INPLASY PROTOCOL

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Corresponding author:
YE CAO

yecao@cuhk.edu.hk

Author Affiliation:
The Chinese University of Hong KongCUHK

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None declared.

Diagnostic Yield of Exome Sequencing in Fetuses with Sonographic Features of Skeletal Dysplasias but Normal Karyotype or Chromosomal Microarray Analysis: A Systematic Review

Tse, KY[1]; Surya, IU[2]; Irwinda, R[3]; Leung, KY[4]; Ting, YT[5]; CAO, Y[6]; Choy, KW[7].

Review question / Objective: **Skeletal dysplasias are a group of diseases characterized by bone and joint abnormalities, which can be detected during prenatal ultrasound. Next Generation Sequencing has rapidly revolu-tionized molecular diagnostic approaches in fetuses with structural anomalies. This review studies the additional diagnostic yield of prenatal exome sequencing in fetuses with prenatal sonographic features of skeletal dysplasias.**
Eligibility criteria: **Studies were included in this review if they met the following criteria: (i) Retrospective or prospective cohorts of pregnancies undergoing ES (whole, clinical or targeted) or WGS for diagnosis of skeletal dysplasias; (ii) CMA/karyotype was negative or non-diagnostic; (iii) Testing was initiated based on the prenatal sonographic phenotype; (iv) Full text report was available in English language. Skeletal dysplasias are defined as fetus reported in-volving abnormal development, growth, and maintenance of the human skeleton system. The criteria is defined by the Fetal Medicine Foundation as either 1) shortening of long bones (usually regarded as at least less than 2 standard deviations); 2) abnormal shape of long bones; 3) reduced echogenicity of bones; and/or 4) absence of extremities.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 12 May 2023 and was last updated on 12 May 2023 (registration number INPLASY202350048).

INTRODUCTION

Review question / Objective: **Skeletal dysplasias are a group of diseases characterized by bone and joint abnormalities, which can be detected during prenatal ultrasound. Next Generation Sequencing has rapidly revolutionized molecular diagnostic approaches in fetuses with structural anomalies. This review studies the additional diagnostic yield of prenatal exome sequencing in**

fetuses with prenatal sonographic features of skeletal dysplasias.

Condition being studied: Fetuses with Sonographic Features of Skeletal Dysplasias.

METHODS

Participant or population: Fetuses who did exome sequencing after normal karyotype or chromosomal microarray analysis.

Intervention: N/A.

Comparator: normal karyotype or chromosomal microarray analysis.

Study designs to be included: Literature reviews.

Eligibility criteria: Studies were included in this review if they met the following criteria: (i) Retrospective or prospective cohorts of pregnancies undergoing ES (whole, clinical or targeted) or WGS for diagnosis of skeletal dysplasias; (ii) CMA/karyotype was negative or non-diagnostic; (iii) Testing was initiated based on the prenatal sonographic phenotype; (iv) Full text report was available in English language. Skeletal dysplasias are defined as fetus reported involving abnormal development, growth, and maintenance of the human skeleton system. The criteria is defined by the Fetal Medicine Foundation as either 1) shortening of long bones (usually regarded as at least less than 2 standard deviations); 2) abnormal shape of long bones; 3) reduced echogenicity of bones; and/or 4) absence of extremities.

Information sources: Pubmed.

Main outcome(s): This study identified 10 out of 85 studies representing 226 fetuses. The pooled additional diagnostic yield was 69.0%. The majority of the molecular diagnoses involved de novo variants (72%), while 8.7% of cases were due to inherited variants. The incremental diagnostic yield of Exome Sequencing over CMA was 67.4% for isolated short long bones and 77.2% for non-isolated cases. Among phenotypic subgroup analysis, features with the highest additional diagnostic yield were abnormal skull (83.3%) and small chest (82.5%). Prenatal exome sequencing should be considered for cases with suspected fetal skeletal dysplasias with or without a negative karyotype or CMA. Certain so-nographic features including abnormal skull and small chest may indicate a potentially higher diagnostic yield.

Quality assessment / Risk of bias analysis: N.A.

Strategy of data synthesis: The following data, where available, were extracted by two reviewers into a datasheet: study setting, sample size, study inclusion criteria, ES approach and its platform, prenatal sonographic phenotypes used for interpretation, number of fetuses with diagnostic variants, variants of uncertain significance, incidental findings, gestation at testing, test turnaround time, pregnancy outcomes, and impact on management. For studies performed with CMA in parallel with sequencing, the cases with negative CMA were extracted, in order to be comparable with other studies where chromosomal abnormalities were ruled out prior to ES.

Subgroup analysis: Various sonographic features of skeletal dysplasias could be identified prenatally. The ultrasound features are extracted from individual studies and their supplementary files. Features that were identified postnatally or during postmortem examination were not included. The different features are then grouped into two major categories which are 1) isolated short long bones – where short long bones was the only feature being described, with no suspicion of other features of skeletal dysplasias and 2) non-isolated short long bones (this category includes all cases with short long bones plus other sonographic fea-tures suggestive of skeletal dysplasias).
To look further into individual sonographic features of skeletal dysplasias and the respective clinical implications, subgroup analysis was also performed according to

the described sonographic features. These features included:
1. abnormal curvature of long bones;
2. suspected fracture of bones, including those with angulated long bones;
3. reduced or abnormal ossification of bones;
4. absent bones (including radius, tibia, etc.),
5. absent phalanges, or poly/syndactyly;
6. abnormal joint posture, including talipes, and contractures;
7. abnormal skull, including abnormal skull shape, macrocephaly;
8. abnormal facial profile, including flattened face, absent nasal bone, retro / microgna-thia;
9. small chest, including bell-shaped thorax, small chest circumference; abnormal spine, including scoliosis;
10. hydropic features, including cystic hygroma, subcutaneous edema, pleural effusion.

Sensitivity analysis: N.A.

Language restriction: English full articles availble only.

Country(ies) involved: Hong Kong SAR, HONG KONG; Indonesia.

Keywords: Whole exome sequencing; CMA; Prenatal diagnosis; Skeletal dysplasia; Systematic review.

Contributions of each author:
Author 1 - Kai Yeung Tse.
Author 2 - Ilham Utama Surya.
Author 3 - Rima Irwinda.
Author 4 - Kwok Yin Leung.
Author 5 - Yuen Ha Ting.
Author 6 - Ye Cao.