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CASE REPORT

Chromosome 6p25 deletion syndrome: A case report and review of ophthalmic features

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Abstract

The 6p25 deletion syndrome is a rare genetic disorder characterized by a wide spectrum of congenital anomalies. Ophthalmic abnormalities appear to be highly associated with the syndrome, although this relationship has not been well characterized to date. We conducted a systematic literature review to highlight the ocular features in patients with this deletion syndrome and describe a 7-month-old female who has a 6.07 MB 6p25.1p25.3 deletion and a 4.25 MB 17q25.3 duplication. Our patient presented with multiple congenital anomalies, including macrocephaly, frontal bossing, low set ears, tent-shaped mouth, saddle nose, flat midface, and hearing impairment. Her ophthalmic features included proptosis, down-slanting palpebral fissures, hypertelorism, nystagmus, bilateral posterior embryotoxon, and decentered and abnormally shaped pupils. A systematic review of the published cases with sufficient clinical eye descriptions included 63 cases with a confirmed 6p25 deletion. The most common eye findings observed were posterior embryotoxon, iris hypoplasia, corectopia, cornea opacity, and glaucoma.

KEYWORDS
6p25 deletion, anterior segment dysgenesis, Axenfeld–Rieger syndrome, corectopia, *FOXC1*, posterior embryotoxon

1 | INTRODUCTION

The 6pter-p24 deletion syndrome (MIM # 612582) is a rare congenital condition that involves a terminal deletion from the end of the short arm of chromosome 6. It is characterized by the presence of CNS abnormalities (Aldinger et al., 2009), dysmorphic facial features, developmental delay, hearing impairment, congenital heart defects, and anterior segment malformations of the eye with a risk for glaucoma (Lin et al., 2005). There is a significant variability in clinical features among individuals with terminal 6p deletions, secondary to differences in deletion sizes, localization of breakpoints, and the gene loss included in the deletion. People with different deletion sizes may have a similar pattern of findings, suggesting that there is a "critical region" of the short arm of chromosome 6 that must be lost for these features to manifest. The smallest region of overlap for a "critical region" has been localized to the distal 1.3 Mb of chromosome 6 in band 6p25 (DeScipio et al., 2005). As a result, this condition has more recently been denoted in the literature as 6p25 deletion syndrome.

The results of genotype–phenotype correlations suggest that many features of 6p25 deletion syndrome are caused by the loss of the *FOXC1* gene, localized to 6p25.3, a transcription factor that has been associated with processes regulating the neural crest cell

development. Pathogenic loss of function variants involving *FOXC1* has been observed in approximately 16% of patients who have Axenfeld–Rieger syndrome (ARS), an autosomal dominant condition wherein patients have malformations that affect the development of the eye (de Vos et al., 2017). Individuals with a terminal 6p deletion that encompasses the *FOXC1* gene demonstrate clinical features that are consistent with those associated with the ARS phenotype. ARS is characterized by cornea defects and iris defects, and approximately 50% of people with this syndrome develop glaucoma. Other anterior segment anomalies reported in individual cases include corneal opacities, strabismus, cataracts, macular degeneration, and retinal anomalies (D'haene et al., 2011; Strungaru et al., 2007; Tümer & Bach-Holm, 2009).

Although reported cases of 6p25 deletion have included variable clinical features, the ophthalmic manifestations associated with the 6p25 deletion have not been well delineated in the literature. We present the clinical findings of a 7-month-old female with confirmed 6p25 deletion and compare her clinical presentation to those previously reported in the literature with a focus on ophthalmic manifestations.

2 | CASE REPORT

Our patient, now a 2-year-old female, was born at 37.4 weeks gestation by C-section to a 28-year-old gravida 2, para 2 mother. Family history was notable for a paternal aunt who died at 2 years of age due to possible complications of cerebral palsy. There was no other family history of birth defects, dysmorphic features, multiple miscarriages, or infant deaths related to the potential of familial balanced or unbalanced translocations in other family members.

The pregnancy was complicated by the identification of multiple congenital anomalies noted on prenatal ultrasound, including straight ribs; hypertelorism; suspected Dandy–Walker variant; mild dilation of the left kidney; pericardial effusion, and pleural effusion. Labor was induced at 37.4 weeks secondary to macrocephaly; the birth weight was 8 lbs 6 oz. The patient was in the NICU for approximately 6 weeks for feeding issues requiring G-tubes placement at 5 weeks of age and for respiratory issues requiring C-PAP.

A prenatal genome-wide SNP microarray analysis revealed an XX sex chromosomal complement that had a 6.07 MB copy number loss (one copy) of the terminal portion of chromosome 6, from 6p25.3 to 6p25.1 and a 4.25 MB copy number gain (three copies) of the distal long arm region of chromosome 17, localized to 17q25.3 (Figure 1). These abnormalities are consistent with an apparently unbalanced translocation. The deletion of euchromatin from the terminus 6p25.3 encompassed the *FOXC1* gene, as well as other genes localized to this region.

At birth, multiple congenital anomalies were noted for this patient, including bilateral down-slanting palpebral fissures, macrocephaly, frontal bossing, low set ears, tent-shaped mouth, hypertelorism, saddle nose, and a flat midface (Figure 2a). The patient also has a history of feeding difficulties and hypotonia; she also failed her newborn hearing screening twice. Past fetal echocardiogram and a postnatal echocardiogram revealed a patent ductus arteriosus. Renal ultrasound revealed dilation of left kidney. Brain MRI findings included mild interior vermian hypoplasia, mildly hypoplastic cerebellar hemispheres, and a suspected Dandy–Walker variant.

At the most recent ophthalmic exam at 7 months of age, her assessment was notable for bilateral horizontal nystagmus with moderate amplitude and frequency, along with hyperopic astigmatism. The patient had several clinical features that were consistent with Axenfeld–Rieger syndrome, including bilateral mild proptosis/prominent eyes, anterior segment dysgenesis, bilateral posterior embryotoxon, abnormally shaped pupil of the left eye, and abnormally shaped, decentered pupil of right eye (Figure 2b). A retinal examination revealed a blunted foveal reflex and tilted optic nerve with an adjacent scleral crescent, bilaterally. No signs of glaucoma were present; normal intraocular pressure in both eyes was noted during the assessment.

3 | LITERATURE REVIEW

We performed a systematic review of the literature to summarize the reported ocular and ophthalmic features in individuals with confirmed 6p25 deletions. A PubMed search of "6p25 Deletion Syndrome" led to a total of 62 articles; these articles, along with their references, were reviewed in search of ophthalmic findings. Additionally, all 19 references used for the OMIM 6pter-p24 deletion syndrome, entry (MIM # 612582) were reviewed along with their references. From the total 78 articles, 39 articles were identified that had adequate eye descriptions of patient with molecular confirmation of 6p25 deletions (Table S1) (Anderlid et al., 2003; Arcot Sadagopan et al., 2015; Atli et al., 2020; Balasubramanian et al., 2015; Beby et al., 2012; Bedoyan et al., 2011; Caluseriu et al., 2006; Cellini et al., 2012; Corona-Rivera et al., 2019; Davies et al., 1999; De Vries, 2003; Delahaye et al., 2012; Fan et al., 2020; Gould et al., 2004; Gripp et al., 2013; Hosono et al., 2020; Kannu et al., 2006; Kapoor et al., 2011; Law et al., 1998; Le Caignec et al., 2005; Linhares et al., 2015; Maclean et al., 2005; Martinet et al., 2008; Martinez-Glez et al., 2007; Mirza et al., 2004; Nakane et al., 2013; Nishimura et al., 1998; Pavone et al., 2019; Piccione et al., 2012; Reis et al., 2012; Tonoki et al., 2011; Vernon et al., 2013). The remaining 39 articles were excluded from this analysis due to either lack of clinical ophthalmic descriptions, published as follow-ups to prior journal articles, or reported findings centered on the cytogenetic investigations related to the chromosomal disorder, with incomplete clinical descriptions. No articles were excluded based on the year published.

Within these selected articles, we identified 63 individuals with confirmed 6p25 deletions that had clinical eye descriptions. After including our patient, we calculated the frequency and prevalence of each ophthalmic finding from the total number of 64 patients with a confirmed deletion and reported clinical eye findings (Table 1). Table S2 presents the clinical characteristics specifically associated with each patient reported.

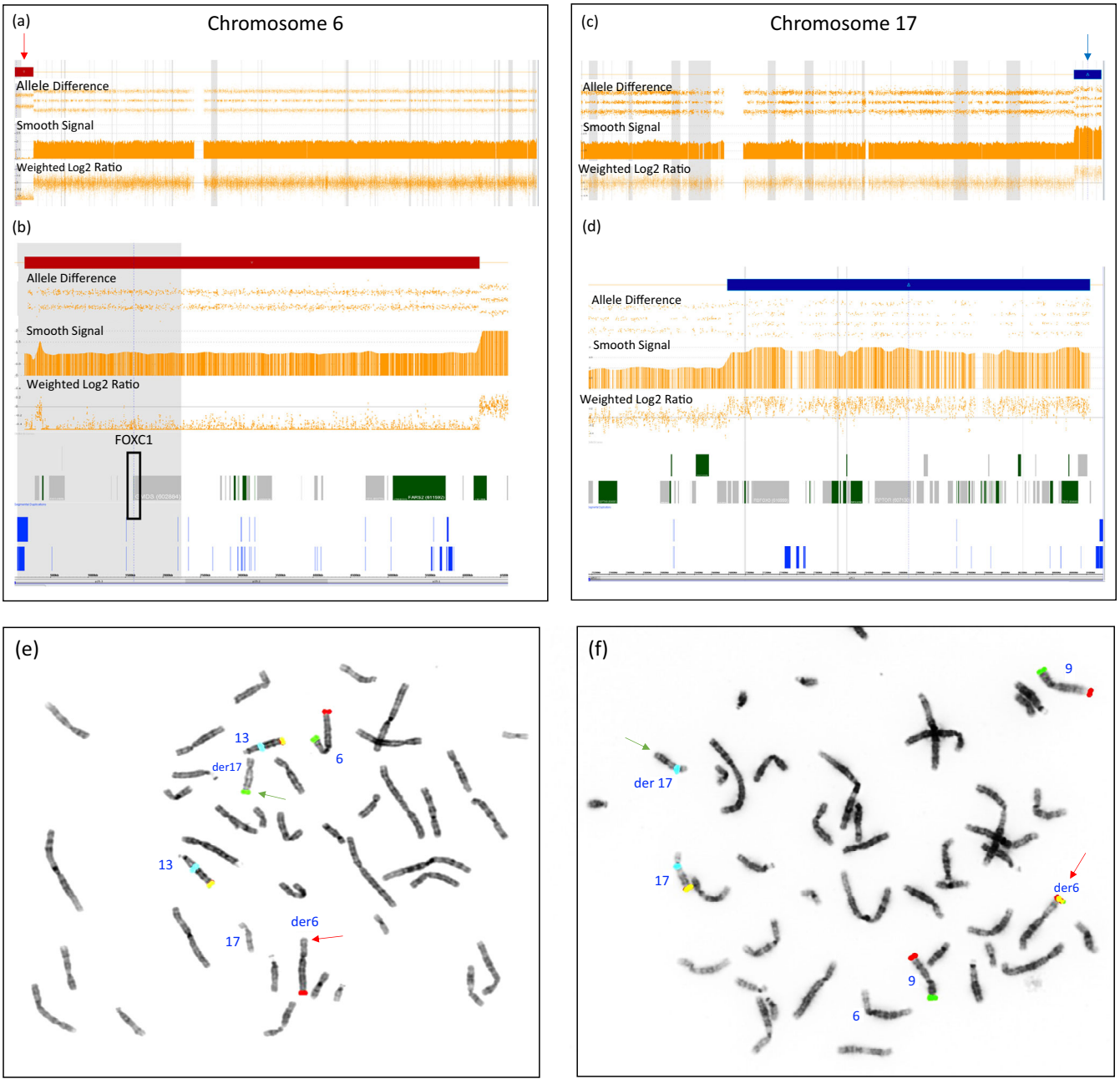

FIGURE 1 Microarray and fluorescence in situ hybridization (FISH) studies showing the chromosome 6 and chromosome 17 abnormalities. The microarray images (a–d) are from the patient, who has an unbalanced complement. (a) The allele difference (top), smooth signal (middle), and weighted log2 ratio (bottom) patterns in this microarray image shows a terminal deletion (red arrow; 1 copy) of 6p. (b) A focused view of this copy number finding shows that the *FOXC1* gene is encompassed in the deletion region (black rectangle). (c) A microarray image (allele difference [top], smooth signal [middle], and weighted log2 ratio [bottom]) shows three copies for distal 17q (blue arrow). (d) A focused view of this copy number finding shows multiple genes localized to this region with partial trisomy. The FISH images (e and f) are from the patient's mother, who is a balanced carrier of a t(6;17). (e) FISH studies show chromosome 6 probes localized to the short arm (green signal) and the long arm (red signal) of a typical chromosome 6; the derivative chromosome 6 (red arrow) is missing a green short arm signal. These sequences were translocated to a derivative chromosome 17 (green arrow). This probe set also includes probes for chromosome 13 bands (yellow and aqua), with those probe patterns being within normal limits. (f) Chromosome 17 probes localized to the long arm (yellow signal) and pericentromeric locus (aqua) of a typical chromosome 17; the derivative chromosome 17 is missing a long arm signal (green arrow). These sequences were translocated to a derivative chromosome 6 (red arrow). This probe set also includes probes for chromosome 9 (green and red), with those probe patterns being within normal limits.

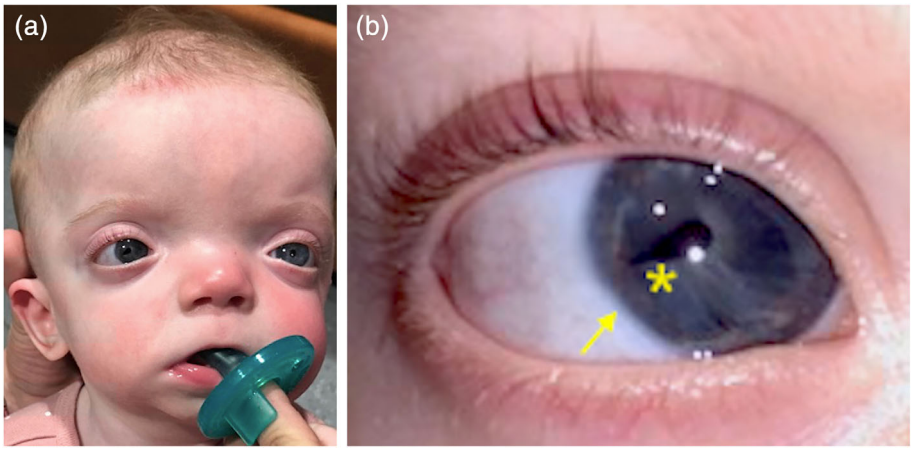

FIGURE 2 Photographs of our patient, who has a 6p25.3 deletion and 17q25.3 duplication, demonstrate (a) the patient's facial features; note the down-slanting palpebral fissures, macrocephaly, frontal bossing, low set ears, tent-shaped mouth, hypertelorism, saddle nose, flat midface, prominent eyes and (b) the patient's right eye; note posterior embryotoxon (arrow) and corectopia (asterisk).

4 | DISCUSSION

To our knowledge, the first case report for a patient with 6p25 deletion was in 1983, wherein a preterm infant with a terminal deletion of 6p24 to 6pter was described as having developmental delay, distinctive facial features, patent ductus arteriosus, Dandy–Walker malformation, Peter anomaly, and corneal opacities (Reid et al., 1983). Zurcher et al. (1990) reported a 28-month-old girl with developmental delay, craniofacial anomalies, combined hearing deficit, and ventriculomegaly. Reported eye anomalies included widely spaced eyes, right esotropia, and severe bilateral hyperopia.

Since then, there have been additional case reports of patients with documented 6p25 deletion in the medical literature; however, the majority of these reports lack ophthalmic descriptions. It is possible that these patients without reported eye manifestations did not have abnormal ophthalmic features, although we suspect that the omission of reported eye features was more frequently related to the particular concentration of topics within each individual report. For example, an article titled "Phenotype of a Belgian Family With 6p25 Deletion Syndrome" by Weegerink et al. (2016) described hearing impairment and radiological characteristics in three patients with confirmed 6p25 deletion syndrome; however, ophthalmic manifestations were not featured.

From our literature review of the reports that included ophthalmic descriptions, the most common ophthalmic manifestations in 6p25 deletion syndrome were anterior eye chamber defects ($n = 58$, *freq* = 90.6%). Specifically, posterior embryotoxon (48.3%), iris hypoplasia (53.6%), corectopia (76.2%), and cornea opacity (52.6%) were the most common reported features (Table 1). The reported patients with these ophthalmic features have in common the harboring of a 6p25 deletion involving the *FOXC1* gene (Table S2). Mutations in the forkhead transcription factor gene *FOXC1* have been frequently associated with anterior-chamber defects. The present description is consistent with a genetic study suggesting that *FOXC1* gene dosage is the probable mechanism responsible for the observed ocular phenotypes (Lehmann et al., 2002).

Our patient's clinical presentation included several dysmorphic features that are commonly associated with chromosome disorders, including down-slanting palpebral fissures, macrocephaly, frontal bossing, low set ears, tent-shaped mouth, hypertelorism, saddle nose, flat midface, hearing impairment, and feeding difficulties (Figure 2a). Our patient was found to have an unbalanced translocation, resulting in the loss of 6p25.3 and gain of 17q25.3. The deletion of 6p23.5 involves the *FOXC1* gene. Ophthalmic features seen in our patient are consistent with the clinical features of 6p25 deletion reported in the literature, including mild proptosis, nystagmus, bilateral posterior embryotoxon, abnormally shaped pupil of the left eye, and abnormally shaped and decentered pupil of right eye (corectopia) (Figure 2b). Considering that the 6p25 deletion includes the coding sequence of *FOXC1* gene and that the ophthalmic features in our patient correspond with the cases reported with *FOXC1* deletions, it is likely that the anterior segment malformations observed in our patient may be attributable to the haploinsufficiency of the *FOXC1* gene. The additional imbalances present in our patient's chromosomal complement may explain the phenotypic features that are not seen with deletion of 6p25. A report in 2010 of a child with a de novo microduplication of 17q25.3 described clinical findings of dysmorphic features, growth retardation, developmental delay, and distal arthrogryposis and cardiovascular malformations (Lukusa & Fryns, 2010). It appears that the most common concerning feature suggested in the literature to be seen with this duplication is cardiovascular abnormalities. Our patient's patent ductus arteriosus is likely associated with the 17q25.3 duplication.

Our patient was also found to have brain MRI findings consistent with mild interior vermian hypoplasia, mildly hypoplastic cerebellar hemispheres, and a suspected Dandy–Walker variant. Brain anomalies, characterized by Dandy–Walker malformation, multifocal cerebral white matter lesions, and underdeveloped corpus callosum have been reported in the literature in individuals with a 6p25 deletion (van der Knaap et al., 2006). These abnormalities can potentially lead to problems with movement, coordination, cognition, and other functions of the nervous system. Therefore, early detection and high suspicion of 6p25 deletion syndrome should be specifically considered in patients presenting with a combination of anterior eye chamber abnormalities, dysmorphic features, and brain anomalies on MR imaging.

In summary, this report and literature review of the 6p25 deletion syndrome contributes to our understanding of the relationship

TABLE 1 Frequency of ophthalmic findings, reported in 64 patients with 6p25 deletions.

Ophthalmic findings	Our patient	Number (*n*)	Frequency (%)
Anterior-chamber defect	+	58	90.6%
Posterior embryotoxon	+	28	48.3%
Iris defects: hypoplasia, adhesion, aniridia, and coloboma	–	28	48.3%
Iris hypoplasia[a]		15	53.6%
Pupil defects: corectopia, polycoria, and irregular shaped	+	21	36.2%
Corectopia[a]		16	76.2%
Cornea defects: opacity, edema, iridocorneal adhesions, megalocornea, and sclerocornea	–	19	32.8%
Cornea opacity[a]		10	52.6%
Axenfeld–Rieger anomaly	+	21	36.2%
Peter anomaly	–	3	5.2%
Other anterior eye chamber anomalies[b]	–	6	10.3%
Oculo-orbital defect			
Hypertelorism or telecanthus	+	45	70.3%
Abnormal palpebral fissures	+	25	39.1%
Down-slanting palpebral fissure[a]	+	23	92.0%
Up-slanting palpebral fissure[a]	–	2	8.0%
Proptosis/exophthalmos	+	7	10.9%
Buphthalmos (due to glaucoma)	–	1	1.6%
Eye motility disorder			
Strabismus	–	23	35.9%
Exotropia (divergent)[a]	–	10	43.5%
Esotropia (convergent)[a]	–	5	21.7%
Hypertropia (vertical)[a]	–	1	4.3%
Unspecified[a]	–	7	30.4%
Nystagmus	+	3	4.7%
Refractive error			
Hyperopia/hypermetropia	+	15	23.4%
Astigmatism	+	7	10.9%
Myopia	–	3	4.7%
Funduscopic findings			
Glaucoma	–	18	28.1%
Retinopathy and optic disc defects	+	9	14.1%

[a]Frequency within the subset of patients presenting with respective defects: iris, pupil, cornea defects, palpebral fissure, and strabismus.
[b]Other anterior eye chamber anomalies: goniodysgenesis, gray-blue sclerae, cataract, and dysplastic ciliary processes.

of the 6p25 deletion and ophthalmic abnormalities. The importance of summarizing ophthalmic features associated with 6p25 deletion may allow for swifter identification and management initiation by providers for patients with this condition. For example, given that a significant percentage of these patients have anterior eye chamber dysgenesis, earlier recognition of 6p25 deletion could prompt consideration for an early referral to a pediatric ophthalmologist.

A limitation of our study was the inability to delineate some clinical features associated with an isolated terminal 6p25 deletions etiology because additional chromosomal imbalances, as in our patients, can lead to overlapping dysmorphic features. Further studies with a larger sample size could help to distinguish whether many of these features are indeed a true correlation with the 6p25 deletion syndrome.

AUTHOR CONTRIBUTIONS

Hong Le: Writing – original draft and formal analysis. **Eva Jin:** writing – review and editing and formal analysis. **Ann Jewell:** writing – review and editing. **Colleen Jackson-Cook:** writing – review and editing.

Gloria T. Haskell: writing – review and editing. **Natario Couser:** conceptualization, supervising, and writing – review and editing.

CONFLICT OF INTEREST STATEMENT

Natario L. Couser, MD, MS is a principal investigator at the Virginia Commonwealth University, Retrophin, Inc./Travere Therapeutics, Inc. (Clinical Trial), National Cancer Institute/Children's Oncology Group (Clinical Trial), Elsevier (Book editor), Patient-Centered Outcomes Research Institute (PCORI; Advisory Panel on Rare Disease), and National Institutes of Health/National Eye Institute (Grant Review Panelist). The other authors declared that they have no conflicts of interest.

DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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