Author Correction: Alterations of the CIB2 calcium- and integrin-binding protein cause Usher syndrome type 1J and nonsyndromic deafness DFNB48

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Saima Riazuddin, Inna A. Belyantseva, Arnaud P. J. Giese, Kwanghyuk Lee, Artur A. Indzhykulian, Sri Pratima Nandamuri, Rizwan Yousaf, Ghanshyam P. Sinha, Sue Lee, David Terrell, Rashmi S. Hegde, Rana A. Ali, Saima Anwar, Paula B. Andrade-Elizondo, Asli Sirmaci, Leslie V. Parise, Sulman Basit, Abdul Wali, Muhammad Ayub, Muhammad Ansar, Wasim Ahmad, Shaheen N. Khan, Javed Akram, Mustafa Tekin, Sheikh Riazuddin, Tiffany Cook, Elke K. Buschbeck, Gregory I. Frolenkov, Suzanne M. Leal, Thomas B. Friedman & Zubair M. Ahmed

Usher syndrome type I (USH1) is a genetically and clinically heterogeneous autosomal recessive disorder characterized by prelingual sensorineural hearing loss, progressive retinitis pigmentosa (RP) and vestibular areflexia[1,2]. As of October 2024, variants of six distinct genes have been reported for USH[1,3] and some variants of four of these genes are associated with nonsyndromic deafness[4]. In 2012, an USH1 phenotype, deafness and retinitis pigmentosa (RP) was reported by us to be segregating in Family PKDF117. The USH1 phenotype in Family PKDF117 was associated with a missense variant [p.(Glu64Asp)] of the *CIB2* gene at the *USH1J* locus[5]. Four additional families in this study were reported to be segregating nonsyndromic deafness DFNB48 and had different homozygous variants of *CIB2*[5].

Family PKDF117 was enrolled from a rural area of Southern Punjab. At the time of enrollment, ages of the four affected individuals in family PKDF117 ranged from 10 to 36 years, and all had bilateral, profound sensorineural hearing loss. According to family history, all four affected individuals had delayed onset of independent ambulation. Romberg and tandem gait testing further indicated vestibular areflexia in all four affected individuals. Funduscopic examination was said in a written report to reveal retinitis pigmentosa in three affected individuals. Based on these clinical reports, Usher syndrome (USH1J) was assigned to the phenotype segregating in family PKDF117[5].

In *Drosophila melanogaster*, knocking down the CIB-related gene, *CG9236*, which codes for a protein 71% similar and 59% identical to human CIB2, resulted in a significantly reduced photo response amplitude, and impaired responses to flicker stimuli at high frequencies[5]. The $cib2^{RNAi}$ flies also failed to sustain an adequate photo response during prolonged stimulation. These findings indicate that Drosophila *cib2* is necessary to achieve a strong, sustained photo response and to track fast light stimuli, further supporting the critical role of CIB2 for normal visual function[5].

Since our original report, several missense and truncating (presumably loss-of-function) variants in *CIB2* have been identified around the world[6–14]. All these other reported variants cause autosomal recessive nonsyndromic hearing loss (DFNB48) in the affected individuals who appear to have intact vision. Subsequently, we developed a *Cib2* knockout mouse and comprehensively analyzed its retinal structure and function. We reported that deficiency of CIB2 in the mouse retina resulted in age-related pathologies, including sub-retinal pigment epithelium (RPE) deposits, marked accumulation of drusen markers APOE, C3, Aβ, esterified cholesterol, and progressively impaired visual function. *Cib2* mutant mice exhibit reduced autophagic clearance, and increased mTORC1 signaling[15]. As these findings resembled those for dry age-related macular degeneration (OMIM #153800) in humans[16–19], we also studied expression of *CIB2*, autophagic and mTORC1 signaling markers in dry-AMD RPE/choroid post-mortem human tissues. We found concordant molecular deficits in dry-AMD RPE/choroid human samples[15]. Taken together our findings in *Drosophila* and mouse eyes were consistent with a function of CIB2 in vision. However, these results also highlight key phenotypic differences in the retinal phenotype in *Cib2* mutant mice, as compared to other USH1 mutant mice[4]. CIB2 function is

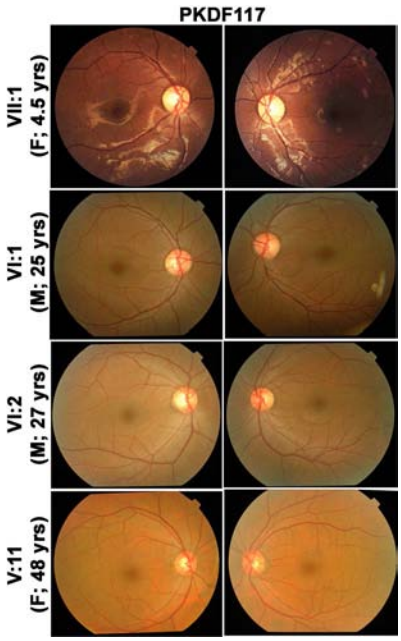

Fig. 1 | Fundus images of hearing-impaired individuals of family PKDF117. No apparent degeneration of the pigment epithelium, attenuation of retinal vasculature, macular atrophy or bony spicules, which are characteristic features of USH1-associated retinitis pigmentosa, were observed in the four affected individuals of family PKDF117, who range in age from 4.5 to 48 yrs. These fundus images are consistent with the normal ERG amplitudes, and intact retinal layers in OCT imaging, observed in all four affected individuals (Table 1).

required in the RPE rather than photoreceptors, the primary cell type implicated in the USH1 retinitis pigmentosa phenotype. However, *Cib2* mutant mice have progressive accumulation of lipids and proteins and degeneration of RPE in the retina.

The above phenotypic discrepancies prompted us to revisit family PKDF117 and re-evaluate their visual function. As family PKDF117 had relocated from their original hometown in Pakistan, it took us years to locate them. We provided transportation to Lahore, Pakistan for the available participants of family PKDF117, where they received a comprehensive eye examination, as limited facilities were available in their residing area. At the time of re-evaluation of retinal exam, the ages of the participating affected individuals ranged from 4.5 to 48 years (Table 1). Sanger sequencing again confirmed homozygosity for the p.Glu64Asp variant in *CIB2*, and pure-tone audiometry confirmed bilateral profound hearing loss in all affected PKDF117 individuals. To assess the visual function and retinal structure, we performed visual acuity, B-scan, optical coherence tomography, funduscopy, and electroretinography analyses. All the affected individuals, including the four that were examined at the time of the initial enrollment in January 2004 in their hometown, had normal visual function and no signs of retinal degeneration (Fig. 1, Table 1). These results clearly indicate that the initial funduscopic examination was not accurate and misreported retinitis pigmentosa. The fact that normal retinal re-examination and profound deafness were found in affected member of family PKDF117 who are homozygous for the p.Glu64Asp variant of *CIB2* indicates that the *USH1J* locus (OMIM #614869) must be castoff, and this locus on chromosome 15q25.1 is associated only with recessively inherited nonsyndromic deafness DFNB48 (OMIM #609439).

What lessons can one draw from this saga? We should have obtained funduscopic images instead of relying on written reports of RP regardless of the limited availability of clinical facilities in remote areas of Pakistan. Furthermore, the availability of retinal examination tests including photography, OCT and ERG has improved significantly globally over the past decade, and thus we were able to comprehensively evaluate the affected individuals of family PKDF117 (Table 1). Based on the updated clinical data available from our cohort as well as review of the literature, variants of *CIB2*, so far, are only associated with congenital profound, nonsyndromic hearing loss. However, all affected individuals inheriting biallelic variants of *CIB2* are young (<50 yrs old)[6–14], and thus we cannot rule out the possibility of developing age-related RPE pathologies, similar to *Cib2*^{ko} mice[15]. Considering the reported shared interactomes of CIB2 protein with canonical USH proteins such as MYO7A, Whirlin and ADGRV1, the dry-AMD-like phenotype of *Cib2* deficient mice, reduced expression of CIB2 in dry-AMD

Table 1 | Clinical assessment of visual function in the hearing-impaired individuals of PKDF117 family that are homozygous for p.Glu64Asp variant of *CIB2*

PKDF117	V:11		VI:1		VI:2		V:11	
Sex	Female		Male		Male		Female	
Age (yrs)	4.5		25		27		48	
Hearing loss	Yes		Yes		Yes		Yes	
Eye*	Right	Left	Right	Left	Right	Left	Right	Left
Visual acuity	6/12	6/12	6/6	6/6	6/6	6/6	6/6	6/6
Color vision	NA	NA	Normal	Normal	Normal	Normal	Normal	Normal
Lens	Clear	Clear	Clear	Clear	Clear	Clear	Clear	Clear
Fundus	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD
IOP (mmHg)	NA	NA	17	17	15	16	19	21
OCT Macula	NA	NA	Normal	Normal	Normal	Normal	Normal	Normal
ERG	NAD	NAD	NAD	NAD	NAD	NAD	NAD	NAD

*External exam and anterior segment were within normal limits for all these individuals. NAD: No abnormality detected; IOP: Intraocular pressure; OCT: Optical coherence tomography; ERG: Electroretinography; NA: No information available.

RPE/choroid human samples, late-onset (≥65 yrs) of dry-AMD phenotype in humans[5,15,20], warrant retinal investigations, especially in individuals older than 60 years who inherit biallelic *CIB2* variants. Prior studies have reported high incidence of hearing loss in subjects with dry-AMD[21–24], and genetic screening of these subjects for *CIB2* might provide new insights about the causal variants. Finally, animal models often unveil unrecognized phenotypes that should be considered in clinical evaluation of genetically diagnosed human subjects with variants of the orthologous gene. The p.Glu64Asp variant in *CIB2* we reported[5] does not cause USH1 and all the affected individuals of Family PKDF117 are now clinically re-classified as having nonsyndromic deafness DFNB48 and their vision, in the fullness of time, will be monitored.

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