Chapter 7

Summary and conclusion
7.1. Summary

- We evaluated 43 patients from 38 families with non-syndromic MVSD.
- A recognizable pattern of segmentation defect is observed in patients with a pathogenic variant in DLL3 and FLNB.
- Eight patients from 7 families had pathogenic variants in DLL3 (SCD I).
- One patient had a pathogenic variant in MESP2 (SCD II).
- Ten patients from 7 families had pathogenic variants in FLNB (SCT).
- All variants in FLNB identified in patients with SCT are truncating.
- We also studied one patient with a possible pathogenic variant in FLNB (non-syndromic MVSD) and one patient with a pathogenic variant in PTCH1 (Gorlin syndrome).
- Despite thorough evaluation by systematic Sanger sequencing of six genes and exome sequencing, 21 patients did not have an identifiable monogenic cause for MVSD.
- We describe 15 novel pathogenic variants in DLL3, MESP2 and FLNB in our cohort.
- We further define the vertebral phenotypes of DLL3 and FLNB related MVSD.
- Cause of several MVSD still remains unknown indicating heterogeneous etiology of this condition.

7.2. Conclusion

In conclusion, we identified a monogenic etiology in 17 families with vertebral segmentation defects and expanded the clinical and molecular repertoire of this highly heterogeneous condition. Patients with pathogenic variants in known genes facilitated further characterization of DLL3 related vertebral segmentation defects. A biallelic
missense variant in FLNB was observed as the likely cause of multiple vertebral segmentation defects in a family. We also present ten additional patients from seven families with spondylocarpotarsal synostosis syndrome and report seven novel deleterious variants in FLNB. Furthermore, we provide clinical and radiological features of these patients thereby characterizing the phenotype better. Our work demonstrates that spondylocarpotarsal synostosis syndrome has a unique pattern of anomalous vertebral segmentation and all the reported patients have truncating variants in FLNB. Our work highlights the clinical and genetic heterogeneity of non-syndromic vertebral segmentation defects.