Case Report

Ocular Manifestations of a Novel Proximal 19p13.3 Microdeletion

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Microdeletions at 19p13.3 are rarely reported in the medical literature with significant phenotypic variability. Among the reported cases, common clinical manifestations have included developmental delay, facial dysmorphism, and hypotonia. Herein we described a child with a de novo 19p13.3 microdeletion, proximal to the reported cases of 19p13.3 microdeletion/duplication, with ocular manifestations of bilateral ocular colobomata complicated with microphthalmos and cataract, associated with short stature. This case highlights the phenotypic heterogeneity of deletions in the 19p13.3 region.

1. Introduction

Chromosome 19 has been identified as having the highest gene density within the human chromosomes, with large gene families of evolutionary significance [1]. Deletions and duplications within the terminal band, 19p13.3, are sparsely reported in the medical literature with significant phenotypic variability. Most patients described within the literature have developmental delay, macrocephaly, and hypotonia with dysmorphic features [2–10]. Risheg et al. described two cases where one case had dysmorphic features including downsloping palpebral fissures, prominent auricular root, cupped ears, and mouth abnormalities [7]. The second case also included ear anomalies, notably a unilateral preauricular skin tag, and helix anomalies [7].

It would also appear that there exist common dysmorphic features within 19p13.3 microdeletions, with various ear abnormalities being the most common association. Deletions at 19p13.3 have been associated with ophthalmologic issues such as amblyopia, myopia, and strabismus as well as congenital cardiac issues [2–4, 6–9]. A comprehensive summary of previously reported phenotypic features is provided in Table 1.

19p13.3 microdeletion/duplication syndrome has been previously described within the literature; however, the shortest region of overlap (SRO) is approximately 150 kb and includes one microRNA (SNORD37) and four genes (PIAS4, ZBTB7A, MAPK2, and partially EEF2). Herein we report a case of a child with a novel deletion, proximal to the SRO, resulting in additional novel ocular structural anomalies.

2. Case Report

2.1. Clinical Case. We report a 6-year-old female born to non-consanguineous parents. Antenatal history is unremarkable, with mother reporting a normal pregnancy and delivery via an elective caesarean section at 38 weeks. Birthweight was 2800 grams (10th%), head circumference was 32 cm (25th%), and length was 45 cm (3rd%) with Apgar scores of 9 at one minute and 9 at 10 minutes. The child was slow to reach early developmental milestones, approximately 6 months behind age appropriate milestone attainment, especially in the domains of gross motor and speech and language.
## Table 1: Summary of phenotypic features.

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## Deletionsize and breakpoint

- arr[GRCh37] 19p13.3 (4399876-4933228)x1 0.81Mb
- Arr[GRCh] 19p13.3 (217145–1027368)x1.ish Del(19)(p13.3p13.3) (RP11-575H1) pat 0.73Mb
- Arr[GRCh] 19p13.3 (217145–1027368)x1.ish Del(19)(p13.3p13.3) (RP11-575H1) mat 0.73Mb
- arrcgh 19p13.3 (217117–1083955)x1.ish del(19)(p13.3p13.3) (RP11-575H1) 0.86Mb
- arrcgh 19p13.3 (217145–1045590)x1.ish Del(19)(p13.3p13.3) (RP11-575H1) 0.82Mb
- arrcgh 19p13.3 (217145–1045590)x1.ish Del(19)(p13.3p13.3) (RP11-575H1) 0.13Mb
- arrcgh 19p13.3 (217117–353272)x1 0.65Mb
- arrcgh 19p13.3 (736690–1395289)x1.ish Del(19)(p13.3p13.3) (RP11-878J15) 610kb
- arrcgh 19p13.3 (3,143,283–4,149,860) 1.1Mb
- arrcgh 19p13.3 (3,256,944–4,136,989) 0.792kb
- arrcgh 19p13.3 (3,814,392–4,605,977) 1.1Mb
- arrcgh 19p13.3 (3,814,392–4,605,977) 0.81Mb
- arrcgh 19p13.3 (39.27–45.78Mb) 5Mb
- arrcgh 19p13.3 (1,103,412–1,253,309) 710kb
- arrcgh 19p13.3 (1,118,914–1,120,329) with a further centromeric deletion (1,829,934–1,837,061)
At age 5, she was assessed by an ophthalmologist and diagnosed with bilateral chorioretinal coloboma, left iris coloboma, left cataract, left sensory exotropia, and left microphthalmos. She was found to have normal vision in her right eye, but left eye was legally blind with only light perception intact. Exploration of her eyes under anaesthesia found left inferior chorioretinal coloboma involving the optic nerve but not the macular with vitreous detachment. It also found a right inferior chorioretinal coloboma not involving the macula. She has an area of dermal hypoplasia in the region of her left occiput, is nondysmorphic, and has an otherwise normal systems review to clinicalexamination. She continued to maintain growth trajectories with the predominante feature of short stature (below 1st centile). Her growth parameters at five years of age were weight 12 kg (below 1st centile), head circumference 44 cm (25th%), and height 92 cm (below 1st centile) and currently at 6 years of age were height 99.5 cm (below 1st centile), weight of 14 kg (below 1st centile), and head circumference 44 cm (25th%).

A brain magnetic resonance imaging scan was normal with no signs of a neuronal migration defect. Transferrin washeight99.5cm(below1stcentile),weightof14kg(below1stcentile)andcurrentlyat6yearsofage. Growth parameters at five years of age were weight 12 kg (below 1st centile), head circumference 44 cm (25th%), and height 92 cm (below 1st centile) and currently at 6 years of age were height 99.5 cm (below 1st centile), weight of 14 kg (below 1st centile), and head circumference 44 cm (25th%).

A de novo 533kb deletion arr[GRCh37] 19p13.3(4399876–4933228) was identified. This is proximal to (and does not encompass) the region reported in association with “19p13.3 microdeletion/microduplication syndrome” [2]. This indicates that this is a previously undescribed deletion within the 19p13.3 region. A search of the DECIPHER database did not find any corresponding previously reported deletion within the exact region;
however, several overlapping deletions with different phenotypes have been described (see Table 1). Each of these overlapping deletions has failed to describe an ocular anomaly, like the one seen in our patient.

Of the genes that span this region, KDM4B has been found in murine models to be active during embryogenesis, specifically within the visual system [19]. It could be theorised, therefore, that the deletion of a portion of this gene could profoundly affect the embryological development of the eye seen in this case study [19]. Additionally, UHRF1 has been found, in murine models, to be localised within the visual system in early embryological development; however, human research is lacking [20]. This may also theoretically cause an additive effect on the deletion outlined in this case. LRG1 has also been demonstrated to have a role in retinal development, with mutation encompassing this gene theoretically implicated in abnormal retinal development [21].

Another gene mapped to this area of 19p13.3 is also CHD7, which may have some functional impact and similarities to CHD7, the causative gene of CHARGE syndrome [14]. It is also hypothesised that LRG1 plays an important role in retinal angiogenesis [22]. Other genes mapped to this area have not been shown to have a role in oculogenesis either in murine models or in human models [23].

In summary, this case study adds further information about chromosome 19p13.3 deletions and the significant phenotypic characteristics of those affected. Further research needs to be completed on the causative genes for further elucidation of the cause of the ocular anomalies within this child.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

References


