DE NOVO IN-FRAME DELETION AND MISSENSE VARIANTS IN MEIS2 RECAPITULATE THE DELETION PHENOTYPE AND EXPAND THE GENOTYPE AND PHENOTYPE SPECTRUM OF THIS NEWLY RECOGNIZED DISORDER

Ginka Douglas, PhD; Megan T. Cho, MS; Daniel Pineda-Azaneo, MD; Susan Winter, MD; Jason Carmichael, MS; Elaine Zackai, MD; Wendy K. Chung, MD, PhD; Jane Juusola, PhD

GeneDx, 207 Perry Parkway, Gaithersburg, MD 20878

Background

- MEIS2 encodes a homeodomain protein, which functions as a transcriptional activator during development (Huang et al. 2005).
- Deletions of MEIS2 (contiguous, whole-gene, and intragenic) have been described (Johansson et al. 2014).
- Shared phenotypes in these patients included ASD/VSD, cleft palate, dysmorphic features, and developmental delay, intellectual disability, or autism.
- Recently, a patient with a de novo single amino acid deletion (p.R333del) was reported with a more severe phenotype (Louw et al. 2015).
- Objective: to investigate the nature and phenotypes of sequencing variants in MEIS2 identified by whole exome sequencing (WES).

Methods

- This study was approved by the Institutional Review Board of Columbia University.
- Informed consent was obtained from all individual participants included in this study.
- Genomic DNA was extracted from whole blood from the affected probands and their family members.
- DNA sequencing was performed at the PGx Lab at GeneDx, Gaithersburg, MD.

Results

- 4 patients were identified with de novo MEIS2 variants: recurrent p.R333del, p.P302L, p.R331K, and p.V335A.
- The three missense variants were predicted deleterious by PhyloP, PolyPhen2, SIFT, CADD, and MutationTaster, and none of the variants were previously observed in the ExAC, 100 Genomes, ECV, or internal xomeDx databases.
- Prior to the implementation of the recent ACMG standards and guidelines for the interpretation of sequence variants (Richards et al. 2015), the three missense variants were classified as likely pathogenic based on affecting conserved residues, observed de novo, being rare, having deleterious predictions, and identified in patients within the phenotype spectrum of MEIS2-related disorders. The single amino acid deletion p.R333del was classified as pathogenic given that it was also previously published.
- All of the variants are located in the highly evolutionarily conserved homeodomain (Gehring et al. 1994), which suggests it may also be a mutation hot-spot.
- p.P302L is found in the region between helix 1 and helix 2, while the rest are located in the DNA binding helix 3 (Figure 1), which is important for the complexing of homeodomain transcription factors to their target DNA.
- The patient phenotypes closely matched those commonly reported previously for MEIS2-related disorders, and included additional features (Table 1).

Conclusions

- To our knowledge, these are the first de novo missense variants in MEIS2, expanding both the known genotype and phenotype spectrum of MEIS2-related disorders.
- The associated phenotype overlaps with other developmental disorders, such as DiGeorge/ Velocardiofacial syndrome (VCFS).
- Because of the large number of potential differential disorders, WES is an efficient way to evaluate patients with multiple congenital anomalies and developmental delays.

References