Clinical Auditory Phenotypes Associated with GATA3 Gene Mutations in Familial Hypoparathyroidism-deafness-renal Dysplasia Syndrome

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Abstract

Background: Hypoparathyroidism-deafness-renal dysplasia (HDR) syndrome is an autosomal dominant disorder primarily caused by haploinsufficiency of GATA binding protein 3 (GATA3) gene mutations, and hearing loss is the most frequent phenotypic feature. This study aimed at identifying the causative gene mutation for a three-generation Chinese family with HDR syndrome and analyzing auditory phenotypes in all familial HDR syndrome cases.

Methods: Three affected family members underwent otologic examinations, biochemistry tests, and other clinical evaluations. Targeted genes capture combining next-generation sequencing was performed within the family. Sanger sequencing was used to confirm the causative mutation. The auditory phenotypes of all reported familial HDR syndrome cases analyzed were provided.

Results: In Chinese family 7121, a heterozygous nonsense mutation c.826C>T (p.R276*) was identified in GATA3. All the three affected members suffered from sensorineural deafness and hypocalcemia; however, renal dysplasia only appeared in the youngest patient. Furthermore, an overview of thirty HDR syndrome families with corresponding GATA3 mutations revealed that hearing impairment occurred earlier in the younger generation in at least nine familial cases (30%) and two thirds of them were found to carry premature stop mutations.

Conclusions: This study highlights the phenotypic heterogeneity of HDR and points to a possible genetic anticipation in patients with HDR, which needs to be further investigated.

Key words: GATA binding protein 3; Genetic Anticipation; Hypoparathyroidism-deafness-renal Dysplasia Syndrome

INTRODUCTION

Hypoparathyroidism-deafness-renal dysplasia (HDR) syndrome (MIM 146255), also known as Barakat syndrome,[1] is a rare autosomal dominant disorder named from a triad of hypoparathyroidism, sensorineural deafness, and renal dysplasia.[2] The individuals affected by HDR syndrome have various heterogeneous clinical characteristics. Sensorineural deafness could be the most common clinical feature, while hypoparathyroidism and renal dysplasia were described by various expressions[1-5] and even could be asymptomatic, making a timely diagnosis of HDR syndrome more important.
[A/T] GATA [A/G] consensus sequence, is the only reported gene responsible for this unusual developmental disease. Located on chromosome 10p15, GATA3 contains two N-terminal transactivating domains (TA1 and TA2) and two C-terminal zinc finger domains (ZnF1 and ZnF2), as shown in Figure 1. To date, more than fifty GATA3 mutations related with both sporadic and familial HDR syndrome have been reported, and GATA3 haploinsufficiency has been considered as the underlying mechanism.\(^6,7\) Compared with sporadic cases, familial cases provide us the opportunity to explore the inheritance pattern and to consider the possible genetic anticipation in patients with HDR.

In the present study, we identified a nonsense mutation in GATA3\(^6\) in a hearing impaired Chinese family with various clinical features of HDR syndrome by using targeted capture and next-generation sequencing (NGS). In addition, auditory phenotype in familial HDR syndrome associated with GATA3 mutation was analyzed by reviewing previous literatures.

**Methods**

**Patients**

A 7-year-old boy (proband) came from Chinese family 7121, a three-generation family with a segregating autosomal dominant hearing loss (HL) as shown in Figure 2, and four family members were recruited and gave written consent. This study was approved by the Ethics Committee of Chinese People’s Liberation Army General Hospital.

**Clinical evaluations for parathyroid glands, renal, and auditory phenotypes**

Their medical histories were collected by a questionnaire. Physical examination, otoscopy, immittance testing, pure tone audiometric examination, and speech audiometry were performed on the three affected members to evaluate the auditory conditions. The diagnosis of sensorineural hearing impairment was made according to the World Health Organization criteria available at http://www.who.int/. The degrees of HL were categorized as mild (26–40 dB HL), moderate (41–60 dB HL), severe (61–80 dB HL), and profound HL (>80 dB HL). A computed tomography (CT) scan for the temporal bone of both ears was also performed on the proband.

Peripheral blood and urine samples were collected to measure the parathyroidal and renal function. Biochemical laboratory tests included serum calcium, magnesium, phosphorus, and intact parathyroid hormone (iPTH) levels, plasma creatinine, and carbamide levels, whereas urinalysis, renal ultrasound, and nuclear examinations were applied to detect the renal anomalies.

**Targeted sequencing and variation analysis**

Genomic DNA was extracted from peripheral blood sample from the three affected members and one unaffected member. After the examination of DNA quality, Beijing Genomics Institute built the DNA libraries by following the Illumina’s protocol, and then 307 deafness-related genes [Supplementary Table 1] including exons, splicing sites, and their flanking introns were captured by using a custom probe and sequenced by Illumina HiSeq2000 (Illumina, San Diego, CA, USA), which had been previously described.\(^8\)

The paired-end reads generated by sequencing were aligned to NCBI37/hg19 assembly by the Burrows-Wheeler Alignment Tool (version 0.7.10, http://bio-bwa.sourceforge.net/), and variant calling was performed by Genome Analysis Toolkit (version 3.3-0, https://software.broadinstitute.org/gatk/index.php).

Variants with allele frequencies higher than 5% in the 1000 Genomes Project and the local database were excluded. Splicing site, frameshift, and nonsense variants would be taken into further consideration. Moreover, SIFT (http://sift.jcvi.org/) and PolyPhen2 (http://genetics.bwh.harvard.edu/pph2/) softwares were used to evaluate the pathogenic possibility of missense variants. Sanger sequencing was performed to establish the co-segregation of the candidate gene mutations with the phenotype in the family members. A three-dimensional structure of GATA3 was built by Swiss-model (http://swissmodel.expasy.org/workspace/) and then visualized by Swiss-PdbViewer (version 4.1, http://spdbv.vital-it.ch/).

![Figure 1: Structure map of GATA3 gene: GATA3 contains 6 exons and the arrow denotes the mutation identified in family 7121 located within exon4; GATA3: GATA binding protein 3. N: N-terminus; TA: Transactivating domains; ZnF: Zinc fingers domains; C: C-terminus.](image1)

![Figure 2: Pedigree of a family with hypoparathyroidism-deafness-renal syndrome. The arrow denotes proband.](image2)
**Analysis of familial cases and related mutations**

Literature review was performed by searching EMBASE and PUBMED databases. The genotypes and auditory phenotypes of these familial HDR syndrome cases were summarized. Then, a comprehensive inter- and intra-family comparison of clinical deafness characteristics was performed.

**RESULTS**

**Mutation detection and analysis**

All the three hearing-impaired family members were identified to carry out the same *GATA3* mutation. The heterozygous c.826C>T (NM_002051.2) is a nonsense mutation located within exon4 that resulted in a premature termination codon (R276*) predicted to lead to *GATA3* haploinsufficiency [Figures 1 and 2]. Co-segregation of this mutation with the disease was confirmed by using Sanger sequencing as shown in Figure 3. The normal member among the siblings did not have the mutation, while the other three affected members were carrying the same nonsense mutation. Moreover, the absence of this mutation in the 1000 Genomes Project and 1751 ethnicity-matched normal hearing individuals further supported the pathogenicity.

**Clinical description**

As shown in Table 1 and Figure 4, the three affected members in family 7121 had early-onset sensorineural deafness. The average hearing thresholds in the better ears of proband and his mother (II2) were 56 and 45 dB HL, respectively, belonging to moderate HL according to the grades of hearing impairment from the World Health Organization. However, grandmother of proband (I2) had profound hearing impairment with the average hearing threshold of 85 dB HL. The proband and his mother (II2) could communicate without any difficulty because their hearing disturbances were not severe. Temporal bone CT scans performed on the proband were normal.

The results of biochemistry tests are summarized in Table 1. Clinically, they all had no symptom for hypoparathyroidism, but the assessment showed hypocalcemia, lower iPTH level, and mild hyperphosphaturia. In contrast, the urinalysis of all the affected members revealed no abnormalities and indicated a normal renal function.

However, nephrosonography showed that the proband had left renal agenesis while the other two affected family members had normal bilateral kidneys without any detectable

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**Table 1: Genetic and clinical characteristics in family 7121**

| Member number | Gender | Age at diagnosis (years) | Genotype | Sensorineural deafness | Hypoparathyroidism | Renal hypoplasia |
|---------------|--------|-------------------------|----------|-----------------------|-------------------|-----------------|
| I-2           | Female | 52                      | Positive | 20 Profound           | 2.1               | Normal          |
| II-2          | Female | 31                      | Positive | 19 Moderate           | 1.92              | Normal          |
| III-1         | Male   | 7                       | Positive | 5 Moderate            | 1.69              | Left renal agenesis |
| II-1          | Male   | 33                      | Negative | Normal                | –                 | –               |
| Normal range  | –      | –                       | –        | –                     | –                 | 2.02–2.6        |

* Represents the stop of coding.

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**Figure 3:** Sanger sequencing results and the co-segregation of the mutation with the phenotype in the family members with hypoparathyroidism-deafness-renal syndrome. Red arrows denote *GATA3* mutation c.826C>T (p.R276*). *GATA3*: GATA binding protein 3.
Table 2: Review of genotype and auditory phenotypes in familial hypoparathyroidism-deafness-renal dysplasia syndrome

| Type                        | Exon | DNA          | Protein           | Relationship | Deafness | Diagnosis time (years or as denoted) | Reference |
|-----------------------------|------|--------------|-------------------|--------------|----------|--------------------------------------|-----------|
| Missense/nonsense           | 2    | c. 64C>T     | p.Gln22*          | Mother female | B        | Adult                               | [7]       |
|                             |      |              |                   | Son male     | B        | 2                                   |           |
|                             |      |              |                   | Daughter female | B     | 16                                  | [9]       |
|                             |      |              |                   | Father female | B      | 7                                   | [10]      |
|                             |      |              |                   | Son male     | B       | Birth                               |           |
|                             | 3    | c. 708delC   | p.Ser237Alafs*29  | Mother female | L > R    | 3                                   | [7]       |
|                             |      |              |                   | Daughter female | B      | 2.5                                 |           |
|                             |      |              |                   | Son male     | B       | Birth                               |           |
|                             |      |              |                   | Father male  | B       | 7                                   | [7]       |
|                             |      |              |                   | Daughter female | B    | 3                                   |           |
|                             |      |              |                   | Sister female| B       | 8                                   |           |
|                             |      |              |                   | Father male  | B       | Childhood                           | [11]      |
|                             |      |              |                   | Daughter female | B   | 3                                   |           |
|                             |      |              |                   | Son male     | B       | 4                                   |           |
|                             | c. 682G>T | p.Gln228* | Mother female | B       | <25                                 | [12]      |
|                             |      |              |                   | Daughter female | L    | NM                                  |           |
|                             |      |              |                   | Son male     | B       | NM                                  |           |
|                             | c. 736delGinsAT | p.G246Mfs57* | Mother female | NM     | NM                                  | [13]      |
|                             |      |              |                   | Daughter female | L  | NM                                  |           |
|                             | 4    | c. 823T>A    | p.W275R          | Mother female | NM      | Childhood                           | [14]      |
|                             |      |              |                   | Daughter female | NM  | Childhood                          |           |
|                             |      |              |                   | Mother female | NM      | Childhood                           | [15]      |
|                             |      |              |                   | Daughter female | NM  | Childhood                         |           |
|                             |      |              |                   | Daughter female | B   | Childhood                         |           |
|                             |      |              |                   | Mother and Son | B   | Unknown                            | [6]       |
|                             |      |              |                   | Grandmother female | B  | 20 (This study)                 |           |
|                             |      |              |                   | Mother female | B   | 19                                  |           |
|                             |      |              |                   | Son male     | B   | 5                                   |           |
|                             |      |              |                   | Father male  | B   | Infancy                            | [16]      |
|                             |      |              |                   | Daughter female | B  | Infancy                         |           |
|                             |      |              |                   | Daughter female | B  | Infancy                        |           |
|                             |      |              |                   | Mother female | B   | 38                                  | [7]       |
|                             |      |              |                   | Daughter female | B  | 7                                   |           |
|                             |      |              |                   | Son male     | B   | 5                                   |           |
|                             |      |              |                   | Father male  | B   | Infancy                            | [16]      |
|                             |      |              |                   | Daughter female | B  | Infancy                         |           |
|                             |      |              |                   | Daughter female | B  | Infancy                        |           |
|                             |      |              |                   | Mother female | B   | 41                                  | [17]      |
|                             |      |              |                   | Daughter female | B  | <27                                 |           |
|                             | 5    | c. 942T>A    | p.C318S          | Father male  | B   | NM                                  | [18]      |
|                             |      |              |                   | Son male     | B   | Elementary school                   |           |
|                             |      |              |                   | Daughter female | B  | NM                                  |           |
|                             |      |              |                   | Mother female | B   | 24                                  | [12]      |
|                             |      |              |                   | Daughter female | B  | 4                                   |           |
|                             |      |              |                   | Father male  | B   | Childhood                           | [19]      |
|                             |      |              |                   | Daughter female | B  | 5                                   |           |
|                             |      |              |                   | Son male     | B   | 4                                   |           |
|                             |      |              |                   | Mother female | B   | Possible childhood                  | [14]      |
|                             |      |              |                   | Daughter female | BM | Possible                          |           |

Overview of familial hypoparathyroidism-deafness-renal dysplasia syndrome

The reported familial cases of HDR syndrome were summarized in Table 2 by different mutations. A total of 30 families carrying various GATA3 abnormalities contained missense/nonsense mutations, small deletions and insertions (indels), splicing, and gross deletions. All the corresponding onset time and laterality of HL observed in the familial cases are shown in Table 2. Remarkably, nine parent-child pairs were proved to have hearing impairment earlier than a decade or more severe in the younger generation, which was observed in 30% of all familial cases. There was a significant difference in the types of the mutations in these...
Table 2: Contd...

| Type          | Exon | DNA                | Protein                  | Relationship | Deafness | Diagnosis time | Reference |
|---------------|------|--------------------|--------------------------|--------------|----------|----------------|-----------|
| Small indel   | 3    | c. 431delG         | p.Gly144Alafs*51         | Mother female | B        | 6              | [20]      |
|               |      |                    |                          | Daughter female |          | 2              |           |
|               | 3    | c. 478delG         | p.Asp160Thrfs*35         | Father male   | B        | Childhood      | [19]      |
|               |      |                    |                          | Son male      | B        | 10             |           |
|               |      |                    |                          | Son male      | B        | 17             |           |
|               | 3    | c. 604delC         | p.Arg202Valfs*4          | Mother female | B        | <30            | [12]      |
|               |      |                    |                          | Son male      | B        | 3              |           |
|               | 3    | c. 709insC         | p.Ser273Glnfs*67         | Mother female | B        | NM             | [21]      |
|               |      |                    |                          | Daughter female | L       | NM             |           |
|               | 4    | c. 901delCinsAACCCT| p.Leu301Asn*57          | Father male   | B        | Childhood      | [14]      |
|               |      |                    |                          | Daughter male | B        | 27             |           |
|               |      |                    |                          | Daughter male |          | ABRnormal 2months |           |
| Small insert  | 2    | c. 255_256insGTGC  | p.Arg86Valfs*219        | Father male   | NM       | NM             | [22]      |
|               |      |                    |                          | Son male      | B        | NM             |           |
|               | 3    | c. 523-528dup      | p.Gln178Profs*19        | 3 generations 5 people | B      | All childhood | [23]     |
| Splicing      | Intron4 | IVS4+2T>GCTTACTTCCC | Mother female           | B            | Children | [19]           |           |
|               | Intron4 | IVS4+4_19del       | Daughter female          | B            | 2        |                |           |
|               | Intron5 | IVS5+1G>C          | Mother female           | B            | Infancy  | [16]           |           |
|               |       |                    | Son male                | B            | Infancy  |                |           |
|               |       |                    | Son male<sup>1</sup>    | B            | 1        | [24]           |           |
|               |       |                    | Father male<sup>1</sup> | NO           | NO       |                | NO        |
|               |       |                    | Grandmother<sup>1</sup> | NO           | NO       |                | NO        |
| Gene deletions| –    | 250 kb deletion    | Deletion of one allele  | Uncle male<sup>1</sup> | B        | Adulthood      | [6]       |
|               |       |                    |                          | Brother male<sup>1</sup> | B        | 1              |           |
|               |       |                    |                          | Niece female<sup>1</sup> | B        | At birth       |           |
|               |       |                    |                          | Niece female<sup>1</sup> | B        | 5              |           |

*Represents the stop of coding, †Hearing impairment occurred earlier at least a decade or more severe in parent-child pairs. B: Bilateral; R: Right ear; L: Left ear; NM: Not mentioned; ABR: Auditory brainstem response; NO: No existence of deafness.

Figure 4: Pure-tone audiograms of the three affected family members with GATA3 mutation p.R276*: blue represents left ear, red represents right ear. HL: Hearing loss; GATA3: GATA binding protein.

nine familial cases, indicating a high proportion of premature stop mutations as much as 66.7%.

**Discussion**

In the present study, a heterozygous GATA3 nonsense mutation c.826C>T (p. R276*) was identified in a Chinese HDR family 7121 by applying a combination of the target deafness genes capture and NGS. Initially, all the affected members from three generations came to consult for their autosomal dominant hearing disturbances. Then, HDR syndrome was diagnosed precisely and effectively by using advanced genetic testing technology although there was no symptom of hypocalcemia and renal agenesis. The mutation c.826C>T (p.R276*) reported in the present study had been identified in a family 12/99 by Van Esch et al.<sup>6</sup> in the year 2000. The identification of R276* in the Chinese family 7121 further ensured its pathogenic possibility in HDR syndrome:

(1) sanger sequencing confirmed the co-segregation of this
GATA3 haplo-insufficiency causes human
functional characterization of GATA3 mutations causing the
domains. GATA3: GATA binding protein 3.

Clinical spectrum of HDR syndrome includes
hypoparathyroidism, sensorineural deafness, and renal
dysplasia. As previously reported, about 62.3% of
the patients had complete clinical triad in HDR syndrome.[27]
The patients carrying the same mutation p.R276* in another
European family displayed different clinical phenotypes.
Contrary to the Chinese family 7121, the two affected
members in 12/99 family did not have any renal anomaly.[16]
Moreover, clinical features of patients with HDR syndrome
were variable even in the same Chinese family 7121, which
was also observed in other cases.[18,19,27] In fact, due to
the high heterogeneous expression in individuals, it is not
easy for clinicians to make a distinction between human
nonsyndromic and syndromic hereditary HL such as HDR
disease. Therefore, NGS technology could be a powerful
tool in early diagnosis and appropriate management.

Genetic anticipation is a biological symptom in successive
generation, in which the pedigrees appear to have earlier
onset or more severity in the disease tendency. Considering
the existing ascertainment bias, we insist on the presence of
genetic anticipation that only a different decade is signifc ant
and reveal that at least 30% of familial cases (a total of 9
families) showed the possible genetic anticipation, which
might be one of the characteristics of familial HDR syndrome.
This information is especially important for assisting with
family planning in genetic consulting. To our knowledge,
a number of genetic diseases such as Charcot-Marie-Tooth
disease,[28] Lynch syndrome,[29] and familial essential tremor[30]
have been recognized with anticipation in the different mechanisms[22,23] including trinucleotide repeat expansion,
telomeric dysfunction as well as epigenetic factors. Regarding
the study, GATA3 mutation analysis in Table 2 reflected a
high proportion of premature stop mutations in familial
patients with the possible genetic anticipation, which might
be associated with the potential mechanism.

In conclusion, we have described a three-generation hearing
impaired family with GATA3 nonsense mutation p.R276*,
which was identified in Chinese population for the first time
by targeted genes capture and NGS technology. An overview
of familial cases revealed a decrease in the age at onset of
deafness or more severity between generations in 30% of
families, indicating the presence of possible anticipation.
Further studies are needed to elucidate the molecular
mechanisms of this phenomenon in HDR syndrome.

Supplementary information is linked to the online version of
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Conflicts of Interest
There are no conflicts of interest.

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| Targeted captured gene names |
|-----------------------------|
| ABR | CKB | ESR2 | HOXB1 | MYH1 | PDZD7 | SMS |
| ACAN | CLDN11 | ESR8B | HS6ST2 | MYH13 | PHEX | SNAI2 |
| ACTG1 | CLDN14 | EYA1 | IFT88 | MYH14 | PLDN | SOBP |
| AIFM1 | CLDN9 | EYA4 | IGFI | MYH2 | PMP22 | SOD1 |
| AKAP12 | CLIC5 | FABP4 | ILDR1 | MYH3 | PNOC | SORBS1 |
| ALDH1A2 | CLRN1 | FAS | ITGA8 | MYH4 | POU1F1 | SOX10 |
| ALSM1 | COCH | FBXO2 | JAG1 | MYH8 | POU3F4 | SOX2 |
| AP3D1 | COL11A | FGF20 | JAG2 | MYH9 | POU4F3 | SOX9 |
| APAF1 | COL11A2 | FGF3 | KCNE1 | MYO15A | PROP1 | SPRY2 |
| APOA1 | COL2A1 | FGFFR1 | KCNJ10 | MYO1A | PRPS1 | ST3GL5 |
| APOQ4 | COL4A3 | FGFRR2 | KCNMA1 | MYO3A | PRRX1 | STRC |
| ATRF2 | COL4A4 | FGRF3 | KCNQ1 | MYO6 | PRRX2 | TAF10 |
| ATOH1 | COL4A5 | FIGN | KCNQ4 | MYO7A | PTK7 | TBX1 |
| ATP2B2 | COL9A1 | FOXG1 | KIT | NAV2 | PTPRQ | TBX10 |
| ATP8B1 | COL9A2 | FOXJ1 | KITLG | NAV3 | RA4A | TCOF1 |
| AXIN1 | CPLX1 | FXN | LAMA2 | NDP | RARB | TECTA |
| BARHL1 | CRYM | FZD3 | LARGE | NDRG1 | RARG | TGF4 |
| BBS1 | DBH | FZD6 | LFNG | NEFL | RASA1 | TGFB2 |
| BBS4 | DDR1 | GAS7 | LHFPL5 | NEU1 | RDX | THRA |
| BCR | DFNA45 | GATA3 | LMO4 | NEURL | SIBP2 | THRB |
| BDNF | DFNB31 | GBA2 | LMX1A | NEUROD1 | SCARB2 | TMM8A |
| BMP4 | DFNB59 | GF1 | LOXHD1 | NEUROG1 | SO1 | TJP2 |
| BSN | DIALO | GPC3 | LRG3 | NF1 | SCRIB | TMC1 |
| BSND | DIAPH 1 | GJA1 | LRP2 | NOTCH1 | SEMA3E | TEMM20 |
| C17orf48 | DIAPH 3 | GJB1 | LRTOMT | NOX3 | SERAC1 | TMIE |
| Clorf125 | DIO2 | GJB2 | MAFB | NOXO1 | SERPINB6 | TMPRSS13 |
| CACNA1D | DIO3 | GJB3 | MAP1A | NRA43 | SFTPC | TMRPSS3 |
| CACNB2 | DLX2 | GJB6 | MARVELD2 | NTF3 | SIX1 | TNC |
| CACNG2 | DLX5 | GLI3 | MCOLN3 | NTN1 | SIX5 | TNFRSF11B |
| CASP3 | DMD | GOT1L1 | MGAT4B | NTRK2 | SLC12A2 | TMEM126A |
| CCDC50 | DNAH7 | GPR98 | MIR182 | NTRK3 | SLC12A6 | TRPN |
| CD36 | DNAH9 | GPSM2 | MIR183 | OC90 | SLC12A7 | TRIOBP |
| CDH23 | DPYS | GPX1 | MIR96 | OPA1 | SLC17A8 | TRPV4 |
| CDKN1B | DSPP | GRHL2 | MIF | OR2T4 | SLC19A2 | TSHR |
| CDKN2D | DYL1 | GRID1 | MKKS | OTOF | SLC1A3 | TUB |
| CEACAM16 | DYL2 | GRCR1 | MOG2 | OTOG | SLC26A4 | TTYP1 |
| CELSR1 | DYL3 | GUSB | MPV17 | OTP1 | SLC26A5 | UCN |
| CHD7 | EDN3 | HAL | MPZ | OTX1 | SLC30A4 | USH1C |
| EPHB1 | EDNRB | HES5 | MSRB3 | OTX2 | SLC4A11 | USH1G |
| HES1 | EGFLAM | HGF | MXS2 | PA2X | SLC4A7 | USH2A |
| MOS | EPFH2 | HMX2 | MTAP | PA3 | SLC9A1 | USP15 |
| OTOA | EPFH8 | HMX3 | MUC4 | PCDH15 | SLC2B1 | VANGL2 |
| chrM | ERBB4 | HOXA1 | MUC6 | PDE8B | SMAD4 | WFS1 |
| CHRNA9 | ESPN | HOXA2 | MUTED | PDSS1 | SMPX | YME1L1 |