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A novel mutation in ACTG1 can cause either isolated hearing loss or Baraitser-Winter syndrome

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Abstract

Baraitser-Winter Syndrome (cerebro-frontofacial syndrome, type 3) is a rare developmental disorder typified by hypertelorism, ptosis, high arched eyebrows, ocular coloboma and brain malformations including lissencephaly. Other common manifestations include hearing loss, short stature, seizures, intellectual impairment and abnormalities of the kidney and urinary system. This syndrome is caused by missense mutations in the genes *ACTB* or *ACTG1*, both of which encode for cytoplasmic actin proteins crucial for proper development of many organs in the human body. We have identified a three generation pedigree segregating a novel mutation in the *ACTG1* gene that leads to Baraitser-Winter Syndrome when fully expressed and isolated hearing loss when incompletely expressed.

Introduction

In 1988, Baraitser and Winter described a new syndrome in a brother and sister as well as an unrelated female patient, which included colobomas of the iris, ptosis, telecanthus, hypertelorism, mental handicap and short stature[1]. What is now referred to as Baraitser-Winter Syndrome was further elucidated by Ramer and colleagues who proposed that brain malformations also play a role in this complex syndrome[2]. Other features described include intellectual disability, hearing loss, seizures, and microcephaly[1,2,3,4,5,6]. The genetic etiology was reported by Riviére and colleagues who found that *de novo* missense mutations in the actin genes *ACTB* and *ACTG1* lead to Baraitser-Winter Syndrome[3]. Recurrent mutations in *ACTG1* have been reported to cause isolated autosomal dominant hearing loss[7]. These variants have also been suspected of causing developmental and neurologic phenotypes in addition to early-onset hearing loss[8]. Here, we report a 3-generation family in which three affected members carry a novel *ACTG1* mutation with variable phenotypes. Two of the affected individuals were diagnosed with isolated hearing loss, while the remaining affected individual is phenotypically characteristic of the full syndrome.

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Clinical Report

Patient 1

Patient 1 presented at age 7 years after failing a school audiogram. She was diagnosed with sensorineural hearing loss and fitted with bilateral hearing aids. Her audiogram was similar to that of her father (see figure 1), who also has sensorineural hearing loss since childhood. She had a history of congenital esotropia requiring bilateral medial rectus recessions followed by bilateral lateral rectus resections. She developed secondary exotropia with V pattern at distance. She has normal visual acuity of 20/20-1 right eye and 20/20-2 left eye. Her optic nerves have an anomalous appearance (see figure 2) with thin retinal nerve fiber layers (see figure 3). Molecular genetic testing was done using a custom targeted genomic enrichment (TGE) panel OtoSCOPE® (University of Iowa), which screens all genes known to cause non-syndromic hearing loss (NSHL), as well as genes causing syndromes which may present as isolated hearing loss.

SureSelect (Agilent Technologies, Santa Clara, CA) TGE, Illumina HiSeq 2000 (Illumina, Inc., San Diego, CA) massively parallel sequencing, custom instance Galaxy analysis, and confirmatory Sanger DNA sequencing methods have been previously described[9].

The analytical sensitivity is greater than 99% for regions sequenced with greater than 10X depth of coverage; 99.45% of the 350,160 targeted base pairs were covered at greater than 10X depth in Patient 1. The results demonstrated a novel variant (p.Ala58Val) in one allele of the *ACTG1* gene with a normal second allele. The proband's father and paternal grandmother both have childhood onset hearing loss and epilepsy, and in addition, her father reported significantly decreased vision from childhood. Both segregate the p.Ala58Val variant in *ACTG1.*

Patient 2

Patient 2 is the father of Patient 1. At 35-years-of-age he presented for ophthalmologic evaluation with a history of lifelong decreased best corrected vision, sensorineural hearing loss and recurrent ptosis and strabismus following surgery during childhood. He was the product of a 36–37 week pregnancy complicated by pre-eclampsia. Labor was induced and he was delivered vaginally without complication at 4 pounds 15 ½ ounces. The immediate neonatal period included physiologic jaundice, which required bilirubin lights. His developmental milestones were appropriate, however a learning disability was later documented. He was diagnosed with moderate high frequency bilateral hearing loss at age 4 years, and at age 6 years, he was diagnosed with a seizure disorder. His surgical history was remarkable for two inguinal herniorrhaphies, two right ptosis surgeries and strabismus surgery for congenital esotropia. He initially had a 35 prism diopter right esotropia; following extraocular muscle surgery he developed a small right exotropia. On examination, he was noted to have bilateral coloboma of the retina and iris (Figures 4 and 5). Visual acuity is 20/40-1 right eye and 20/25-2 left eye with large absolute scotomas corresponding to the chorioretinal colobomas. Upon molecular genetic testing, he was found to carry the p.Ala58Val variant in *ACTG1.*

Patient 3

This patient, the mother of Patient 2, was diagnosed with sensorineural hearing loss in early childhood. At the time this was attributed to chronic otitis media and serous otitis. She has worn bilateral hearing aids since childhood and has a speech deficit related to hearing loss. She has esotropia and a seizure disorder. She developed breast cancer at age 57. Upon molecular genetic testing, she was found to carry the p.Ala58Val variant in *ACTG1.*

Discussion

Following whole-exome sequencing of three proband-parent trios affected by Baraitser-Winter Syndrome, Riviére and colleagues identified *de novo* missense mutations in the *ACTB* and *ACTG1* genes in one and two probands, respectively. In subsequent sequencing of these two genes in 15 additional affected individuals, they found disease-causing mutations in all probands, including two recurrent mutations, one a p.Arg196His missense mutation in *ACTB* and the other, a p.Ser155Phe missense mutation in *ACTG1*[3]. These findings confirm the association of the Baraitser-Winter Syndrome phenotype with missense variants in *ACTB* and *ACTG1* and suggest that this phenotype represents the severe end of the *ACTB*/*ACTG1* mutation spectrum, which ranges from non-syndromic hearing loss to Baraitser-Winter Syndrome[3].

The patients we describe segregate a previously unreported variant in *ACTG1.* Variants were only considered if the Phred-like quality score was >50. This variant is conserved, as calculated by GERP and SiPhy and is predicted to be pathogenic by SIFT, Mutation Taster, Mutation Assessor, FATHMM, Radial SVM, and LR prediction tools. It is located within subdomain 2 within the actin protein and is in close proximity to previously reported pathogenic variants. This variant segregates with the hearing loss in this family, who exhibit hearing loss similar to previously observed DFNA20/26 NSHL[10]. The variant is associated with variable expressivity in the reported family. All three family members we examined had significant early-onset hearing loss, which improved with hearing aids, and esotropia, which was treated surgically in for patients 1 and 2. Two of the 3 affected family members have early-onset hearing loss and epilepsy, although no connection was previously made between these two conditions.

ACTG1 encodes γ-actin, the predominant isoform in auditory hair cells, and its specific expression pattern compared to other actins is thought to account for the nonsyndromic hearing loss caused by mutations in this gene [11,12,13]. In our patients, such a mutation may have caused both the autosomal dominant sensorineural hearing loss seen in patients 1 and 3, and the Baraitser-Winter syndrome seen in patient 2. In addition the mutation likely explains both the sensorineural hearing loss and the epilepsy in patients 2 and 3. It should be noted, however, that although patient 2 fits the syndromic criteria for Baraitser-Winter syndrome, an alternative explanation is that he has isolated hearing loss related to *ACTG1* mutation, plus an additional syndrome. The finding of a seizure disorder in Patients 2 and 3, which is a feature of Baraitser Winter syndrome, and the anomalous although not colobomatous optic nerves in Patient 1, makes variable expressivity more likely as these may be *forme frustes* of the complete syndrome. *ACTG1* has also been postulated to play a role in oncogenesis, and patients with mutations have been reported to have an increased risk

of hematologic malignancies. Patient 3 is currently being treated for breast cancer, which has not been previously reported to be associated with mutations in this gene. Since breast cancer is common, this may be an unrelated finding but warrants further study.

It is possible that esotropia is an additional feature of the Baraitser-Winter syndrome phenotype, although this association has not yet been reported previously. The understanding of the etiology of congenital and accommodative esotropia, which often co-exist, is limited, but it is possible that a developmental gene such as *ACTG1* could play a role. Alternatively, since esotropia is common in the population, this finding could be coincidental.

In summary, we have described a family segregating a novel mutation in *ACTG1* that causes either Baraitser-Winter Syndrome or apparently isolated hearing loss in the same family. In this 3-generation pedigree, the full syndrome of chorioretinal and iris coloboma, ptosis, seizures and developmental delay, as expected for Baraitser-Winter Syndrome, was present in only one person, another person has hearing loss and seizures, and the third affected person has hearing loss and anomalous optic nerves. Patients with isolated hearing loss should have *ACTG1* screened as part of their genetic work-up. Patients with mutations in *ACTG1* would benefit from genetic counseling regarding the possibility that their offspring may be more or less severely affected than themselves. In addition, genetic variants in this gene should be considered in patients with ocular coloboma, especially if ptosis and hearing loss are present. Further reports of phenotypes associated with mutations in this gene will help elucidate genotype-phenotype correlations.

Acknowledgments

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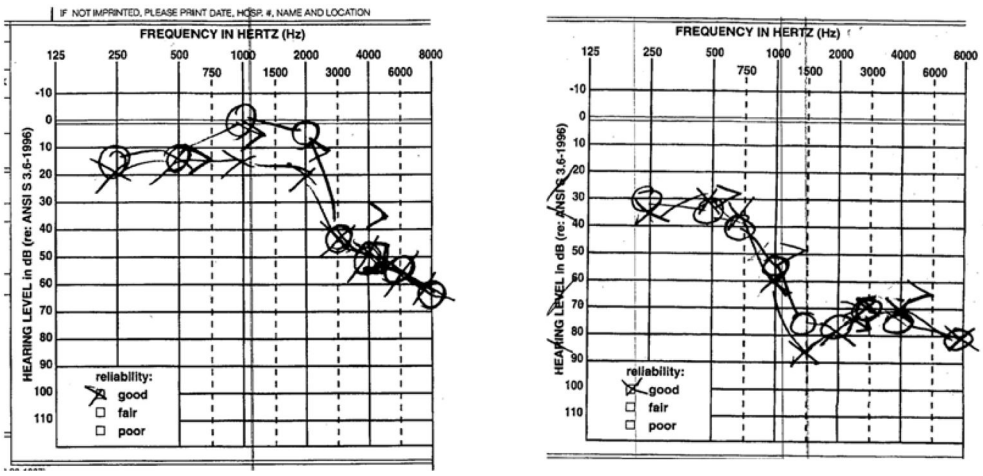

Figure 1.
Audiogram of Patient 1 (left) and audiogram of Patient 2 (right)

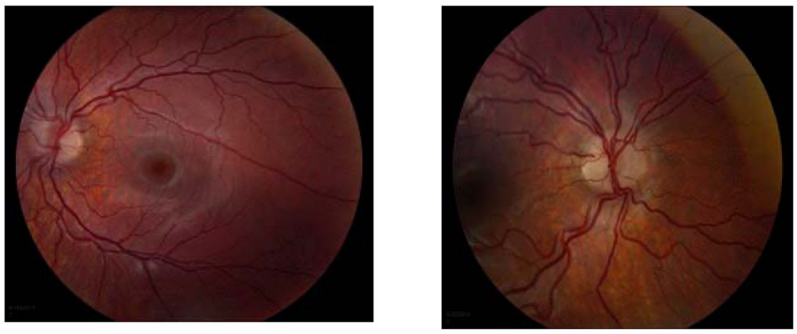

Figure 2.
Fundus photograph of Patient 1, left eye on the left photograph; close up of optic nerve on the right photograph. Note that nerves are tilted, crowded, and small.

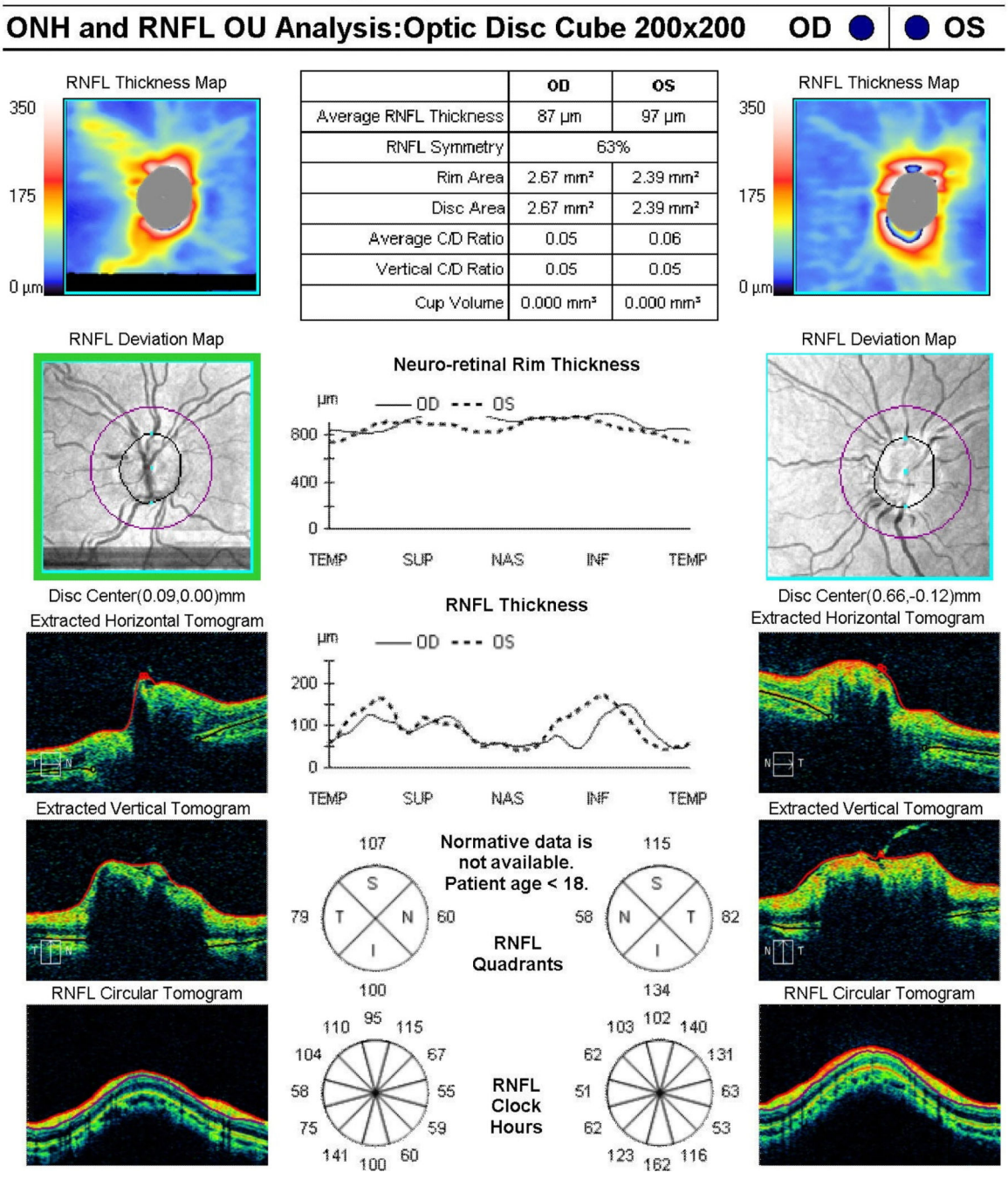

Figure 3.

OCT of Patient 1 showing small optic nerve areas with the appearance of elevation, however the average retinal nerve fiber layer thickness is thin (less than 100 in both eyes).

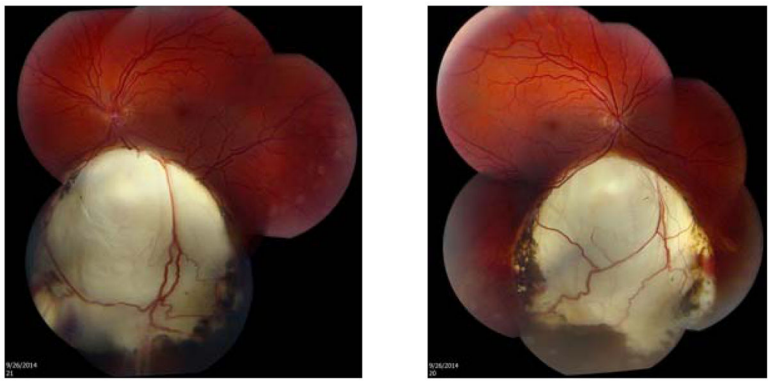

Figure 4.
Fundus photographs of Patient 2 showing large inferior colobomas sparing the optic nerves and maculas.

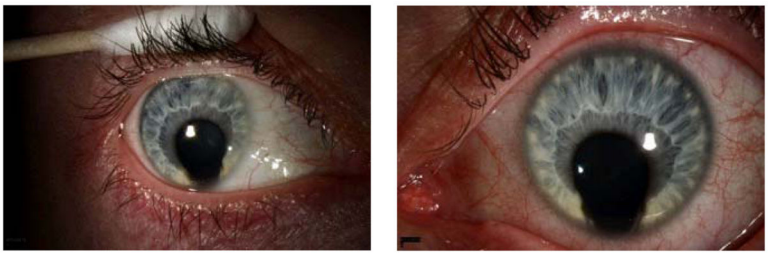

Figure 5.
Irides of Patient 2 showing inferonasal iris colobomas.