Background

- SHOX is located in the pseudoautosomal region 1 (PAR1) of the sex chromosomes and is implicated in human growth. SHOX-related haplosufficiency causes Leri-Weill dyschondrosteosis (LWD), a skeletal dysplasia characterized by short stature and/or the Madelung deformity (bending of the radius and dorsal dislocation of the distal ulna), and isolated idiopathic short stature (ISS). Additionally, copy number variants (CNVs) confined to the SHOX downstream regulatory domain (DRD) only (see Figure 1) without involvement of the SHOX gene itself have been reported in cohorts of individuals with LWD and ISS. A recurrent 47.5 kb deletion, located 160 kb downstream of the SHOX gene, has been suggested to cause LWD and ISS. As these prior studies were performed in affected cohorts, there is a concern for ascertainment bias.

Methods

- Retrospective review of 18,646 postnatal chromosomal microarray (CMA) cases for deletions or duplications involving the SHOX DRD without involvement of the SHOX gene
- The following was collected for all cases with a CNV within the SHOX DRD:
  - CNV coordinates
  - Whether the CNV was a deletion or duplication
  - Additional reportable alteration(s) detected
  - Parental inheritance (if known)
  - Age of proband
  - Gender
  - Indication for testing (see Table 1)

Results

- 107 patients had CNVs within the SHOX DRD (0.57% of all CMA cases) (see Table 2)
- 85 with recurrent 47.5 kb deletion
- 22 with variable duplications
- 19 cases were excluded from analysis (17 with deletion, 2 with duplication)
  - 5 with no clinical information provided
  - 14 with the presence of a known pathogenic CNV which fully explained the phenotype (all deletions)
- 88 cases of SHOX DRD CNVs were used in the analysis
- 8 patients had an additional CNV of uncertain significance (9% of the study population)
- Indications for CMA testing included primarily the standard neurodevelopmental phenotypes (autism, learning disability/intellectual disability/developmental delay, dysmorphic features, congenital heart defect, and seizures)
- 8 patients had a spectrum of phenotypic features including short stature or possible LWD (6%)
- 20 of the 88 cases had parental testing performed; all CNVs involving the SHOX DRD were inherited
  - 2 of the mothers had a phenotype suggestive of LWD
    - aplastic anemia and slight abnormality at the elbow
    - child with phenotype including short stature
    - short stature and bowing of legs
    - child with phenotype of autism spectrum disorder

Conclusions

- No consistent phenotype was observed in individuals with CNVs in the SHOX DRD in our population of individuals having CMA
- Suggests SHOX DRD CNVs either are not pathogenic or show greatly reduced penetrance
- A minority (2%) of individuals with CNVs in the SHOX DRD in our population had a phenotype suggestive of LWD and none had isolated short stature
- As Madelung deformity develops in mid-to-late childhood, it is possible that some of the probands in this study could develop a phenotype more consistent with LWD
- SHOX DRD CNVs were relatively common (0.57% cases sent for CMA)

References