Exome analysis of prenatal and postnatal cases referred with skeletal dysplasia: an overview of genomic and phenotypic findings

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INTRODUCTION

Skeletal dysplasias represent approximately 5% of all congenital anomalies. They are a highly heterogeneous, with approximately 400 known gene/disorder associations. Many are detected in pregnancy but accurate diagnosis in both prenatal and postnatal settings often relies on expert interpretation of radiological findings since clinical findings are often non-specific. Patient outcomes vary across the cohort of disorders and traditionally treatment for patients has been focused on surgical interventions to manage life threatening complications. New therapeutic developments, such as vosoritide and infigratinib for children with achondroplasia have highlighted the need to provide accurate and timely diagnosis for this patient cohort.

METHODS:

We have reviewed a cohort of 777 cases that have undergone exome sequencing (ES) over approximately 2.5 years as part of a research service provided by Congenica Ltd., and the South West Thames regional Genetics Service, London, UK. In total 53 cases were received with a referral of possible skeletal dysplasia or associated phenotypic terms, representing 6.8% of cases referred for ES. Here we discuss the genotypic and phenotypic findings of the 53 cases.

RESULTS:

A molecular diagnosis was obtained in 49% of cases. **A higher diagnostic yield was obtained in prenatal (64%) than postnatal (35.7%) cases**. Case structure had an impact on the number of diagnoses obtained in both clinical settings with trio's providing the greatest diagnostic yield.

Causal variants were identified in 26 genes and only one gene, *SLC26A2,* was identified as causal in more than one family (see Table 1).

Autosomal recessive inheritance was most commonly observed accounting for 61.5% (16/26) of diagnosed cases, *de novo* variants were associated with 26.9% (7/26) of cases and X-linked inheritance observed in 3.8% (2/26). In one case a compound genotype was identified with *de novo* and X-linked causal variants identified in two genes.

Variant types identified included coding, non-coding and CNVs, for example; *MYH3 5'UTR splice donor variant* c.-10_-9+24del, *FLNB* 4.7kb deletion encompassing exons 9-12

ALPL	*FAM111A*	*P3H1*	*SLC26A2*
ANKH	*FGD1*	*PAPSS2*	*SMAD6*
COL1A1	*FGFR3*	*RBM8A*	*SOX9*
COL1A2	*FLNB*	*RMRP*	*TRAPPC2*
D2HGDH	*GNPTAB*	*SEC24D*	*RERE,/PHKA2*
EVC	*MYH3*	*SLC17A5*	
EVC2	*NIPBL*	*SLC26A2*	

Table 1: Genes associated with skeletal dysplasia identified in cohort. Genes in green/blue indicate a diagnosis in a prenatal setting

CASE STUDY and DISCUSSION

The molecular diagnosis was not always concordant with the suspected clinical diagnosis, particularly in the prenatal setting as demonstrated by the following 3 cases.

Case Details	Diagnosis
?Chondrodysplasia punctata. shortening of fetal long bones detected at second trimester scan	**mucolipidosis II alpha/beta** *GNPTAB*
?Osteogenesis imperfecta or thanatophoric dysplasia severe skeletal dysplasia and fetal oedema	**campomelic dysplasia** *SOX9*
?Thanatophoric dysplasia three sibling fetuses identified with limb shortening and bowing and thoracic narrowing at 12 weeks scan	**hypoplasia / anauxetic dysplasia spectrum of disorder** *RMRP*

Patient Management

The diagnostic yield observed in this cohort is high at 49% and illustrates the importance of comprehensive analysis of both genes (1) and variant types. Unexpected diagnoses are not uncommon, and the phenotypic presentation of some gene/disorders has been extended in at least two cases (*RMRP* and *FAM111A*) (2, 3).

Timely diagnosis has provided accurate prognostic and recurrence information for the families and has directly influenced patient management, including two cases of spondylocarpotarsal synostosis, where surveillance for cervical spine instability was initiated and one prenatal case of hypophosphatasia where timely diagnosis provided appropriate management of pregnancy and access to therapeutic intervention.

References: 1. PanelApp - panelapp.genomicsengland.co.uk/panels 2. PMID: 33567347, 3. PMID:31910817