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Short Report

Chromosome imbalances in syndromic hearing loss

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The cause of hearing impairment has not been elucidated in a large proportion of patients. We screened by 1-Mb array-based comparative genomic hybridization (aCGH) 29 individuals with syndromic hearing impairment whose clinical features were not typical of known disorders. Rare chromosomal copy number changes were detected in eight patients, four *de novo* imbalances and four inherited from a normal parent. The *de novo* alterations define candidate chromosome segments likely to harbor dosage-sensitive genes related to hearing impairment, namely 1q23.3–q25.2, 2q22q23, 6p25.3 and 11q13.2–q13.4. The rare imbalances also present in normal parents might be casually associated with hearing impairment, but its role as a predisposition gene remains a possibility. Our results show that syndromic deafness is frequently associated with chromosome microimbalances (14–27%), and the use of aCGH for defining disease etiology is recommended.

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Profound or severe pre-lingual hearing loss affects about 0.1% of the population, 30% of which is acquired, the remainder being either hereditary (60%) or idiopathic (10%). In the last decade, the identification of many genes associated with hereditary deafness has greatly contributed to the understanding of basic hearing mechanisms (review in Ref. (1)).

Array-based comparative genomic hybridization (aCGH) has proved useful in determining the etiology of idiopathic mental retardation, in which 13–17% of the patients carry *de novo* microdeletions or duplications (2, 3). Characterization of some of these imbalances has led to the identification of novel genes involved in malformation syndromes (4).

We investigated DNA segment copy number changes (CNCs) in individuals with idiopathic syndromic hearing loss, aiming to identify dosage-sensitive genes or chromosome regions involved in their phenotypes. In addition, we evaluated the impact of array-CGH on the diagnosis and genetic counseling of these patients and their families.

Patients and methods

Patients

Patients were referred to the hearing impairment laboratory of the Genetic Counseling Service, Institute of Bioscience, University of São Paulo, by three clinical centers from the State of São Paulo, Brazil, namely: (a) Clinical Genetics Unit, Instituto da Criança, Hospital das Clínicas, University of São Paulo – Sao Paulo; (b) Division of Education and Rehabilitation of Communication Disorders (DERDIC) of the Catholic University of São Paulo (PUC – São Paulo); (c) Clinical Genetics Unit, Hospital de Reabilitação de Anomalias Craniofaciais, University of São Paulo, Bauru, Brazil.

The 29 patients included in this study were selected for presenting other clinical signs and/or mental retardation, in addition to hearing loss. The children's histories, according to parental or guardian reports, failed to reveal episodes of infections that could explain the etiology of hearing disabilities in these patients, although detailed medical records were not available in every case. Clinical genetic evaluations could not determine the causes of the abnormal phenotypes or classify those individuals with unknown syndromes. Only patients with normal G-banded karyotypes and who were negative for the following frequent hearing impairment mutations were included: 35delG and 167delT (*GJB2* gene), del(*GJB6*-D13S1830), del(*GJB6*-D13S1854) (*GJB6* gene) and the mitochondrial mutation A1555G (*MTRNR1* gene).

To evaluate the hearing abilities of the patients, the exams described below were used in most cases; however, because patients were referred from different centers, and the protocols are not well established in public health services in Brazil, not every exam was performed in each case. These included tympanometry and acoustic reflex thresholds, tonal and vocal audiometry with conditioning methods according to the patient's age; transiently evoked oto-acoustic emissions (OEA) and their distortion product. Pure tone audiometry was carried out to test for air (250–8000 Hz) and bone conduction (250–4000 Hz). Audiological evaluation by auditory brain stem responses (ABR) was also performed.

The study was approved by the Ethics Committee of the Institute of Bioscience, University of São Paulo, and informed consent was obtained from all patients and/or their legal guardians.

Methods

Screening of frequent deafness-related mutations

Genomic DNA was extracted from peripheral blood samples by standard procedures. The c.35delG mutation was investigated by polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) as described in Ref. (5). The c.167delT mutation was investigated by PCR-RFLP, with the restriction enzyme *PstI*. The del(*GJB6*-D13S1830) and the del(*GJB6*-D13S1854) mutations in the *GJB6* gene were tested by amplifying the breakpoint-containing fragments as described in Ref. (6). The A1555G mutation in the *MTRNR1* gene was screened according to the protocol described in Ref. (7).

Cytogenetic analysis

Short-term cultures of peripheral blood lymphocytes were performed according to standard procedures. The chromosomes were analyzed after GTG-banding.

Array-CGH

Patients presenting an apparently normal karyotype were investigated by 1-Mb bacterial artificial chromosome (BAC) arrays as previously described (8). Information regarding the array clone set is available at the Wellcome Trust Sanger Institute mapping database site (Ensembl genome browser: http://www.ensembl.org/). Some of the rearrangements detected by the 1-Mb array were mapped

at higher resolution using one of the following: (i) 105K (Syndrome Plus from Oxford Gene Technology) or 44K (Agilent Technologies) oligonucleotide microarrays, according to the manufacturer's protocols; (ii) multiplex ligation-dependent probe amplification (MLPA) using customized kits to investigate specific regions, namely 15q15.3 (9) and 6p25.3p25.2.

Fluorescent in situ hybridization analysis

All array-CGH imbalances were verified by fluorescent *in situ* hybridization (FISH), performed according to the standard protocols (10, 11) and using the same BAC probes that showed altered ratios on the array. FISH was also used to investigate whether the imbalances were inherited.

Results

The hearing impairment was classified according to the criteria presented by Finsterer and Fellinger (12). One patient presented with conductive and another mixed hearing loss, in both cases caused by ear malformations. The remaining 27 patients presented with neurosensorial hearing loss. Table 1 describes the hearing impairment and summarizes the additional clinical findings of the patients with genomic imbalances. Besides the hearing impairment, almost all patients (seven out of eight) presented with mental retardation and or developmental delay. Clinical features seen in more than one patient included short stature, epicanthic folds, high palate, cardiac defects, broad thumbs, brachydactyly and clinodactyly. These clinical features are quite common among syndromic individuals carrying chromosomal aberrations, and do not define a more specific phenotype related to hearing impairment.

In the 29 cases screened with aCGH, we detected rare CNCs in eight of them, four being *de novo* (Patients 1, 2, 3, and 4) and four inherited from a normal parent (Patients 5, 6, 7, and 8). In addition to the 1-Mb aCGH performed for all patients followed by FISH analysis in positive cases, oligoarrays were performed for Patients 3 and 7, and MLPA for Patients 3 and 8, to map further their detected rearrangements. Table 2

Table 1. Clinical findings of the patients with genomic imbalances

Patient	Age	Gender	Hearing loss[a]	Clinical findings	Rearrangement
1	8y5m	M	SN, BL, PF	Short stature, optic nerve atrophy, horseshoe kidneys, cryptorchidism, inguinal hernia, brachydactyly, broad thumbs	del(1)(q23.3q25.2)
2	11y9m	M	SN, BL, PF	Mental retardation, short stature, heterochromia iridis, epicanthic folds, broad nose, low-set ears with abnormal lobules, palm hyperkeratosis	dup(2)(q22.2q23.3)
3	6y5m	F	SN, BL, PF	Craniosynostosis, prominent frontal, dental malocclusion, congenital cardiac defect[b] (VSD, ASD, PDA), brachydactyly, clinodactyly (5th fingers), broad thumbs	dup(6)(p25.2p25.3)
4	2y5m	F	SN, BL, MS	Developmental delay, congenital cardiac defect (PDA), small and sparse lower teeth	del(11)(q13.2q13.4)
5	12y6m	M	SN, BL, MD	Mental retardation, short stature, microcephaly, high nasal bridge, epicanthic folds, high and narrow palate, ears with large lobules, discret *pectus excavatum*, clinodactyly (5th fingers), *pes cavus*	dup(2)(q12.3q12.3)
6	2y5m	M	SN, BL, SV(L), MD(R)	Developmental delay, synophrys, slight brachycephaly, persistent volar pads, clinodactyly (5th fingers)	del(4)(q23q24)
7	5y3m	M	SN, BL, MD(L), SV(D)	Developmental delay, hypertelorism, prominent ears, *pectus excavatum*, shawl scrotum, postaxial polydactyly (5th toe) at left , brachydactyly	del(7)(q31.1q31.1)
8	4y7m	M	SN, BL, PF(L), MD(R)	Developmental delay, high and narrow palate, downslanting palpebral fissures, dysplastic ears, joint hypermobility, syndactyly (fingers 3/4).	del(15)(q15.3q15.3)

[a]Hearing loss: SN = sensorineural; BL = bilateral; PF = profound; SV = severe; MD = moderate; MS = moderately severe; L = left; R = right.

[b]Congenital cardiac defects: VSD = ventricular septal defect; ASD = atrial septal defect; PDA = patent ductus arteriosus.

Table 2. Description of the genomic imbalances detected in eight patients with syndromic hearing loss. Genomic positions are given according to Human Genome Building NCBI36.1, HG18

Patient	DECIPHER ID	Rearrangement	Genomic position (Mb)[a]		Minimum Size (Mb)	Inheritance
			Proximal breakpoint	Distal breakpoint		
1	USP00002396	del(1)(q23.3q25.2)	160.19 . . . **161.21**	**175.27** . . . 175.56	14.06	*de novo*
2	USP00248386	dup(2)(q22.2q23.3)	143.67 . . . **144.59**	**150.78** . . . 150.86	6.19	*de novo*
3	USP00001448	dup(6)(p25.2p25.3)	2.98 . . . **2.86**	**1.26** . . . 1.32	1.60	*de novo*
4	USP00002389	del(11)(q13.2q13.4)	67.55 . . . **68.07**	**70.31** . . . 70.60	2.24	*de novo*
5	USP00002394	dup(2)(q12.3q12.3)	107.03 . . . **108.13**	**108.34** . . . 108.50	0.21	Maternal
6	USP00002392	del(4)(q23q24)	101.15 . . . **101.51**	**101.96** . . . 103.22	0.46	Paternal
7	USP00002391	del(7)(q31.1q31.1)	109.93 . . . **110.06**	**110.31** . . . 110.39	0.25	Maternal
8	USP00002390	del(15)(q15.3q15.3)	41.41 . . . **41.68**	**41.85** . . . 42.76	0.17	Maternal

First and last clones with abnormal $\log_2$ ratios of the regions with copy number alterations are given.
[a]Genomic positions of the minimum (bold) and maximum (non-bold) size of the rearrangement are given.

summarizes the detected chromosome rearrangements and their genomic locations, according to the NCBI 36.3 assembly of the Human Genome. The 1-Mb clones which showed abnormal log ratio intensities are listed under the Cytoview window, 1 Mb set, on the Ensembl database site (Ensembl genome browser: http://www.ensembl.org/). The deletion on Patient 7 was refined to ~250 kb using a 44K oligoarray, and was shown to comprise just exons 4 and 5 of the *IMMP2L* gene. Oligoarray data for Patient 3 (Fig. 1) allowed mapping the deletion to a <1.8 Mb segment, and the MLPA test showed that the probe (chromosome 6:1258826 bp) located within the *FOXQ1* single exon was not duplicated, defining the location of the telomeric end of the duplication. In Patient 8, three MLPA probes for the *STRC* gene (chromosome 15: 41682988, 41684880 and 41694012 bp) showed that the heterozygous deletion detected by aCGH encompassed the active copy of this gene, rather than its pseudogene. Figure 1 shows an example of a chromosome imbalance detected by BAC aCGH, and its more detailed mapping by oligoarray. Information on all chromosomally imbalanced patients was deposited in the DECIPHER database (Database of Chromosomal Imbalances and Phenotype in Humans using Ensembl Resources; *http://www.sanger.ac.uk/PostGenomics/decipher*), and their DECIPHER number is given in Table 2.

Discussion

We investigated 29 patients with idiopathic syndromic deafness by 1-Mb aCGH; in eight of them (27%), rare chromosome imbalances varying in size between 250 kb and 15 Mb were detected. FISH investigation on metaphases from the parents showed that the rearrangements were *de novo* in four patients (Patients 1–4), pointing to chromosome segments likely to harbor dosage-sensitive genes related to hearing abilities. The deletion in *Patient 1* at 1q23.3q25.2 encompassed ~100 known genes, making it impossible to determine which genes contributed to the phenotype. However, the segment includes the *DFNA7* locus, known to be involved in dominantly inherited, sensorineural non-syndromic hearing impairment (13), which could explain the hearing loss *per se*. *Patient 2* had a duplication stretching between 2q22.2 and 2q23.3. A single duplication overlapping this segment has been reported previously (14), but with no association with hearing impairment at 3 years of age. Although the combination of deafness, mental retardation and heterochromia of irides observed in the patient is suggestive of Waardenburg syndrome (WS), *PAX3*, one of the genes that causes WS, maps 70 Mb away from the duplication and is extremely unlikely to be involved in the phenotype. At least eight microdeletions within or overlapping this segment have been reported (15) associated with phenotypes much more severe than in our patient; phenotypes associated with deletions are frequently more severe than with duplications. It is noteworthy that deafness was not a feature associated with these particular deletions. *Patient 3* carried a <1.8 Mb duplication at 6p25.3p25.2 and presented with profound sensorial deafness and heart defects, which are common features of the 6p25 microdeletion syndrome (16). The genotype–phenotype correlation in patients with these 6p distal deletions indicates the presence of a gene involved in hearing abilities at 6p25 (17, 18). Duplications of this region have also been reported, mainly in association with ocular developmental anomalies and glaucoma (19); however, hearing impairment has not been noticed, except in a patient with a *de novo* partial tetrasomy of 6p25 (20). To investigate if the rearrangement could cause deafness in Patient 3 by

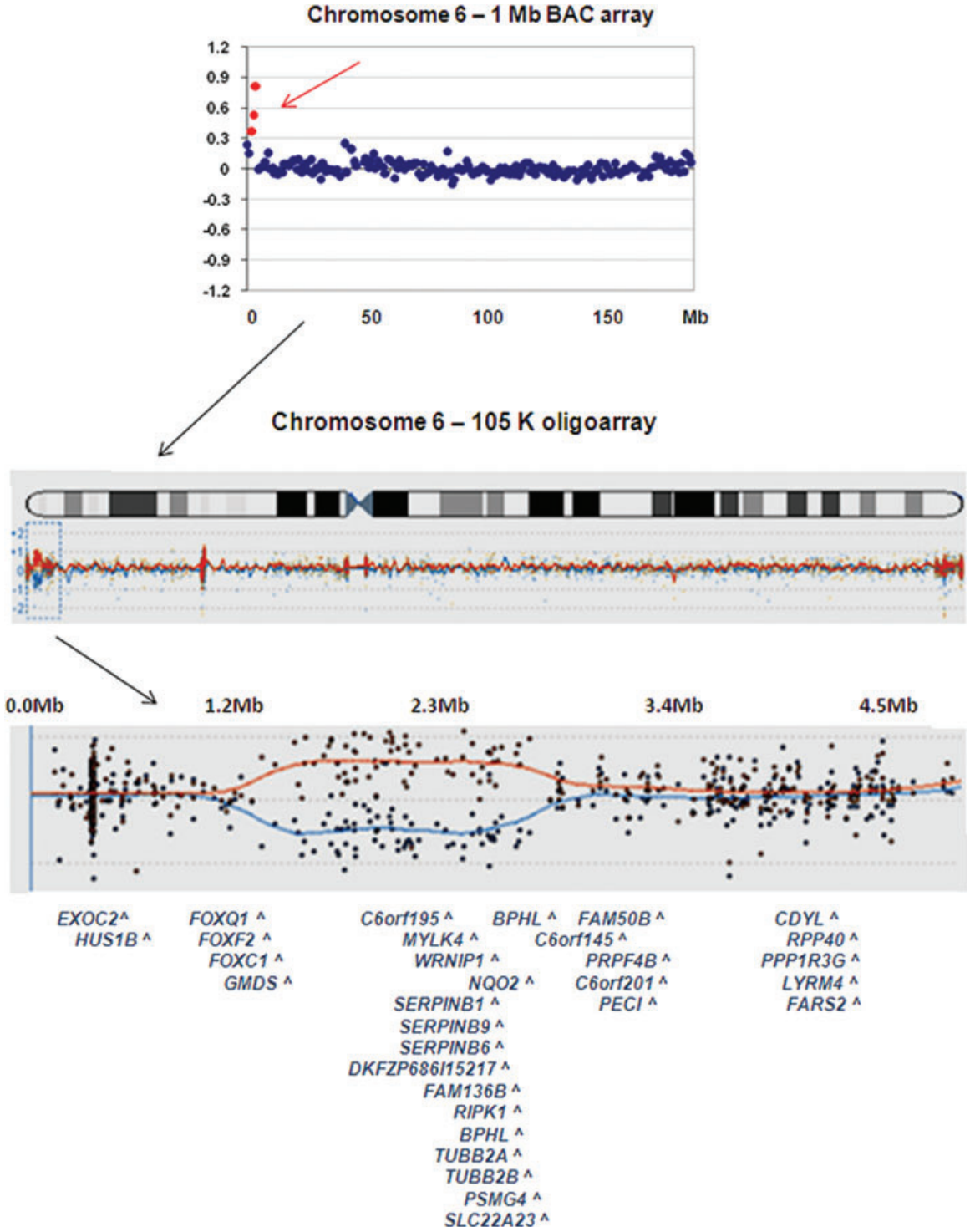

Fig. 1. 6p25.2–p25.3 duplication detected on Patient 3. Array-based comparative genomic hybridization profile of chromosome 6 shows a duplication (arrow and red dots) detected by an 1-Mb array, and underneath further mapping by 105K oligoarrays. The duplicated segment on the oligoarray profile is shown as a bubble due to the superimposition of the graphic displays resulting from dye swap hybridizations. The genes which map to this genomic segment are also depicted.

disrupting or down-regulating a gene on 6p25.3, we further mapped the breakpoint regions using a high-resolution oligoarray and MLPA. The mapping data in Fig. 1 shows that the distal breakpoint maps in the region between *FOXF2/FOXC1* genes (duplicated) and the proximal segment of *FOXQ1* gene (not duplicated). Because the MLPA probe covers only a part of the single exon of *FOXQ1*,

rearrangement in the remaining portion cannot be excluded. Furthermore, while the *FOXQ1* gene appears not to be duplicated, regulatory elements for the gene have been predicted at genomic position *chromosome 6:1.33 Mb, that is, within the duplicated segment (www.sisred.org/human9/). Alternatively, alteration of *FOXF2* and/or *FOXQ1* expression by the proximity to the breakpoint remains a possibility. *Patient 4* has a deletion at 11q13 and many genes are located in the deleted segment. Importantly, haploinsufficiency of *FGF3* causes the autosomal dominant oto-dental syndrome, which includes sensorineural hearing loss (21). Homozygous mutations in the *FGF3* gene were recently shown to cause autosomal recessive congenital sensorineural deafness, microtia and microdontia (22, 23). Interestingly, although our patient did not present the severe features of the oto-dental syndrome, she did exhibit small and sparse inferior teeth.

Four of our patients (Patients 5–8) inherited a chromosome imbalance from a normal parent. It is possible that some or all of these chromosome rearrangements are causally involved in the phenotype of these patients through mechanisms other than a dominant and fully penetrant mode of inheritance, as showed for Peters-Plus (MIM 261540) (24) and TAR syndromes (25). *Patient 5* had a $\leq$1.5 Mb duplication on 2q12.3, and another patient with profound deafness and a larger duplication fully encompassing that in our patient is documented in the DECIPHER database (Patient LEI00248451), suggesting the presence of a predisposing gene in the overlapping region. *Patient 6* had a deletion at 4q24 and no gene involved in hearing loss has been mapped to this segment. *Patient 7* carried a maternally inherited deletion which was mapped using an oligoarray to a 25–46 kb deletion comprising exons 4 and 5 of the *IMMP2L* gene (inner mitochondrial membrane peptidase 2-like). Mutations of this gene are known to affect mitochondrial function in mice (26). *Patient 8* had a heterozygous deletion in chromosome region 15q15. Although deletion of this segment was described as a normal variant in the Database of Genomic Variants (DGV), it results in loss of the *STRC* gene, known to cause deafness either through homozygous point mutations (27) or deletions (9). The presence of point mutations in the *STRC* gene in the non-deleted allele of Patient 8 is under investigation.

The genetics of deafness is highly heterogeneous and each of the available screening tests detects a small number of alterations. Failure to identify a plausible cause of hearing deficiency greatly impairs genetic counseling in many families. Importantly, our results show that aCGH can help elucidate the cause of hearing impairment in a significant number of patients, and is currently one of the most efficient tools in defining the etiology of idiopathic syndromic deafness. Our results suggest that aCGH should be incorporated as a routine diagnostic tool in syndromic hearing loss.

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Electronic Databases

DGV: Database of Genomic Variants (*http://projects.tcag.ca/variation/*)

DECIPHER database: Database of Chromosomal
Imbalances and Phenotype in Humans using Ensembl Resources (*http://www.sanger.ac.uk/PostGenomics/decipher*).

Ensembl genome browser (*http://www.ensembl.org/*)

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