11p13 Microdeletion Involving Partial Deletion of *ELP4* in a Newborn Patient without Aniridia

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BACKGROUND

- Here we report a newborn male patient with a 532 kb deletion at 11p13 involving 4 genes resulting in the partial deletion of *ELP4.*
- Alterations involving *PAX6* are associated with aniridia and related ocular abnormalities.
- *ELP4* is located just distal to the *PAX6* gene and is a member of a complex of proteins which regulates the migration of multiple cell types (Johansen, 2008), is involved in transcriptional elongation, the modification of tRNA, and polarized exocytosis (Wittschieben, 1999; Huang, 2005).
- *ELP4* contains regulatory elements for *PAX6* expression (Bhatia, 2013; Fantes, 1995; Kleinjan, 2001).
- Conflicting evidence exists regarding a possible association between single nucleotide polymorphisms (SNPs) in *ELP4* and rolandic epilepsy (Strug, 2009; Gkampeta, 2014; Reinthaler, 2014).
- Deletions involving *ELP4* distal to *PAX6* have the potential to disrupt *PAX6* expression and have been observed in sporadic and familial aniridia patients (Bayrakli, 2009; Cheng, 2011; Wawrocka 2012; Zhang, 2009).

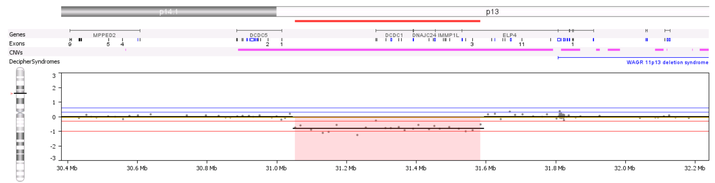
CLINICAL HISTORY

Clinical features and neonatal health history	• Prolonged vaginal delivery with right parietal fracture • Neonatal seizures, respiratory distress • Hypoxic-ischemic encephalopathy • Suspected talipes equinovarus • Appearance of small ears, wide-spaced nipples, fullness of posterior neck
Family history	• Maternal uncle with single febrile seizure as toddler
Lab tests with normal results	• Lysosomal enzyme panel • Routine blood work • Sepsis work-up • Newborn screen
Ophthalmology evaluation	• Negative for aniridia and associated ocular abnormalities • Small retinal hemorrhages consistent with birth history • Possible macular hemorrhage versus cherry red spot
Orthopedic evaluation	• Negative for talipes equinovarus
Clinical status at 6 months of age	• Pediatric genetics evaluation pending • Concern for distinctive features resolved • Possible mild communication delay with otherwise normal development • Seizure free and off of anticonvulsant medication since NICU discharge

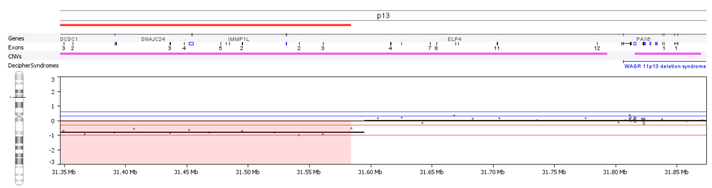
METHODS

- Genomic deoxyribonucleic acid (gDNA) is isolated from the patient's specimen using a standardized kit and quantified by Nanodrop. The aCGH method is based on the hybridization of fluorescently labeled patient genomic DNA (Cy-5) with fluorescently labeled reference DNA (Cy-3) to a 180K oligonucleotide array. Genomic patient DNA relative to the reference DNA are represented as fluorescent ratios (Cy5/Cy3) that are further quantified by image analysis software and analytical software. Quantified results indicate each targeted-DNA sequence as loss of copy number (deletion), gain of copy number (duplication) or normal copy number. This technology has been validated using patients with known microdeletions/duplications and other unbalanced karyotypes detected by traditional cytogenetic methods.
- The Ambry CMA: 180K Oligo array V2 contains 180,000 probes covering >400 genetic disorders. Exon level resolution is achieved in ~ 680 disease causing genes. The backbone spacing of the probes is set at an average of 13 Kb throughout the entire human genome and at 5 Kb on the X chromosome. The array also includes probes for the pericentromeric and subtelomeric regions with dense probe coverage spanning 10 Mb at each subtelomere. There is no probe coverage of the pseudoautosomal regions 1 and 2 (PAR1 and PAR2) on the X and Y chromosomes.

Figure 1. Patient's 180K Oligo Array
arr[hg19] 11p13(31,052,845-31,584,388)x1



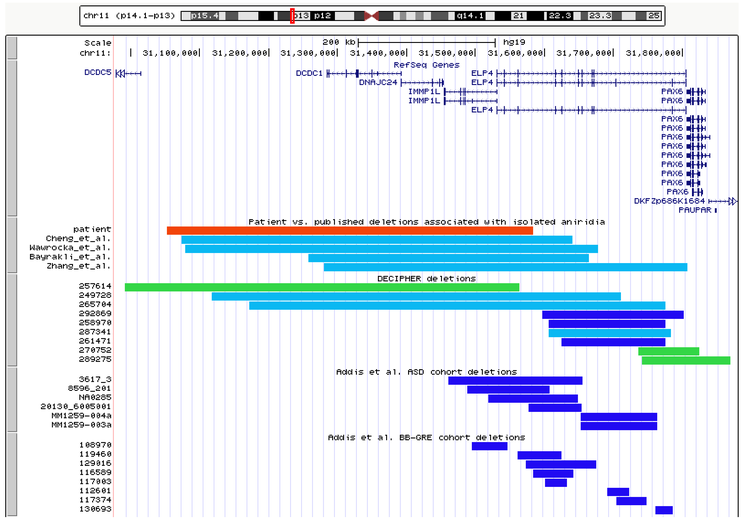
a. Full view of 11p13 deletion



b. Proximal deletion breakpoint demonstrating proximity to *PAX6*

- Ambry CMA: 180K Oligo array identified an interstitial single copy loss in chromosome region 11p13, approximately 532 kb in size and involving four genes, *DCDC1, DNAJC24, IMMP1L,* and *ELP4* (Figure 1). The deleted interval partially overlaps the *ELP4* gene including exons 1-3. The proximal breakpoint is approximately 222kb from the 3' end of *PAX6.* No additional copy number variations (CNVs) were identified. The deletion was reported as a variant of uncertain significance as the proximal breakpoint and its relationship to *PAX6* regulatory elements could not be determined.
- Parental FISH analysis was performed at an outside laboratory and determined the deletion to be inherited from the reportedly unaffected mother.

Figure 2. Patient's 11p13 Deletion Versus Overlapping Deletions from Published Literature and DECIPHER



- Patient's deletion in red. Published or DECIPHER deletions associated with isolated aniridia or eye anomalies in light blue. Published deletions associated with neurodevelopmental phenotypes in dark blue. Deletions associated with both eye anomalies and neurodevelopmental phenotypes in green.

DISCUSSION

- Similar deletions with varying breakpoints but identical gene content including partial deletion of *ELP4* have been described in several families with dominantly inherited isolated aniridia (Figure 2).
- The absence of aniridia or associated optical anomalies in this patient suggests that *PAX6* regulatory elements were unaffected by the partial *ELP4* deletion.
- A publication reporting similar familial deletions in which both affected and unaffected family members were tested demonstrated complete penetrance for the aniridia phenotype associated with deletions overlapping *ELP4* (Bayrakli, 2009).
- Evolving information: Addis *et al.* identified smaller deletions involving *ELP4* to be enriched in a cohort of patients with a wide range of indications including developmental delay, autism spectrum disorder (ASD), or congenital anomalies, compared to controls (Fig. 2 BB-GRE cohort). Smaller deletions overlapping and within *ELP4* were also enriched in a cohort of patients with ASD vs. control population (Fig. 2 ASD cohort). Based on the phenotypic data for patients with CNVs involving *ELP4* across cohorts, the authors assert that disruptions of *ELP4* are associated with neurodevelopmental phenotypes including ASD, social communication difficulties, speech and language disorder, developmental delay, and epilepsy (2015).
- If the association with neurodevelopmental abnormalities is confirmed, it is unclear why some patients and families present with isolated aniridia without neurodevelopmental disorder. It is possible that different deletion intervals and gene content influence this phenotype correlation. Alternatively, CNVs involving *ELP4* may represent a susceptibility region that require additional genetic or environmental factors to manifest either or both phenotypes.

TAKE-HOME POINTS

- We report a newborn male patient with a 532 kb deletion at 11p13 involving 4 genes and resulting in the partial deletion of *ELP4*. Available literature describes several similar deletions in patients with isolated aniridia; however, this patient does not have aniridia or associated optical anomalies.
- Partial deletions of *ELP4* may or may not result in isolated aniridia depending on the location of the breakpoint and whether *PAX6* regulatory elements are disrupted.
- Emerging literature suggests that CNVs involving *ELP4* may also be associated with neurodevelopmental disorders.
- Additional studies are necessary to further investigate complex genotype-phenotype correlation for CNVs in this region.

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