Corrigendum to “Five Novel Mutations in LOXHD1 Gene Were Identified to Cause Autosomal Recessive Nonsyndromic Hearing Loss in Four Chinese Families”

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In the article titled “Five Novel Mutations in LOXHD1 Gene Were Identified to Cause Autosomal Recessive Nonsyndromic Hearing Loss in Four Chinese Families” [1], there were errors in Section 2.3, Section 3.2, footnote of Table 3, and Figure 4. These errors are shown below:

In Section 2.3, Mutation Confirmation by Sanger Sequencing, “LOXHD1 mRNA (RefSeq NM_144612.6)” should say “LOXHD1 mRNA (RefSeq NM_144612.6 and NM_001308013.1)”.

In Section 3.2, Novel Mutations in LOXHD1 Gene Were Demonstrated to Cause ARNSHL, “PLAT 4 domain” should say “the region between PLAT 11 and PLAT 12 domain”.

In the footnote of Table 3, “LOXHD1 sequence (RefSeq NM_144612.6)” should say “LOXHD1 sequence (RefSeq NM_144612.6 and NM_001308013.1)”.

In Figure 4, the location of mutation should be c.1255+3A>G.

The corrected Section 2.3, Section 3.2, footnote of Table 3, and Figure 4 are shown below. Figure 4 is listed as Figure 1 and Table 3 is listed as Table 1.

2.3. Mutation Confirmation by Sanger Sequencing

We performed Sanger sequencing to verify the mutations in subjects and 200 controls. PCR was employed to amplify the regions corresponding to these mutations (Table 3). LOXHD1 mRNAs (RefSeq NM_144612.6 and NM_001308013.1) were used as a reference to align the sequences with the Lasergene-SeqMan software.

3.2. Novel Mutations in LOXHD1 Gene Were Demonstrated to Cause ARNSHL

Five novel mutations (family F098*, F564*, SD1226*, and SD1391*) in LOXHD1 gene were identified pathogenic variants based on predictive analysis using PolyPhen2, SIFT, and Mutation Taster. Sanger sequencing was used in all the subjects to verify variants in LOXHD1. The c.2329C>T (p.Q777X) and c.5888delG (p.G1963Asfs*136) mutations were both found in family F098* and family F564*. The c.611-2A>T mutation was verified in family SD1226*, while c.277G>A (p.D93N) and c.1255+3A>G were verified in family SD1391*. Sequencing results are shown in Figures 2 and 3, and the schematic diagrams of protein structure are shown in Figure 4.

In general, according to ACMG guidelines [13], the mutations of c.611-2A>T, c.1255+3A>G, c.2329C>T (p.Q777*), and c.5888delG (p.G1963Asfs*136) were classified as pathogenic; in addition, the mutation of c.277G>A (p.D93N) was classified as likely pathogenic. Moreover, all the mutations were newly identified and never reported previously (Figure 4). Those mutations were absent in all of 200 control subjects with the method of Sanger sequencing.
| Mutations                  | Ethnicity          | Age of HL diagnosis | Severity of HL | Progression of HL | Reference |
|---------------------------|--------------------|---------------------|----------------|-------------------|-----------|
| c.71delT (p.L24Rfs74)     | Turkish            | Congenital or prelingual | Severe or profound | NA                | [16]      |
| c.246-1G>C                | Japanese           | Congenital          | Profound        | Progressive       | [17]      |
| c.277G>A (p.D93N)         | Chinese            | Congenital          | Severe-profound | Stable            | This study |
| c.442A>T (p.K148)         | NA                 | NA                  | NA              | NA                | [18]      |
| c.486 487delCTinsGG        | Saudi Arabian      | NA                  | NA              | NA                | [19]      |
| c.611-2A>T                | Chinese            | 3 years             | Severe-profound | Stable            | This study |
| c.894T>G (p.Y298)         | NA                 | Congenital          | Mild-moderate   | NA                | [20]      |
| c.1255+3A>G               | Chinese            | Congenital          | Severe-profound | Stable            | This study |
| c.1270+4A>C               | Japanese           | 36 years            | Mild            | Progressive       | [17]      |
| c.1588G>T (p.E530)        | Qatari             | Childhood           | Severe-profound | Progressive       | [19]      |
| c.1603G>T (p.R535)        | American           | Childhood           | Mild-moderate   | NA                | [21]      |
| c.1618dupA (p.T540Nfs24)  | Dutch              | Congenital—1 year   | Moderate        | Progressive       | [10]      |
| c.1730G>T (p.L577R)       | Dutch              | Congenital—1 year   | Moderate        | Stable-progressive| [10]      |
| c.1730G>T (p.L577R)       | NA                 | Congenital          | Severe-profound | NA                | [20]      |
| c.1751C>T (p.T584M)       | Chinese            | NA                  | NA              | NA                | [6]       |
| c.1828G>T (p.E610)        | Dutch              | 2–4 years           | Mild            | Stable            | [10]      |
| c.1843C>T (p.R615W)       | Chinese            | NA                  | NA              | NA                | [8]       |
| c.1904T>C (p.L635P)       | Dutch              | 2–3 years           | Mild            | Stable-progressive| [10]      |
| c.1938G>A (p.K646K)       | NA                 | Childhood           | Mild-moderate   | NA                | [20]      |
| c.1938G>A (p.K646K)       | American           | Childhood           | Mild-moderate   | NA                | [21]      |
| c.2008C>T (p.R670)        | Iranian            | 7–8 years           | Mild            | Progressive       | [20]      |
| c.2329C>T (p.Q777)        | Chinese            | Congenital          | Severe-profound | Stable            | This study |
| c.2641G>A (p.G881R)       | Dutch              | 2–4 years           | Mild            | Stable            | [10]      |
| c.2696G>C (p.R899P)       | Dutch              | 5 years             | Moderate        | Stable            | [10]      |
| c.2696G>C (p.R899P)       | Dutch              | Congenital          | Mild            | Too young to determine | [10]      |
| c.2726C>T (p.T909M)       | Japanese           | 30 years            | Profound        | Progressive       | [17]      |
| c.2825 2827delAGA (p.K942del) | NA                | Childhood           | Mild-moderate   | NA                | [20]      |
| c.2863G>T (p.E955)        | Turkish            | NA                  | NA              | NA                | [22]      |
| c.3061C>T (p.R1021)       | Indian             | Congenital          | Severe          | Stable            | [10]      |
| c.3061G>A                 | Dutch              | Congenital          | Moderate        | NA                | [10]      |
| c.3076G>T (p.V1026F)      | Japanese           | 3 years             | Profound        | Stable            | [23]      |
| c.3169C>T (p.R1057)       | Dutch              | Congenital          | Severe          | Stable            | [10]      |
| c.3281A>G (p.D1094G)      | Chinese            | NA                  | NA              | NA                | [8]       |
| c.3371G>A (p.R1124H)      | Cameroonian        | Prelingual          | Profound        | NA                | [20]      |
| c.3571A>G (p.T1191A)      | Spanish            | Congenital          | Severe-profound | NA                | [24]      |
| c.3578C>T (p.A1193V)      | Japanese           | Congenital          | Moderate        | NA                | [17]      |
| c.3596T>G (p.L1199P)      | NA                 | NA                  | NA              | NA                | [20]      |
| c.3748+1G>C               | Dutch              | Congenital          | Moderate        | Stable-progressive| [10]      |
| c.3834G>C (p.W1278C)      | Dutch              | 5 years             | Moderate        | Stable            | [10]      |
| c.3857G>T (p.G1286V)      | Japanese           | Congenital          | Mild            | Progressive       | [17]      |
| c.3979T>A (p.F1327I)      | Cameroonian        | Prelingual          | Profound        | NA                | [20]      |
| c.4099G>T (p.E1367)       | NA                 | Congenital          | Severe-profound | NA                | [20]      |
| c.4212A>G                  | Japanese           | Congenital          | Moderate        | Stable            | [25]      |
| c.4212G>A                 | Japanese           | Congenital—7 years  | Mild-profound   | Progressive       | [26]      |
| c.4213G>A                 | Japanese           | 5 years             | Mild            | NA                | [17]      |
| c.4217C>T (p.A1406V)      | NA                 | NA                  | NA              | NA                | [18]      |
| c.4217C>T (p.A1406V)      | NA                 | Childhood           | Mild-moderate   | NA                | [20]      |
| Mutations         | Ethnicity       | Age of HL diagnosis | Severity of HL | Progression of HL | Reference |
|-------------------|-----------------|---------------------|----------------|-------------------|-----------|
| c.4375+1G>T       | Japanese        | 3 years             | Profound       | Stable            | [23]      |
| c.4480C>T (p.R1494) | Turkish        | NA                  | NA             | NA                | [22]      |
| c.4480C>T (p.R1494) | NA             | Congenital          | Mild-moderate  | NA                | [20]      |
| c.4480C>T (p.R1494) | Caucasian      | 40 years            | Severe-profound| Progressive       | [27]      |
| c.4480C>T (p.R1494) | Japanese       | 1–6 years           | Moderate-severe| Stable            | [25]      |
| c.4480C>T (p.R1494) | NA             | Childhood           | Severe-profound| NA                | [20]      |
| c.4526G>A (p.G1509E) | Caucasian      | 40 years            | Severe-profound| Progressive       | [27]      |
| c.4623G>G (p.Y1541) | Czech          | Congenital          | Severe         | NA                | [26]      |
| c.4678T>C (p.C1560R) | Dutch         | 2-3 years           | Mild            | Stable-progressive| [10]      |
| c.4714C>T (p.R1572) | Ashkenazi Jewish| Congenital-prelingual| Severe-profound| NA                | [28]      |
| c.4734C>G (p.Y1578) | Japanese       | Congenital          | Profound       | Progressive       | [17]      |
| c.4936C>T (p.R1646) | NA             | Childhood           | Mild-moderate  | NA                | [20]      |
| c.5086-3C>A       | Japanese        | 30 years            | Severe         | Progressive       | [17]      |
| c.5545G>A (p.G1849R) | Czech          | Congenital          | Severe         | NA                | [26]      |
| c.5608C>T (p.R1870W) | Japanese      | 36 years            | Mild           | Progressive       | [17]      |
| c.5674G>T (p.V1892F) | Japanese      | Congenital—7 years  | Mild-profound  | Progressive       | [29]      |
| c.5734G>A (p.D1912N) | Japanese      | 30 years            | Severe         | Progressive       | [17]      |
| c.5815G>A (p.D1939N) | Chinese        | NA                  | NA             | NA                | [6]       |
| c.5869G>T (p.E1957) | Japanese       | 1–6 years           | Moderate-severe| Stable            | [25]      |
| c.5885C>T (p.T1962M) | Indian        | Congenital          | Severe         | Stable            | [10]      |
| c.5888delG (p.G1963Afs136) | Chinese      | Congenital          | Severe-profound| Stable            | This study|
| c.5984dupG (p.G1965fs) | Arab          | Prelingual          | Profound       | NA                | [30]      |
| c.5933G>A (p.G1978D) | Japanese      | 32 years            | Profound       | Progressive       | [17]      |
| c.5943C>T (p.G1978G) | Dutch         | Congenital          | Mild           | Too young to determine| [10]      |
| c.5944C>T (p.R1982) | NA             | Congenital          | Severe-profound| NA                | [20]      |
| c.5948C>T (p.S1983F) | Chinese        | Congenital          | Profound       | Stable            | [7]       |
| c.6037G>A (p.G2013R) | Japanese      | 5 years             | Profound       | Progressive       | [17]      |
| c.6162_6164delCCT (p.F2055del) | NA          | Congenital          | Severe-profound| NA                | [20]      |
| c.6168delC (p.C2057Vfs42) | Japanese    | 3 years             | Severe         | Progressive       | [17]      |
| c.6353G>A (p.G2118E) | NA             | Congenital          | Mild-moderate  | NA                | [20]      |
| c.6353G>A (p.G2118E) | Dutch         | Congenital          | Moderate       | NA                | [10]      |
| c.6353G>A (p.G2118E) | Dutch         | Congenital          | Severe         | Stable            | [10]      |
| c.6353G>A (p.G2118E) | Dutch         | Congenital          | Moderate-severe| Stable-progressive| [10]      |
| c.6598delG (p.D2200Mfs22) | NA           | Childhood           | Severe-profound| NA                | [20]      |

*LOXHD1 sequence (RefSeq NM_144612.6 and NM_001308013.1) was used as a reference.
The mutation of c.2329C>T (p.Q777X) is a nonsense mutation, which leads to a stop codon in PLAT 6 domain. The variant c.277G>A (p.D93N) is also a missense mutation found in PLAT 1 domain. But the mutation of c.5888delG (p.G1963Afs*136) is a frameshift mutation in PLAT 14 domain, resulting in a truncated protein of LOXHD1. In addition, the mutations of c.611-2A>T and c.1255+3A>G can cause defects in alternative gene splicing of PLAT 2 and the region between PLAT 11 and PLAT 12 domain, respectively. Figure 4 shows all the previously reported mutations in LOXHD1 that cause DFNB77 deafness, as well as novel mutations identified in this study. These results showed that LOXHD1 mutations are found throughout all PLAT domains.

References

[1] X. Bai, C. Zhang, F. Zhang et al., "Five novel mutations in LOXHD1 gene were identified to cause autosomal recessive nonsyndromic hearing loss in four Chinese families," BioMed Research International, vol. 2020, 9 pages, 2020.