INPLASY PROTOCOL

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Conflicts of interest:
None declared.

Diagnostic yield of prenatal Exome Sequencing in fetal Central Nervous System Anomalies: systematic review and meta-analysis

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Review question / Objective: **The aim of this study is to assess the incremental diagnostic yield of prenatal exome sequencing analysis after inconclusive result of karyotype and Chromosomal Microarray Analysis in Central Nervous System fetal anomalies detected by ultrasound.**
Eligibility criteria: **Inclusion criteria: papers describing fetuses with the indication to perform genome-wide sequencing studies based on prenatal imaging findings who underwent previous inconclusive karyotype and Chromosomal Microarray Analyses. The diagnostic yields of prenatal exome sequencing analysis OR prenatal genome sequencing analysis (with ≥20–30x depth of coverage and including only Single Nucleotide Variants) will be pooled in a meta-analysis. Exclusion Criteria: case reports and papers describing less than 5 cases; papers not describing the application of genome-wide sequencing studies based on prenatal imaging findings; papers describing genome-wide sequencing studies performed after negative targeted panels; papers describing fetuses with recurrent phenotypes as an explicitly selection criterium.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 01 May 2023 and was last updated on 01 May 2023 (registration number INPLASY202350001).

INTRODUCTION

Review question / Objective: **The aim of this study is to assess the incremental diagnostic yield of prenatal exome sequencing analysis after inconclusive result of karyotype and Chromosomal Microarray Analysis in Central Nervous System fetal anomalies detected by ultrasound.**

Rationale: **The molecular prenatal diagnosis of fetal structural anomalies is a dynamic growing field. Genome-wide**

sequencing analysis through Next Generation Sequencing technologies (prenatal exome sequencing and genome sequencing) has rapidly revolutionized clinical genetics and diagnostics, with a significant impact in prenatal diagnosis.
Optimized indications, detection rates in different categories of fetal anomalies, and interpretation of variants pathogenicity are still under investigation.
In this systematic review and meta-analysis we decided to focus on Central Nervous System anomalies, to assess the incremental diagnostic yield of trio-based prenatal exome sequencing application, after karyotype and Chromosomal Microarray Analysis inconclusive results.

Condition being studied: Fetuses affected by Central Nervous System Anomalies, apparently isolated or non-isolated at time of inclusion, detected by prenatal ultrasound scans.

METHODS

Search strategy: The research was conducted following PRISMA guidelines (Page et al., 2021). We searched the Pubmed database (https://pubmed.ncbi.nlm.nih.gov/,) lastly accessed on 28-2-2023 for ("fetus" OR "fetuses" OR "foetus" OR "foetuses" OR "fetal" OR "foetal" OR "prenatal" OR "pre-natal") AND ("Central nervous system" OR "CNS" OR "brain" OR "cerebral" OR "cerebellar" OR "cerebellum" OR "vermis" OR "vermian" OR "blake" OR "Blake's" OR "hemispheres" OR "hemispheric" "hemisphere" OR "interhemispheric" OR "posterior fossa" OR "cisterna magna" OR "MCM" OR "Dandy-Walker" OR "Dandy Walker" OR "DWM" OR "hydrocephaly" OR "hydrocephalus" OR "ventriculomegaly" OR "corpus callosum" OR "callosal" OR "ACC" OR "pACC" OR "DCC" OR "Probst" OR "septo-optic dysplasia" OR "SOD" OR "cavum" or "CSP" OR "chiari" OR "acrania" OR "spina bifida" OR "anencephaly" OR "anencephalia" OR " anencephalic" OR "hydranencephaly" OR "hydranencephalia" OR "schizencephaly" OR "schizencephalic" OR "porencephaly" OR "porencephalic" OR "cephalocele" OR "encephalocele" OR "meningocele" OR "meningoencephalocele" OR "neural tube" OR "cerebrospinal fluid" OR "spinal fluid" OR "CSF" OR "NTD" OR "microcephaly" OR "megalencephaly" OR "hemimegalencephaly" OR "holoprosencephaly" OR "HPE" OR "cortical" or "cortex" OR "sulcus" OR "sulci" OR "fissure" OR "fissures" OR "gyrus" OR "gyri" OR "gyra" OR "subcortical" OR "lissencephaly" OR "cobblestone" OR "pachygiria" OR "polymicrogyria" OR "agyria" OR "heterotopia" OR "telencephalon" OR "telencephalic" OR "prosencephalon" OR "prosencephalic" OR "diencephalon" OR "diencephalic" OR "brainstem" or "brain stem" OR "mesencephalon" OR "mesencephalic" OR "pons" OR "pontine" OR "pontocerebellar" OR "medulla" OR "medullar" OR "arachnoid" OR "dural" OR "neuronal migration" OR "migrational" OR "encephalomalacia" OR "rhombencephalosynapsis" OR "grey matter" OR "white matter" OR "periventricular" OR "encephalopathy" OR "encephalopaties" OR "leukoencephalopathy" OR "acqueduct" OR "ependymal" OR "ependyma") AND ("WES" OR "CES" OR "exome sequencing" OR "Mendeliome" OR "genome sequencing" OR "GS" OR "WGS" OR "Whole-exome" OR "Whole-genome" OR "medical-exome" OR "clinical-exome") with a 10-year filter for publication date.

Participant or population: Fetuses presenting with Central Nervous System Anomalies detected at prenatal ultrasound and undergoing genome-wide sequencing studies.

Intervention: Not applicable.

Comparator: Not applicable.

Study designs to be included: Prospective and Retrospective Cohorts Studies.

Eligibility criteria: Inclusion criteria: papers describing fetuses with the indication to perform genome-wide sequencing studies based on prenatal imaging findings who underwent previous inconclusive karyotype

and Chromosomal Microarray Analyses. The diagnostic yields of prenatal exome sequencing analysis OR prenatal genome sequencing analysis (with ≥20–30x depth of coverage and including only Single Nucleotide Variants) will be pooled in a meta-analysis. Exclusion Criteria: case reports and papers describing less than 5 cases; papers not describing the application of genome-wide sequencing studies based on prenatal imaging findings; papers describing genome-wide sequencing studies performed after negative targeted panels; papers describing fetuses with recurrent phenotypes as an explicitly selection criterium.

Information sources: Electronic Databases (PubMed), Literature Search, Citation Searching from included studies.

Main outcome(s): The effect of interest is the incremental diagnostic yield of prenatal exome sequencing analysis over karyotype and chromosomal microarray analysis in fetuses affected by Central Nervous System Anomalies.

Additional outcome(s): None.

Quality assessment / Risk of bias analysis: The risk of bias will be assessed with Newcastle-Ottawa Scale.

Strategy of data synthesis: We fit a logistic random mixed-effects model with intercept only. The choice of a mixed-effect model, with a random component, is driven by the need of accounting for between-study heterogeneity. 95%-Clopper-Pearson confidence intervals (C.I.) for individual studies are calculated. All statistical analysis is performed in R 4.2.2 (R Core Team (2022) using the meta package v6.1-0 (Balduzzi et al., 2019; Harrer et al., 2019).

Subgroup analysis: The fetuses will be divided in the following subgroups: apparently isolated Central Nervous System anomaly, non-isolated anomalies (two or more anomalies in Central Nervous System or extra-Central Nervous System), CNS-only related anomalies (one or more).
The data synthesis strategy and sensitivity analysis stated in point 22 and 24 will be applied to each subgroup.

Sensitivity analysis: The effect of interest of the meta-analysis is the incremental diagnostic yield of prenatal exome sequencing over karyotype and Chromosomal Microarray Analysis in fetuses affected by CNS anomalies.
Firstly, we will pool in a meta-analysis the reported diagnostic yield of prenatal exome sequencing over the number of non-diagnosed fetuses through karyotype and Chromosomal Microarray Analysis in all studies included from the systematic literature review.
Secondly, we will fit a different model considering also the available prenatal genome sequencing studies in literature and only including the reported diagnostic yield for Single Nucleotide Variants (SNVs) and prenatal genome sequencing analyses performed with ≥20–30X depth of coverage. We underline that the SNVs included are also detectable with prenatal exome sequencing analysis. However, we will fit the two models to observe if the results will be affected by the decision of including or not prenatal genome sequencing studies.
Thirdly, we will estimate the between-study variance (Tau-squared) through maximum likelihood estimator. Our study may present a risk of bias in this sense, because some studies present a much higher number of total cases than others. To better analyze the influence of heterogeneity on the fitted model, the leveraging of the different studies on the pool estimate will be analyzed. In particular, a leave-one-out analysis will be performed and a Baujat plot (Baujat et al., 2002) will be inspected.

Language restriction: Only papers with full text available in English language are included.

Country(ies) involved: Italy.

Keywords: prenatal exome sequencing, genome-wide prenatal exome sequencing, prenatal genome sequencing, Central Nervous System Malformations.

Contributions of each author:

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