto-palato-digital and Wildervanck cervico-oculo-acoustic (West et al. 1989) syndromes.

From a genetic point of view, it may also be useful to classify deafness syndromes according to the stage of embryonic development at which the gene defect is manifested. In 1988, Jardin and Vignaud provided such a classification, which is based on high-resolution computed tomography (CT) in the axial and coronal planes: (1) stage I—absent labyrinth or single vesicle (complete labyrinth aplasia and no anterior vs. posterior differentiation), which gives evidence for an arrest of the inner-ear development by 25 d after fertilization; (2) stage II—"pseudo-Mondini"

Received July 20, 1994; accepted for publication October 10, 1994.

Address for correspondence and reprints: Dr. Charles Piussan, Pédiatrie Génétique, Centre Hopital-Universitaire, Hôpital Nord, 80054 Amiens, France.

0002-9297/95/5601-0029$02.00

(i.e., Mondini-like), rough and sketchy labyrinth with dilatation of semicircular canals (mainly the lateral one); ill-coiled cochlea with developmental arrest 27–47 d after fertilization; (3) stage III—first described by Mondini in 1791, normal posterior labyrinth, large vestibular aqueduct and endolymphatic sac, partial cochlear aplasia with <1.5 coils (resulting from arrested development at 45-70 d after fertilization); (4) stage IV—hypoplastic but well-shaped labyrinth and cochlea (indicates an arrest at 70-90 d after fertilization); and (5) stage V—isolated dilatation of the aqueduct of vestibule (suggests an arrest after slightly less than 4 mo of fetal life).

It is noteworthy that this five-stage classification does not include malformations of the internal acoustic meatus (IAM), whose osteogenesis depends not on the labyrinth ossification but on specific ossification centers conditioned by the organogenesis of the CNS (Jardin and Vignaud 1988). Furthermore, in this classification, some malformations, such as the pseudo-Mondini dysplasia (type II), are associated with a high risk of perilymphatic fistula with cerebrospinal fluid leak, which may lead to an initial clinical presentation of either otitis media or meningitis (Bluestone 1988; Jardin and Vignaud 1988; Wilson et al. 1990–1991).

Patients and Methods

Patients

In two generations of a large pedigree, we have identified seven males affected with a severe X-linked "progressive" mixed deafness and at least four heterozygous females presenting with mild to moderate hearing loss. Most of the patients were referred to the audiological center of Amiens in order to have complete audiogram and high-resolution CT scanning with thin axial and coronal planes, after initial screening tests had been performed. The average hearing loss was evaluated on the usual three-tone 500-1,000-2,000 MHz frequencies. Two of the deaf family members, II15 and II16, died accidentally. Their brother II1 presented with a very early prelingual deafness. Another (II17), presently living in Poland, is said to be profoundly deaf but has not been examined clinically. Four of their seven sisters have a moderate hearing loss, three of whom have each had a severely affected son (fig. 1). All affected males showed evidence of important speech impairment and learning disabilities, but, as usual in profound deafness, it may be quite difficult to assess the severity of the mental retardation.

Molecular Studies

Genomic DNA was extracted from peripheral blood samples by standard procedures. Agarose-gel electrophoresis, Southern transfer, hybridization, and autoradiography were performed according to methods described elsewhere (Oberle et al. 1986). All probes used either in linkage analysis or for deletion mapping have been described by Mandel et al. (1992) and include pRX21 (DXS339), pRX214 (DXS441), pX65H7 (DXS72), pX104f (DXS169), pHU16 (DXS26), and pJL68 (DXS232). PCR amplification of the DXS453 microsatellite marker was performed using primers and conditions described by Weber et al. (1990). The relative order of the four markers used in the linkage analysis, Xcen–DXS339–DXS453–DXS441–DXS72–Xtel (fig. 1), is derived from available mapping data (Barker and Fain 1993). Pairwise linkage was performed using the LINKAGE package (Lathrop et al. 1985).

Results

Clinical examination of all patients and female transmitter carriers did not show any choroideremia, obesity, or other phenotypic association. However, it is noteworthy that all of the affected males are childless and not married (fig. 1). Hormonal investigations of gonadal axis showed a normal response to luteinizing-hormone–releasing-hormone stimulation in all of them, while tests of baseline testosteronemia were normal, except for one patient displaying a low testosterone rate. Because of ethical reasons, no spermogram has been performed. Average sensorineural loss is −50 dB, and there are no stapedial reflexes despite normal tympanograms (fig. 2). Three of the heterozygous females are moderately affected: II5 and II13 with a pure sensorineural loss (average −24 dB), normal stapedial reflexes, and normal tympanograms. On the other hand, II11 carrier is affected with a slight mixed hearing loss, not only sensorineural (average −6 dB) but also conductive (average −14 dB), and the absence of stapedial reflexes despite normal tympanograms suggests a stapes fixation.

X-ray examination (fig. 3), performed by high-resolution CT scanning (axial and coronal planes), displayed in most of the affected patients a pseudo-Mondini (Mondini-like) stage II dysplasia (fig. 3), according to the embryologic classification by Jardin and Vignaud (1988), which implies an early arrest of embryogenesis of the inner ear between 25 and 47 d after fertilization. The findings included dilated (1) superior vestibular, (2) cochlear, and (3) facial nerve canals; (4) dilated internal acoustic meatus and fully connected fundus with cochlea, raising the possibility of increased endolymphatic pressure; (5) partial cochlea hypoplasia involving also the upper part of the basal turn, with an abnormal columella; and (6) wide bulbous posterior labyrinth in patient III13—but without any dilatation of vestibular or cochlear aqueducts. The CT scans did not reveal any ossicular anomaly of the middle ear: in every patient tympanic membranes and footplate of stapes were normal, as were oval windows. Nevertheless, the discrepancy between the absence of stapedial reflexes despite normal tympanograms makes the stapes fixation very likely in most of the explored individuals and must strongly dissuade the physician from doing any implantation or reconstructive surgery.

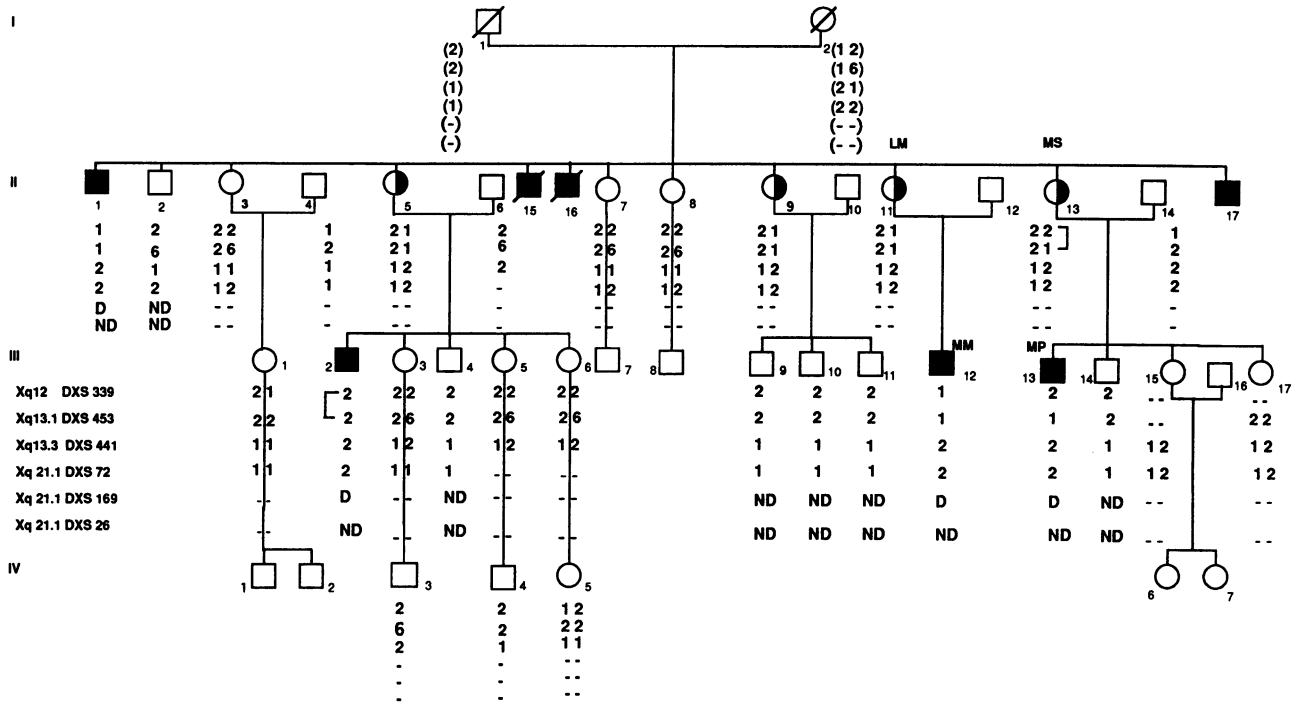

Figure 1 Pedigree. Seven males are affected with severe X-linked mixed deafness, and four heterozygous females present with a milder but recently increasing hearing loss.

DNA analysis initially performed, using four polymorphic markers from the Xq13-q21 region, suggested that the responsible gene in this family was located at Xq13-q21, closely linked to DXS441 and DXS72 (Z_{max} = 3.21 and 1.88, respectively, at $\theta = 0$) (table 1). Haplotype analysis was consistent with a localization of the disease gene distal to DXS453 (fig. 1). Further evidence for this location came with the identification of a microdeletion of the DXS169 marker locus in the four affected males, with no hybridization of the corresponding probe pX104f,

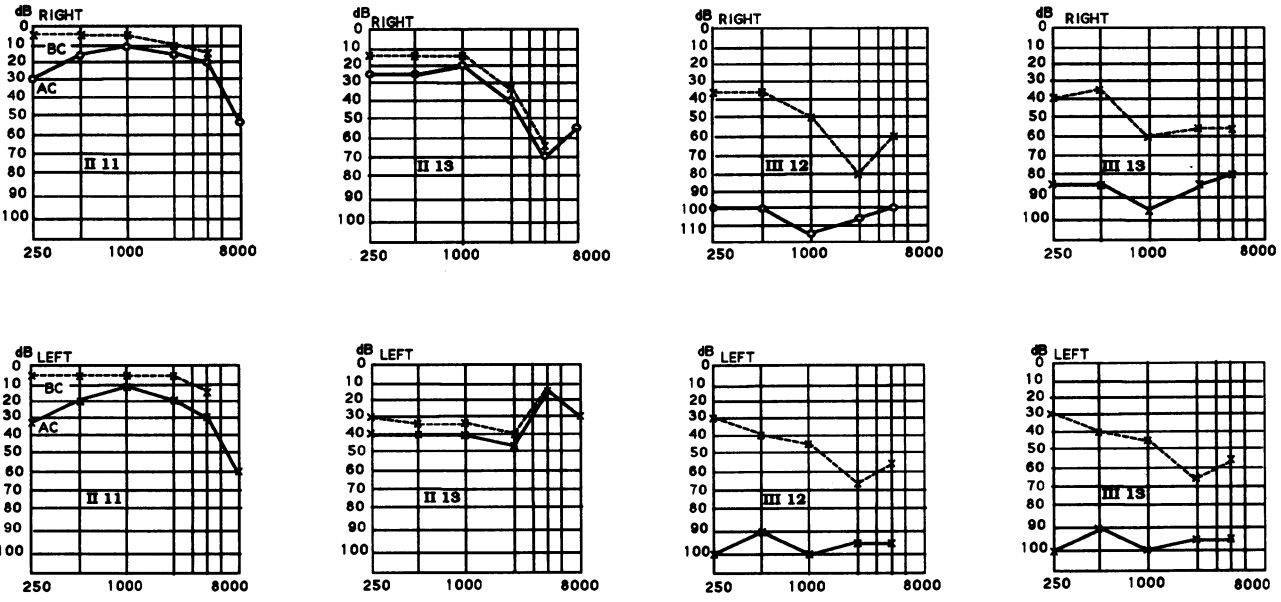

Figure 2 Audiograms. Profound bilateral mixed deafness is shown in affected males (III12, III13), and slight mixed hearing loss and sensorineural hearing loss is shown in carrier females (II11, II13).

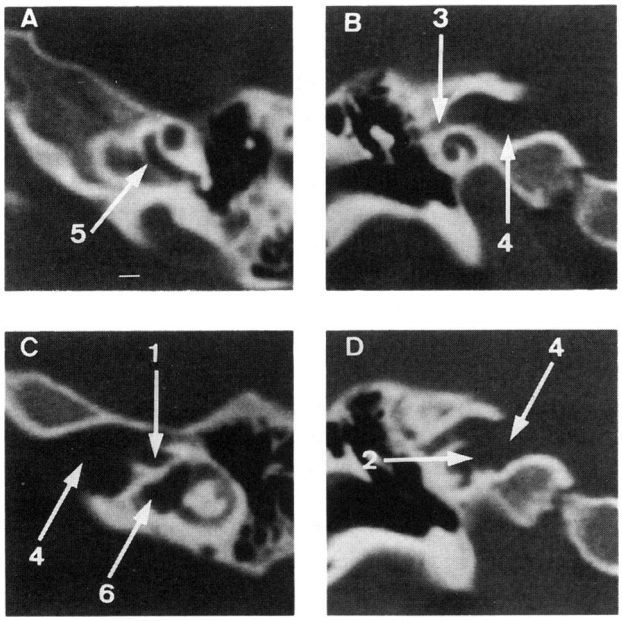

Figure 3 High-resolution CT scanning. Axial planes: panels *A* and *C*; coronal planes: panels *B* and *D*. Dilatation of vestibular (1), cochlear (2), and facial nerve canals (3) is shown, as are dilatation of IAM, fully connected fundus with cochlea (4), partial cochlea hypoplasia and abnormal columella (5), and wide bulbous posterior labyrinth (6).

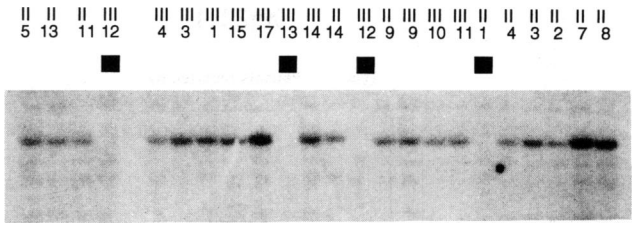

Figure 4 Hybridization of genomic DNAs digested with *PstI* from the members of the family with probe pX104F at DXS169 (blackened squares correspond to affected males).

whereas a normal band of the expected size was found in all normal males (fig. 4).

Only one carrier female showed a reduced-density band, which could be in favor of a possible dose effect (II11). In all individuals, normal hybridization patterns were observed for probes pX65H7 (DXS72) and for probe pHU16 (DXS26)—respectively the closest known proximal and distal flanking markers of DXS169—and for the more distal probe p-JI68 (DXS232). Hence, it seems that this deletion is limited to DXS169 and is more proximal and much smaller than previously described DFN3 deletions (fig. 5).

Discussion

X-linked deafness with perilymphatic gusher was first described by Nance (1971). Because it is often undetected in early life and first noted at variable ages, the hearing deterioration is assumed to be progressive and acquired in childhood but can in fact progress so rapidly that it may produce a congenital deafness (Reardon et al. 1991). The hearing loss is bilateral and severe, usually involving the high frequencies initially but progressing rapidly with age to involve the lower frequencies as well, yielding average perceptive losses of −95 dB at frequencies >500 Hz and a poor residual sound perception at 125–500 Hz (Zachmann et al. 1992). A mixed sensorineural and conductive hearing loss is typically found and vestibular function may often be impaired in affected males. Among heterozygous females ⩾50% have a moderate perceptive or mixed hearing loss without vestibular dysfunction (Brunner et al. 1988). As observed in our family where all affected males and one transmitter female did not show any stapedial reflex despite normal tympanograms, a decrease of the stapes mobility without anatomic fixation of the footplates is often suspected on audiological examination, but this has not been proved in most reported patients, given the likelihood of a "gusher" (Dumas et al. 1991) at the time of stapes mobilization. Indeed, repeated episodes of otitis media and/or recurrent meningitis can herald the onset of hearing loss and may reflect the occurrence of spontaneous perilymphatic fistulae (Bluestone 1988; Wilson et al. 1990–1991).

Clinical examination, radiologic findings, and genetic inquiry usually enable the investigator to rule out autosomal and syndromic forms of deafness, while CT may reveal, in at least half of the patients, a variety of abnormalities,

Table 1

Two-Point Lod Scores for the Disease Locus versus Xq13-q21 Markers

	Lod Score at θ =							
Marker Loci	.00	.01	.05	.10	.20	.30	θ_{max}	Z_{max}
DXS339	−∞	−1.44	−.21	.17	.33	.27	.21	.33
DXS453	−∞	.27	.85	.98	.90	.64	.12	.98
DXS441	3.21	3.15	2.90	2.58	1.93	1.26	.00	3.21
DXS72	1.88	1.85	1.72	1.56	1.23	.86	.00	1.88

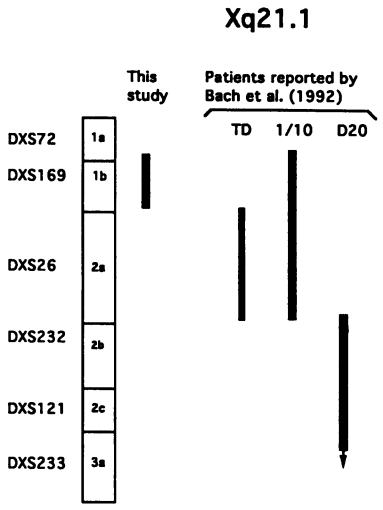

Figure 5 The order of probes used in this analysis is from Xcen (*top*) to Xqter (*bottom*) and is taken from Bach et al. (1992*a*).

including bony labyrinth malformations (Dumas et al. 1991); small cochleas with reduced vertical diameters or hypoplastic structural changes of cochlea, causing incomplete separation of perilymphatic and cerebrospinal fluids (Phelps et al. 1991; Phelps 1992); reduced area of the oval window >2 SDs below the mean (Okuno and Sando 1988); and dilated facial canals and bilateral dilatation of internal auditory canals or of the IAM (Phelps et al. 1991; Bach et al. 1992*a*; Phelps 1992; Reardon et al. 1992). This dilatation of the IAM and the characteristic inner-ear osseous anomaly with a structural separation defect between IAM and the basal turn of the cochlea could be typical of DFN3. On the other hand, the too-wide communication between subarachnoidic space and the middle ear can be related to a poor development not only of the cartilage bar between this space and the tympanic cavity, but also of the otic capsule in the hook portion of the basal turn of the cochlea (Okuno and Sando 1988) close to the lateral end of the IAM. The resulting increase in the perilymphatic pressure causes hydrops and can lead to a "gusher" if the stapes is disturbed, which contraindicates cochlear implant or reconstructive middle-ear surgery (Phelps 1992). Whether or not associated with a decreased stapedial mobility, the perilymphatic gusher arises from a sudden flood of cerebrospinal fluid during irrelevant surgery and results from an abnormal communication, between the subarachnoidic space and the inner ear, that is found in the pseudo-Mondini–type dysplasia (Cremers et al. 1989; Phelps 1992). Most of these malformations were present in our family. Unlike the present cases, the isolated enlargement of the vestibular aqueduct with progressive and acquired hearing deterioration seems to be a distinct clinical variant of Mondini dysplasia (Lacombe et al. 1989; Levenson et al. 1989) and to our knowledge has not been described in X-linked deafness.

These varied malformations, as well as the presence of the same structural abnormality of the inner- or middle-ear anatomy in the same families and their radiologic separation between different familial groups, suggests the involvement of distinct alleles and/or loci (Reardon et al. 1991, 1992). Because of this variability, it should be interesting to categorize them according to the developmental stage of fetal life at which the defect is first manifested, as established by the Jardin and Vignaud classification (Jardin and Vignaud 1988). Conversely, absent or moderate radiologic findings in individuals affected with a typical X-linked form of deafness (Reardon et al. 1991) provide evidence for clinical heterogeneity if the CT scanning has been thoroughly performed, and such variations would cast some doubts on a classification based only on audiological or radiologic criteria.

DFN3 gene mutations are probably the most frequent causes of X-linked deafness. The initially reported linkage studies had shown that a gene responsible for X-linked mixed deafness with perilymphatic gusher was located in Xq13-q21 (Brunner et al. 1988; Wallis et al. 1988). Various deletions involving this region provided further support for this assignment for the DFN3 locus (Ayazi 1981; Brunner et al. 1988). In some of those reported cases, there have been associated findings, including choroideremia and/or mental retardation (Nussbaum et al. 1987; Rosenberg et al. 1987; Reardon et al. 1991; Wells et al. 1991), raising the possibility of a "contiguous-gene syndrome." This localization of DFN3 to Xq21 was further refined by additional linkage studies to a chromosome segment defined by only three probes and confirmed by small corresponding deletions found in probands with classical and isolated choroideremia (Brunner et al. 1988; Cremers et al. 1989). Molecular characterization of some of these deletions allowed Bach et al. (1992*a*, 1992*b*) to map the DFN3 gene to the small segment of Xq21 proximal to DXS121.

A localization in the close vicinity of the DXS26 marker was later suggested by two deletions involving this very region, which were associated with hypogonadism in one deaf patient who showed an isolated deletion of DXS26 (patient TD) and a second patient who carried a deletion involving both DXS26 and DXS169 (patient 1/10). A third patient (D20), who was deaf and mentally retarded, showed a deletion of DXS232 as well as more distal markers but not for DXS26 or DXS169, leading Bach et al. (1992*a*) to place DFN3 between DXS26 and DXS232. However, the presence of two different deafness genes, one spanned by the TD and 1/10 deletions and the second by the D20 deletion, could not be excluded. If the presence of two separate loci on the X chromosome could be confirmed, a genetic heterogeneity would be established. Furthermore, the presence of such associated features as X-linked mental retardation, choroideremia, or hypogonadism in some patients with deletions would support the hypothesis for a contiguous-gene syndrome and could lead

to the isolation of candidate genes for these disorders (Bach et al. 1992*b*).

Our observation of a DFN3 family with an isolated deletion of DX169 could fit with the hypothesis that there are at least two deafness genes in Xq21.1. One gene, spanned by deletions TD, 1/10, and that from the present study, would map between DXS26 and DXS169; and another gene, slightly more distal, would map within the region spanned by the deletion D20. An alternative explanation would be that a single gene causes deafness by its absence in all deletion patients. However, this would imply a very large gene that encompasses the distance separating the D20 deletion from the deletion of the present study. According to pulsed-field gel electrophoresis studies reported by Bach et al. (1992*a*), this distance spans ⩾800 kb. A last possibility would be that, rather than a simple deletion, a more complex rearrangement may have occurred in patients, although there is no evidence to suggest this. To address this question, the cloning of the deletions' end points and a detailed molecular characterization of the region will be necessary.

Note added in proof.—After submission of the manuscript of the present report, Huber et al. (1994) identified two overlapping YAC clones that contained the DFN3 gene as determined by studies of individuals who had microdeletions within one of the sequences, also limiting the DFN3 gene to a domain of ~400 kb.

Acknowledgments

We are grateful to Dr. Walter Nance for his suggestions and comments on the manuscript. C.P. would also like to thank him for his continuous and friendly support.

References

Ayazi S (1981) Choroideremia, obesity and congenital deafness. Am J Ophthalmol 92:63–69

Bach I, Brunner HG, Beighton P, Ruvalcaba RHA, Reardon W, Pembrey ME, van der Velde-Visser SD (1992*a*) Microdeletions in patients with gusher-associated X-linked mixed deafness (DFN3). Am J Hum Genet 51:38–44

Bach I, Robinson D, Thomas N, Ropers HH, Cremers FP (1992*b*) Physical fine mapping of genes underlying X-linked deafness and non fra(X)-X-linked mental retardation at Xq21. Hum Genet 89:620–624

Barker DF, Fain PR (1993) Definition and mapping of STSs at STR and RFLP loci in Xp11-Xq22. Genomics 18:712–715

Bluestone CD (1988) Otitis media and congenital perilymphatic fistula as a cause of sensorineural hearing loss in children. Pediatr Infect Dis J Suppl 7:141–145

Brunner HG, Van Bennekom CA, Lambermon EMM, Lian Oei T, Cremers CWRJ, Wieringa B, Ropers HH (1988) The gene for X-linked progressive mixed deafness with perilymphatic gusher during stapes surgery (DFN3) is linked to PGK. Hum Genet 80:337–340

Chan KH, Eelkema EA, Furman JM, Kamerer DB (1991) Familial sensorineural hearing loss: a correlative study of audiologic, radiographic and vestibular findings. Ann Otol Rhinol Laryngol 100:620–625

Cremers FP, Van De Pol DJ, Diergaarde PJ, Wieringa B, Nussbaum RL, Schwartz M, Ropers HH (1989) Physical fine mapping of the choroideremia locus using Xq21 deletions associated with complex syndromes. Genomics 4:41–46

Dumas G, Charachon R, Vasdev A, Mouret P, Richard J (1991) Malformations du labyrinthe osseux et surdités. Ann Otolaryngol Chir Cervicofac 108:1–12

Fraser GR (1965) Sex-linked recessive congenital deafness and the excess of males in profound childhood deafness. Ann Hum Genet 29:171–196

Huber I, Bitner-Glindzicz M, de Kok YJM, van der Maarel SM, Ishikawa-Brush Y, Monaco AP, Robinson D, et al (1994) X-linked mixed deafness (DFN3): cloning and characterization of the critical region allows the identification of novel microdeletions. Hum Mol Genet 3:1151–1154

Jardin C, Vignaud J (1988) Malformations de l'oreille: Bilan radiologique. Encyclopedie Med-Chir 20047-A:30–39

Johnsen T, Videbaek H, Olesen KP (1989) CT-scanning of the cochlea in Pendred's syndrome. Clin Otolaryngol 14:389–393

Koningsmark BW, Gorlin RJ (1976) Genetic and metabolic deafness. WB Saunders, Philadelphia

Lacombe H, Moatti L, Cotin G, Garabedian N, Gelin Y (1989) The dilated vestibular aqueduct syndrome. Ann Otol Rhinol Laryngol 106:152–157

Lathrop GM, Lalouel JM, Julier C, Ott J (1985) Multilocus linkage analysis in humans: detection of linkage and estimation of recombination. Am J Hum Genet 37:482–498

Levenson MJ, Parisier SC, Jacobs M, Edelstein DR (1989) The large vestibular aqueduct syndrome in children: a review of 12 cases and the description of a new clinical entity. Arch Otolaryngol Head Neck Surg 115:54–58

Mandel JL, Monaco AP, Nelson D, Schlessinger D, Willard HF (1992) Report of the committee on the genetic constitution of the X chromosome. Cytogent Cell Genet 1:588–640

Mondini C (1791) Anatomica surdi nato sectio. Bononiensi: scientorum et artium instituto atque academia commentarii In: Schukuecht H. Pathology of the ear, 2d ed. Lea & Febiger, Philadelphia, pp 21–28, 419–431

Nance WE, Setleff R, McLeod A, Sweeney A, Cooper C, McConnel F (1971) X-linked mixed deafness with congenital fixation of the stapedial footplate and perilymphatic gusher. Birth Defects 7:64–69

Nussbaum RL, Lesko JG, Lewis RA, Ledbetter SA, Ledbetter DA (1987) Isolation of anonymous DNA sequences from within a sub-microscopic X chromosomal deletion in a patient with choroideremia, deafness and mental retardation. Proc Natl Acad Sci USA 84:6521–6525

Oberle I, Camerino G, Kloepfer C, Moisan JP, Grzeschik KH, Hellkuhl B, Hors-Cayla MC, et al (1986) Characterization of a set of X-linked sequences and of a panel of somatic cell hybrids useful for the regional mapping of the human X chromosome. Hum Genet 72:43–49

Okuno H, Sando I (1988) Anomaly of the round window: a histopathological study using a graphic reconstruction method. Auris Nasus Larynx 15:147–154

Ostri B, Johnsen T, Bergman I (1991) Temporal bone findings in

a family with branchio-oto-renal syndrome (BOR). Clin Otolaryngol 16:163–167

Phelps PD (1992) The basal turn of the cochlea. Br J Radiol 65: 370–374

Phelps PD, Reardon W, Pembrey M, Bellman S, Luxom L (1991) X-linked deafness, stapes gushers and a distinctive defect of the inner ear. Neuroradiology 33:326–330

Reardon W, Middleton-Price HR, Malcom S, Phelps P, Bellman S, Luxon L, Martin JA, et al (1992) Clinical and genetic heterogeneity in X-linked deafness. Br J Audiol 26:109–114

Reardon W, Middleton-Price HR, Sandkuijl L, Phelps PD, Bellman S, Luxon L, Pembrey ME (1991) A multipedigree linkage study of X-linked deafness: linkage to Xq13-q21 and evidence for genetic heterogeneity. Genomics 11:885–894

Rosenberg T, Niebuhr E, Yang HM, Parvey A, Schwartz M (1987) Choroideremia, congenital deafness and mental retardation in a family with an X-chromosomal deletion. Ophthalmic Paediatr Genet 8:139–143

Wallis C, Ballo R, Wallis G, Beighton P, Goldblatt J (1988) X-linked deafness with stapes fixation in a Mauritian kindred: linkage to Xq probe pDP34. Genomics 3:299–301

Weber JL, Kwitek AE, May PE, Polumeropoulos MH, Ledbetter SA (1990) Dinucleotide repeat polymorphism at the DXS453, DXS454 and DXS458 loci. Nucleic Acids Res 18:4037

Wells S, Mould S, Robins D, Robinson D, Jacobs P (1991) Molecular and cytogenetic analysis of a familial microdeletion of Xq. J Med Genet 28:163–166

West PD, Gholkar A, Ramsden RT (1989) Wildervanck's syndrome—unilateral Mondini dysplasia identified by computed tomography. J Laryngol Otol 103:408–411

Wilson JT, Leivy SW, Sofferman RA, Wald SL (1990–1991) Mondini dysplasia: spontaneous cerebrospinal fluid otorrhea: new perspectives in management. Pediatr Neurosurg 16:260–264

Zachmann M, Fuchs E, Prader A (1992) Progressive high frequency hearing loss: an additional feature in the syndrome of congenital adrenal hypoplasia and gonadotrophin deficiency. Eur J Pediatr 151:167–169