# Genetically-modified animals as models of neurodevelopmental conditions: an umbrella review

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## CRediT Contributions

EW = Conceptualisation; Project administration; Writing – original draft

GC = Writing – review & editing

MM = Supervision; Writing – review & editing

PK = Supervision; Writing – review & editing

ESS = Supervision; Writing – review & editing

## Funding

EW is funded by a Simons Initiative for the Developing Brain PhD studentship (SFARI #529085).

## Conflicts of interests

The authors declare no conflicts of interest.

## Ethics approval

This study will only examine data from published systematic reviews, so ethical approval is not required.

## Supplements

Completed PRISMA 2020 for Abstracts Extension: https://osf.io/bczkv

Completed PRISMA 2015 for Protocols Extension: https://osf.io/2cmwb

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# Abstract

## Objective

Using genetically-modified animals to model neurodevelopmental conditions (NDCs) helps better our understanding of their underlying biology. *In vivo* research has unique characteristics not shared with clinical research, meaning approaches to systematic review must be adapted to this context. We aim to conduct an umbrella review to identify the quantity, characteristics, and reporting quality of systematic reviews which synthesise research using genetically-modified animals to model NDCs.

## Search strategy

We will search PubMed, Embase, and Web of Science and include systematic reviews synthesising research using genetically-modified animals to model NDCs where the modified gene is one of a list of 102 genes associated with NDCs identified through large-scale exome sequencing, or FMR! Or MECP2 We will place no restriction on publication date or language and will include conference abstracts and preprints in addition to peer-reviewed journal articles.

## Screening and annotation

Two independent reviewers will screen studies based on full text, and extract data from included reviews. We will annotate various characteristics from included systematic reviews and assess the reporting quality of each included review using an adapted version of the PRISMA checklist (PRISMA-Pre). We will not conduct a risk of bias assessment.

## Data synthesis

We will present a descriptive, tabular summary of the data and PRISMA-Pre assessment scores.

## Funding and registration

This review is funded by a Simons Initiative for the Developing Brain PhD studentship (SFARI:#529085). The funder played no role in the development of this Stage 1 Registered Report. This Report is registered on the Open Science Framework (DOI:10.17605/OSF.IO/7C5WU).

Abstract word count: 249

## Keywords

Umbrella review; Evidence synthesis; Neurodevelopmental conditions; Epilepsy; Autism spectrum condition; Intellectual disability; Animal models

# Strengths and limitations of this study

* By pre-registering our study using the Registered Report format, our rationale and proposed methods have been peer-reviewed, meaning we have been able to make improvements to our proposed study design prior to beginning our research.
* To maximise the sensitivity (recall) of our search, we will use broad search terms related to neurodevelopmental conditions, intellectual disability, epilepsy, and autism spectrum condition, in parallel with terms related to individual associated genes, and screen studies based on full text to avoid erroneously excluding systematic reviews which do not report their inclusion criteria in their abstract.
* We will use a draft extension of the PRISMA guidelines specifically designed for systematic reviews of animal studies (PRISMA-Pre), to assess the reporting quality of included systematic reviews.
* This extension remains in draft, is not yet an official extension to PRISMA and may be subject to change. However, for this review, we will use the version of the extension that is published in Hunniford et al. (2021; also included in appendix 2).

# Abbreviations

ASC Autism Spectrum Condition

ASySD Automated Systematic Search Deduplicator

DOI Digital Object Identifier

FXS Fragile X Syndrome

ID Intellectual Disability

NCBI National Center for Biotechnology Information

NDC Neurodevelopmental Condition

PRISMA Preferred Reporting Items for Systematic reviews and Meta-Analyses

PRISMA\_Pre Preferred Reporting Items for Systematic reviews and Meta-Analyses of Preclinical Research

RTT Rett Syndrome

SyRF Systematic Review Facility

# Introduction

Up to 40% of neurodevelopmental conditions (NDCs), characterised by intellectual disability (ID), epilepsy, and autism spectrum condition (ASC), are caused by single genetic alterations, often occurring *de novo* in that individual (Brunet et al., 2021). These single gene alterations provide an opportunity to develop animal models harbouring those alterations, which may give insights into NDC pathophysiology and treatment more generally, including NDCswith polygenic or environmental causes. Such models can be used to investigateassociated cellular, circuit, and behavioural traits. Researchers have developed numerous genetically-modified animal models to study ASD. Research using these models plays a vital role in developing our understanding of the biology underlying NDCs (basic research) and in the testing of potential drug treatments (preclinical research). However, despite extensive research, successful translation of laboratory findings to the clinic is rare (Pankevich et al., 2013; Silverman et al., 2022).

Systematic review provides a well-developed method for identifying areas of poor methodological quality or high risk of bias within research literature. Systematic review is a research method used to summarise and appraise all available evidence related to a pre-specified topic (Egger et al., 2001), and can identify areas for improvements which might increase internal validity and research rigour and reproducibility.

Clinicians have used systematic reviews to inform evidence-based healthcare since the 1980s. Findings from such reviews have led to considerable improvements in the way clinical trials are conducted and reported (Plint et al., 2006). Over the last two decades, researchers have adopted systematic review methods to summarise and appraise evidence from laboratory animal studies (de Vries et al., 2014) and have achieved similar success in research improvement (McCann et al., 2016; Ramirez et al., 2017). However, the fundamental differences between clinical and animal studies mean that systematic review methodologies must be appropriately adapted (Hunniford et al., 2021). The development of several tools has been instrumental in supporting researchers conducting systematic reviews and meta-analyses of animal studies, including checklists for assessing the risk of bias (Hooijmans et al., 2014) and reporting quality (Macleod et al., 2004) of laboratory animal studies, and a protocol template for systematic reviews of animal intervention studies (de Vries et al., 2015). Despite this, reporting quality of animal systematic reviews is low (Mueller et al., 2014; Hunniford et al., 2021). Currently in development is an extension to the PRISMA guidelines specifically designed for preclinical systematic reviews (PRISMA-Pre), which aim to improve the reporting quality of preclinical systematic reviews (Hunniford et al., 2021).

Here, we aim to conduct an umbrella review to identify the quantity, characteristics, and reporting quality of systematic reviews which synthesise research using genetically-modified animals to model NDCs. We will assess the reporting quality of included systematic reviews using the PRISMA-Pre checklist. We are interested in models with alterations in any of the 102 high-confidence genes identified via large-scale exome sequencing by Satterstrom et al. (2020), and models of Fragile X Syndrome (FXS) and Rett Syndrome (RTT) which have alterations in the FMR1 and MECP2 genes respectively. Although neither FXS nor RTT are included in the list of 102 genes, they are extensively researched monogenic NDCs.

This review will not synthesise evidence from existing reviews. The rationale behind this review is that by identifying the quantity and reporting quality of existing systematic reviews in this area, we can inform guidance on how future systematic reviews within this research field should be conducted. Findings from this review will be used to inform the development of a living evidence summary of research using genetically-modified animals to model NDCs, a preliminary protocol for which has been preregistered on the Open Science Framework (OSF; DOI:10.17605/OSF.IO/GFTZP).

# Methods

To date, we have completed preliminary searches and optimised our search strategy to inform the development of this protocol.

## Bibliographic search

We will conduct a systematic literature search on three electronic databases: PubMed including Medline (accessed via NCBI), Embase (accessed via Ovid), and Web of Science Core Collection.

Our search strategy includes three components: (1) broad terms related to NDCs, ID, epilepsy, and ASC, and associated genes; (2) terms related to animal models, and (3) terms related to systematic reviews or meta-analyses. Terms used to identify animal models were taken from van der Mierden et al. (2022) and terms used to identify systematic reviews and meta-analyses were taken from Langendam et al. (2021). Full search terms are given in Appendix 1. We will also contact authors of PROSPERO registrations of systematic reviews relating to autism to establish if their review has been published.

Where citations appear in multiple databases, we will remove duplicate versions of the citation using the ASySD tool (Hair et al., 2021).

## Screening

We will upload our search results, with duplicate citations removed, to the Systematic Review Facility (SyRF) platform (Bahor et al., 2021) for screening, data extraction and management of records. Two independent reviewers will screen each publication for inclusion and any disagreements will be reconciled by a third independent reviewer. We plan one round of screening, where we will screen the full texts of all studies retrieved from our searches against our inclusion and exclusion criteria, to avoid potentially excluding systematic reviews where the decision for inclusion rests on information contained in the full text but not in the abstract (Wilson et al., 2022).

We will retrieve full text PDF files using in-house full text retrieval code or via hand-searching. If we cannot access the full text using our institutional subscriptions, we will request the full text via interlibrary loan. The full texts of relevant articles which are not written in English will be translated into English using Google Translate.

## Inclusion and exclusion criteria

Studies will be screened according to the criteria outlined below:

* **Study design** – We will only include systematic reviews or meta-analyses that include animal studies, either as a review limited to animal studies or ones which include them alongside other study types (e.g. clinical studies) and exclude all other study designs.
* **Animal models** – We will only include systematic reviews synthesising research using genetically-modified animals to model NDCs where the modified gene appears on the list of 102 genes identified via large-scale exome sequencing by Satterstrom et al. (2020); or genetically-modified animal models of Fragile X Syndrome or Rett Syndrome; or other genetic models of NDCs characterised by ID, epilepsy, and ASC. Animal models may be of any species. . A diverse range of other models of NDCs are available but are not the focus of this review and will not be included.
* **Publication type** – We will include systematic reviews published in peer-reviewed journals, as conference abstracts, or as preprints (where they are identified in searches). We will not search dedicated preprint servers. We will place no restriction on publication date or language.

# Data extraction

Two independent reviewers will conduct data extraction. Discrepancies between reviewer decisions will be reconciled by a third independent reviewer. We will carry out data extraction using the SyRF platform, and will collect the following information:

## Bibliographic data

We will extract the names of first authors, year of publication, title, and DOI of each included study.

## Characteristics

To understand the purpose and scope of included systematic reviews, we will extract the following characteristics from each:

* The aim of each systematic review and the primary research question each review seeks to ask
* Whether the review only included animal studies, or also included clinical or in vitro studies
* Which animal models the review included
* The total number of studies included in the systematic review
* The total number of studies investigating relevant animal models

## Reporting quality

There are two broad approaches to evaluating the quality of systematic reviews: addressing the completeness of reporting or assessing the risks of bias arising from the approaches which were taken. Precise evaluation of the second requires completeness of the first, so these are overlapping but distinct. Here we will assess the completeness of reporting (reporting quality) of each included systematic review using the 46-point checklist developed by Hunniford et al. (2021). The checklist is adapted from the PRISMA guidelines for systematic reviews and is more specific to systematic reviews of animal studies. However, the checklist is not currently an official extension to PRISMA. Although it is not recommended to use the general PRISMA guidelines to assess *in vivo* systematic review reporting quality, the adapted checklist for preclinical systematic reviews has been designed for this purpose. There are no validated tools for assessing risks of bias in systematic reviews of *in vivo* research, and we will not conduct a formal assessment of risk of bias.

The checklist items are written in full in Appendix 2.

# Data synthesis

We will not conduct a meta-analysis. However, we will present a descriptive, tabular summary of the bibliographic, characteristics, and reporting quality data extracted from each included systematic review. We will score each included systematic review using the PRISMA-Pre checklist and provide a summary table detailing which items of the checklist each review met. Additionally, the checklist will allow us to assess which tools are currently being used to conduct systematic reviews in this field, including the tools used to screen studies (Checklist Item 6a), extract numerical data (Checklist Item 17a), and measure study quality or risk of bias (Checklist Item 19).

## Data availability

This protocol will be shared under a Creative Commons by Attribution (CC-BY) license. Data generated from this umbrella review, and the code used to process the data, will be shared online under a Creative Commons by Attribution (CC-BY) license. The final manuscript will be published open access.

# Appendices

## Appendix 1: Final full search terms

Animal models search terms are taken from van der Mierden et al. (2022) and systematic review search terms are taken from Langendam et al. (2021).

|  |  |
| --- | --- |
| **NCBI PubMed search strategy** | |
| **#** | **Search terms** |
| 1 | "neurodevelopmental disorders"[MeSH] OR neurodevelopment[TiAb] OR "neurodevelopmental delay"[TiAb] OR intellectual disability[MeSH] OR "intellectual disability"[TiAb] OR "intellectual disabilities"[TiAb] OR epilepsy[MeSH] OR epilepsy[TiAb] OR "autism spectrum disorder"[MeSH] OR ASD[TiAb] OR autism[TiAb] OR autistic[TiAb] |
| 2 | "Fragile X Syndrome"[MeSH] OR "fragile x mental retardation protein"[MeSH] OR "Fragile X Syndrome"[TiAB] OR "fragile x mental retardation protein"[TiAB] OR "FMR1"[TiAB] OR "Rett Syndrome"[MeSH] OR "Methyl-CpG-Binding Protein 2"[MeSH] OR "Rett Syndrome"[TiAB] OR "Methyl-CpG-Binding Protein 2"[TiAB] OR MECP2[TiAb] |
| 3 | "CHD8"[TiAb] OR "SCN2A"[TiAb] OR "SYNGAP1"[TiAb] OR "ADNP"[TiAb] OR "FOXP1"[TiAb] OR "POGZ"[TiAb] OR "ARID1B"[TiAb] OR "SUV420H1"[TiAb] OR "DYRK1A"[TiAb] OR "SLC6A1"[TiAb] OR "GRIN2B"[TiAb] OR "PTEN"[TiAb] OR "SHANK3"[TiAb] OR "MED13L"[TiAb] OR "GIGYF1"[TiAb] OR "CHD2"[TiAb] OR "ANKRD11"[TiAb] OR "ANK2"[TiAb] OR "ASH1L"[TiAb] OR "TLK2"[TiAb] OR "DNMT3A"[TiAb] OR "DEAF1"[TiAb] OR "CTNNB1"[TiAb] OR "KDM6B"[TiAb] OR "DSCAM"[TiAb] OR "SETD5"[TiAb] OR "KCNQ3"[TiAb] OR "SRPR"[TiAb] OR "KDM5B"[TiAb] OR "WAC"[TiAb] OR "SHANK2"[TiAb] OR "NRXN1"[TiAb] OR "TBL1XR1"[TiAb] OR "MYT1L"[TiAb] OR "BCL11A"[TiAb] OR "RORB"[TiAb] OR "RAI1"[TiAb] OR "DYNC1H1"[TiAb] OR "DPYSL2"[TiAb] OR "AP2S1"[TiAb] OR "KMT2C"[TiAb] OR "PAX5"[TiAb] OR "MKX"[TiAb] OR "GABRB3"[TiAb] OR "SIN3A"[TiAb] OR "MBD5"[TiAb] OR "MAP1A"[TiAb] OR "STXBP1"[TiAb] OR "CELF4"[TiAb] OR "PHF12"[TiAb] OR "TBR1"[TiAb] OR "PPP2R5D"[TiAb] OR "TM9SF4"[TiAb] OR "PHF21A"[TiAb] OR "PRR12"[TiAb] OR "SKI"[TiAb] OR "ASXL3"[TiAb] OR "SPAST"[TiAb] OR "SMARCC2"[TiAb] OR "TRIP12"[TiAb] OR "CREBBP"[TiAb] OR "TCF4"[TiAb] OR "CACNA1E"[TiAb] OR "GNAI1"[TiAb] OR "TCF20"[TiAb] OR "FOXP2"[TiAb] OR "NSD1"[TiAb] OR "TCF7L2"[TiAb] OR "LDB1"[TiAb] OR "EIF3G"[TiAb] OR "PHF2"[TiAb] OR "KIAA0232"[TiAb] OR "VEZF1"[TiAb] OR "GFAP"[TiAb] OR "IRF2BPL"[TiAb] OR "ZMYND8"[TiAb] OR "SATB1"[TiAb] OR "RFX3"[TiAb] OR "SCN1A"[TiAb] OR "PPP5C"[TiAb] OR "TRIM23"[TiAb] OR "TRAF7"[TiAb] OR "ELAVL3"[TiAb] OR "GRIA2"[TiAb] OR "LRRC4C"[TiAb] OR "CACNA2D3"[TiAb] OR "NUP155"[TiAb] OR "KMT2E"[TiAb] OR "NR3C2"[TiAb] OR "NACC1"[TiAb] OR "PTK7"[TiAb] OR "PPP1R9B"[TiAb] OR "GABRB2"[TiAb] OR "HDLBP"[TiAb] OR "TAOK1"[TiAb] OR "UBR1"[TiAb] OR "TEK"[TiAb] OR "KCNMA1"[TiAb] OR "CORO1A"[TiAb] OR "HECTD4"[TiAb] OR "NCOA1"[TiAb] OR "DIP2A"[TiAb] |
| 4 | #1 OR #2 OR #3 |
| 5 | (animal experimentation[MeSH] OR models, animal[MeSH] OR Animals[Mesh:noexp] OR animal population groups [MeSH] OR chordata[MeSH Terms:noexp] OR vertebrates[MeSH Terms:noexp] OR amphibians[MeSH] OR birds[MeSH] OR fishes[MeSH] OR reptiles[MeSH] OR mammals[MeSH Terms:noexp] OR primates[MeSH Terms:noexp] OR eutheria[MeSH Terms:noexp] OR artiodactyla[MeSH] OR carnivore[MeSH] OR cephalopoda[MeSH] OR cetacea[MeSH] OR chiroptera[MeSH] OR elephants[MeSH] OR hyraxes[MeSH] OR insectivora[MeSH] OR lagomorpha[MeSH] OR marsupialia[MeSH] OR monotremata[MeSH] OR perissodactyla[MeSH] OR Proboscidea Mammal[MeSH Terms:noexp] OR rodentia[MeSH] OR scandentia[MeSH] OR sirenia[MeSH] OR cingulata[MeSH] OR haplorhini[MeSH Terms:noexp] OR strepsirhini[MeSH] OR platyrrhini[MeSH] OR tarsii[MeSH] OR catarrhini[MeSH Terms:noexp] OR cercopithecidae[MeSH] OR hylobatidae[MeSH] OR hominidae[MeSH Terms:noexp] OR gorilla gorilla[MeSH] OR pan paniscus[MeSH] OR pan troglodytes[MeSH] OR pongo[MeSH]) OR ((rat[tiab] OR rats[tiab] OR animal[tiab] OR animals[tiab] OR mice[tiab] OR in vivo[tiab] OR mouse[tiab] OR rabbit[tiab] OR rabbits[tiab] OR murine[tiab] OR pig[tiab] OR pigs[tiab] OR dog[tiab] OR dogs[tiab] OR bovine[tiab] OR fish[tiab] OR vertebrate[tiab] OR vertebrates[tiab] OR cat[tiab] OR cats[tiab] OR rodent[tiab] OR rodents[tiab] OR mammal[tiab] OR mammals[tiab] OR chicken[tiab] OR chickens[tiab] OR monkey[tiab] OR monkeys[tiab] OR sheep[tiab] OR canine[tiab] OR canines[tiab] OR porcine[tiab] OR cattle[tiab] OR bird[tiab] OR birds[tiab] OR hamster[tiab] OR hamsters[tiab] OR primate[tiab] OR primates[tiab] OR cow[tiab] OR cows[tiab] OR chick[tiab] OR horse[tiab] OR horses[tiab] OR avian[tiab] OR avians[tiab] OR calf[tiab] OR swine[tiab] OR swines[tiab] OR xenopus[tiab] OR turkeys[tiab] OR bear[tiab] OR bears[tiab] OR frog[tiab] OR frogs[tiab] OR zebrafish[tiab] OR goat[tiab] OR goats[tiab] OR equine[tiab] OR calves[tiab] OR poultry[tiab] OR macaque[tiab] OR macaques[tiab] OR mole[tiab] OR moles[tiab] OR ovine[tiab] OR lamb[tiab] OR lambs[tiab] OR fishes[tiab] OR diptera[tiab] OR amphibian[tiab] OR amphibians[tiab] OR snake[tiab] OR snakes[tiab] OR ruminant[tiab] OR ruminants[tiab] OR hen[tiab] OR hens[tiab] OR piglet[tiab] OR piglets[tiab] OR feline[tiab] OR felines[tiab] OR simian[tiab] OR simians[tiab] OR laevis[tiab] OR trout[tiab] OR trouts[tiab] OR teleost[tiab] OR teleosts[tiab] OR salmon[tiab] OR salmons[tiab] OR seal[tiab] OR seals[tiab] OR bull[tiab] OR bulls[tiab]OR ewe[tiab] OR ewes[tiab] OR hedgehog[tiab] OR hedgehogs[tiab] OR macaca[tiab] OR macacas[tiab] OR proteus[tiab] OR pigeon[tiab] OR pigeons[tiab] OR bat[tiab] OR bats[tiab] OR duck[tiab] OR ducks[tiab] OR chimpanzee[tiab] OR chimpanzees[tiab] OR baboon[tiab] OR baboons[tiab] OR deer[tiab] OR rana[tiab] OR ranas[tiab] OR carp[tiab] OR carps[tiab] OR heifer[tiab] OR swallow[tiab] OR swallows[tiab] OR lizard[tiab] OR lizards[tiab] OR canis[tiab] OR sow[tiab] OR sows[tiab] OR cynomolgus[tiab] OR quail[tiab] OR quails[tiab] OR reptile[tiab] OR reptiles[tiab] OR turtle[tiab] OR turtles[tiab] OR buffalo[tiab] OR gerbil[tiab] OR gerbils[tiab] OR boar[tiab] OR boars[tiab] OR squirrel[tiab] OR squirrels[tiab] OR oncorhynchus[tiab] OR mus[tiab] OR toad[tiab] OR toads[tiab] OR fowl[tiab] OR fowls[tiab] OR rerio[tiab] OR danio[tiab] OR ara[tiab] OR aras[tiab] OR musculus[tiab] OR tadpole[tiab] OR tadpoles[tiab] OR mulatta[tiab] OR salmo[tiab] OR ram[tiab] OR eagle[tiab] OR eagles[tiab] OR ferret[tiab] OR ferrets[tiab] OR goldfish[tiab] OR catfish[tiab] OR whale[tiab] OR whales[tiab] OR fox[tiab] OR foxes[tiab] OR ape[tiab] OR apes[tiab] OR elephant[tiab] OR elephants[tiab] OR bos[tiab] OR marmoset[tiab] OR marmosets[tiab] OR cod[tiab] OR cods[tiab] OR shark[tiab] OR sharks[tiab] OR wolf[tiab] OR eel[tiab] OR eels[tiab] OR auratus[tiab] OR rattus[tiab] OR zebra[tiab] OR zebras[tiab] OR tilapia[tiab] OR tilapias[tiab] OR gilt[tiab] OR camel[tiab] OR camels[tiab] OR squid[tiab] OR 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amniotes[tiab] OR elasmobranch[tiab] OR emu[tiab] OR emus[tiab] OR peromyscus[tiab] OR hominid[tiab] OR hominids[tiab] OR bubalus[tiab] OR crotalus[tiab] OR gull[tiab] OR gulls[tiab] OR anas[tiab] OR anura[tiab] OR lemur[tiab] OR lemurs[tiab] OR crow[tiab] OR crows[tiab] OR camelus[tiab] OR gibbon[tiab] OR gibbons[tiab] OR waterfowl[tiab] OR parrot[tiab] OR parrots[tiab] OR eels[tiab] OR cob[tiab] OR stickleback[tiab] OR sticklebacks[tiab] OR columba[tiab] OR mesocricetus[tiab] OR ambystoma[tiab] OR raven[tiab] OR ravens[tiab] OR gadus[tiab] OR penguin[tiab] OR penguins[tiab] OR orangutan[tiab] OR orangutans[tiab] OR sturgeon[tiab] OR sturgeons[tiab] OR cuniculus[tiab] OR aves[tiab] OR virginianus[tiab] OR cephalopod[tiab] OR cephalopods[tiab] OR cebus[tiab] OR sparus[tiab] OR tortoise[tiab] OR tortoises[tiab] OR guttata[tiab] OR morhua[tiab] OR unguiculatus[tiab] OR dogfish[tiab] OR vulpes[tiab] OR mallard[tiab] OR mallards[tiab] OR apodemus[tiab] OR alligator[tiab] OR 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OR gobiocypris[tiab] OR bearded dragon[tiab] OR bearded dragons[tiab] OR sarotherodon[tiab] OR talpa[tiab] OR discoglossus[tiab] OR hagfishes[tiab] OR sphenodon[tiab] OR gudgeon[tiab] OR amphiuma[tiab] OR aythya[tiab] OR tenrec[tiab] OR tenrec[tiab] OR hominidae[tiab] OR risoria[tiab] OR salamandridae[tiab] OR camelidae[tiab] OR columbiformes[tiab] OR latimeria[tiab] OR plover[tiab] OR plovers[tiab] OR afrotheria[tiab] OR falco sparverius[tiab] OR polecat[tiab] OR polecats[tiab] OR crotalinae[tiab] OR salvadora[tiab] OR tarsier[tiab] OR lucioperca[tiab] OR anchovies[tiab] OR lungfishes[tiab] OR terrapin[tiab] OR dromaius novaehollandiae[tiab] OR lateolabrax[tiab] OR eigenmannia[tiab] OR pelamis[tiab] OR theropithecus[tiab] OR murinae[tiab] OR gander[tiab] OR gymnotus[tiab] OR pseudacris[tiab] OR gymnophiona[tiab] OR gymnotiformes[tiab] OR laticauda[tiab] OR falconiformes[tiab] OR dugong[tiab] OR dugongs[tiab] OR pintail[tiab] OR pintails[tiab] OR rook[tiab] OR rooks[tiab] ORl asiurus[tiab] OR catshark[tiab] OR catsharks[tiab] OR micropogonias[tiab] OR red junglefowl[tiab] OR paddlefish[tiab] OR ophiophagus[tiab] OR hollandicus[tiab] OR nymphicus[tiab] OR pimelodidae[tiab] OR aepyceros[tiab] OR cobitidae[tiab] OR strigiformes[tiab] OR cobitis[tiab] OR dormice[tiab] OR alytes[tiab] OR calloselasma[tiab] OR guanaco[tiab] OR phasianidae[tiab] OR round goby[tiab] OR trichogaster[tiab] OR catarrhini[tiab] OR eelpout[tiab] OR eelpouts[tiab] OR galaxias[tiab] OR gaur[tiab] OR pungitius[tiab] OR suslik[tiab] OR susliks[tiab] OR flatfishes[tiab] OR percidae[tiab] OR caprinae[tiab] OR todarodes[tiab] OR osmerus[tiab] OR ameiurus[tiab] OR anthropoidea[tiab] OR castor canadensis[tiab] OR pouting[tiab] OR poutings[tiab] OR tetraodontiformes[tiab] OR arvicolinae[tiab] OR siamang[tiab] OR siamangs[tiab] OR castor fiber[tiab] OR nomascus[tiab] OR red knot[tiab] OR red knots[tiab] OR syngnathidae[tiab] OR iguanidae[tiab] OR eretmochelys[tiab] OR ursidae[tiab] OR 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OR centrarchidae[tiab] OR gloydius[tiab] OR laurasiatheria[tiab] OR limosa[tiab] OR psittacula[tiab] OR leporidae[tiab] OR proteidae[tiab] OR zander[tiab] OR zanders[tiab] OR arapaima[tiab] OR bagridae[tiab] OR cyprinodontidae[tiab] OR mithun[tiab] OR pandion[tiab] OR jackdaw[tiab] OR jackdaws[tiab] OR procyonidae[tiab] OR carus[tiab] OR jaculus[tiab] OR salmoniformes[tiab] OR common sole[tiab] OR common soles[tiab] OR protobothrops[tiab] OR calamita[tiab] OR brachyteles[tiab] OR trionyx[tiab] OR turdidae[tiab] OR boidae[tiab] OR luscinia[tiab] OR pugnax[tiab] OR euarchontoglires[tiab] OR saithe[tiab] OR saithes[tiab] OR symphalangus[tiab] OR aardvark[tiab] OR aardvarks[tiab] OR oystercatcher[tiab] OR oystercatchers[tiab] OR arius[tiab] OR corydoras[tiab] OR poacher[tiab] OR poachers[tiab] OR aurochs[tiab] OR cebuella[tiab] OR crecca[tiab] OR lemuridae[tiab] OR sirenia[tiab] OR lemmus[tiab] OR perdix[tiab] OR glires[tiab] OR lepidosaur[tiab] OR muskox[tiab] OR deinagkistrodon[tiab] OR 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bushbabies[tiab] OR muscicapidae[tiab] OR alligatoridae[tiab] OR fuligula[tiab] OR bush baby[tiab] OR guineafowl[tiab] OR spoonbill[tiab] OR spoonbills[tiab] OR viverridae[tiab] OR catostomidae[tiab] OR zebrafishes[tiab] OR ibexes[tiab] OR vendace[tiab] OR estrildidae[tiab] OR monotremata[tiab] OR sepiella[tiab] OR ambystomatidae[tiab] OR shelduck[tiab] OR shelducks[tiab] OR treeshrew[tiab] OR treeshrews[tiab] OR hoplobatrachus[tiab] OR pochard[tiab] OR hoolock[tiab] OR hoolocks[tiab] OR lynxes[tiab] OR antilope[tiab] OR antilopes[tiab] OR blackbuck[tiab] OR blackbucks[tiab] OR cricetinae[tiab] OR paramisgurnus[tiab] OR skylark[tiab] OR skylarks[tiab] OR soleidae[tiab] OR allobates[tiab] OR northern wheatear[tiab] OR northern wheatears[tiab] OR pitheciidae[tiab] OR takin[tiab] OR theria[tiab] OR vanellus[tiab] OR galaxiidae[tiab] OR lorisidae[tiab] OR ostralegus[tiab] OR palaeognathae[tiab] OR stone loach[tiab] OR alauda[tiab] OR callitrichinae[tiab] OR caniformia[tiab] OR 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osteoglossidae[tiab] OR paenungulata[tiab] OR struthioniformes[tiab] OR ferina[tiab] OR sanderling[tiab] OR sanderlings[tiab] OR spheniscidae[tiab] OR cuttlefishes[tiab] OR cygnet[tiab] OR dasycneme[tiab] OR gadwall[tiab] OR gadwalls[tiab] OR pelobates fuscus[tiab] OR wryneck[tiab] OR wrynecks[tiab] OR afrosoricida[tiab] OR culaea[tiab] OR dover sole[tiab] OR dover soles[tiab] OR paralichthyidae[tiab] OR passeridae[tiab] OR osteolaemus[tiab] OR song thrushes[tiab] OR bluethroat[tiab] OR bluethroats[tiab] OR hydrophiidae[tiab] OR megrim[tiab] OR mephitidae[tiab] OR strepsirhini[tiab] OR tomistoma[tiab] OR epidalea[tiab] OR osmeriformes[tiab] OR bush babies[tiab] OR tarsiiform[tiab] OR atelinae[tiab] OR bufotes[tiab] OR eurasian coot[tiab] OR eurasian coots[tiab] OR galagidae[tiab] OR geopelia[tiab] OR philomachus[tiab] OR tubulidentata[tiab] OR bombinatoridae[tiab] OR pelobatidae[tiab] OR tachysurus[tiab] OR ailuridae[tiab] OR woodlark[tiab] OR woodlarks[tiab] OR alcelaphinae[tiab] OR redshank[tiab] OR redshanks[tiab] OR salientia[tiab] OR sand smelt[tiab] OR sand smelts[tiab] OR woodmice[tiab] OR woodmouse[tiab] OR dasyproctidae[tiab] OR eurasian wigeon[tiab] OR eurasian wigeons[tiab]OR garganey[tiab] OR garganeys[tiab] OR lemon sole[tiab] OR lemon soles[tiab] OR common dab[tiab] OR common dabs[tiab] OR graylag[tiab] OR graylags[tiab] OR leucorodia[tiab] OR osphronemidae[tiab] OR bewickii[tiab] OR common moorhen[tiab] OR common moorhens[tiab] OR decapodiformes[tiab] OR gobbler[tiab] OR gobblers[tiab] OR odontophoridae[tiab] OR paddlefishes[tiab] OR eutheria[tiab] OR salmonine[tiab] OR esociformes[tiab] OR eurasian woodcock[tiab] OR eurasian woodcocks[tiab] OR european smelt[tiab] OR european smelts[tiab] OR goldfishes[tiab] OR tenches[tiab] OR tyranni[tiab] OR common chaffinch[tiab] OR common chaffinchs[tiab] OR common redstart[tiab] OR common redstarts[tiab] OR common roach[tiab] OR common roachs[tiab] OR great knot[tiab] OR great knots[tiab] OR potoroidae[tiab] OR alytidae[tiab] OR coregonine[tiab] OR dipteral[tiab] OR leveret[tiab] OR poeciliopsis gracilis[tiab] OR amphiumidae[tiab] OR batrachoidiformes[tiab] OR bighead goby[tiab] OR heteropneustidae[tiab] OR lullula[tiab] OR norway pout[tiab] OR norway pouts[tiab] OR sipunculida[tiab] OR dogfishes[tiab] OR sebastidae[tiab] OR tarsiidae[tiab] OR alethinophidia[tiab] OR common nase[tiab] OR common nases[tiab] OR common sandpiper[tiab] OR common sandpipers[tiab] OR eurasian blackcap[tiab] OR eurasian blackcaps[tiab] OR pterocnemia[tiab] OR syngnathiformes[tiab] OR common chaffinches[tiab] OR eupleridae[tiab] OR octopodiformes[tiab] OR phascolarctidae[tiab] OR scophthalmidae[tiab] OR starry smooth-hound[tiab] OR starry smooth-hounds[tiab] OR whitefishes[tiab] OR cuniculidae[tiab] OR european sprat[tiab] OR european sprats[tiab] OR rosy bitterling[tiab] OR rosy bitterlings[tiab] OR common dace[tiab] OR common daces[tiab] OR lesser weever[tiab] OR lesser weevers[tiab] OR scaldfish[tiab] OR water rail[tiab] OR water rails[tiab] OR alouattinae[tiab] OR centrarchiformes[tiab] OR common whitethroat[tiab] OR common whitethroats[tiab] OR gavialidae[tiab] OR grey gurnard[tiab] OR grey gurnards[tiab] OR lateolabracidae[tiab] OR rheiformes[tiab] OR tubgurnard[tiab] OR tub gurnards[tiab] OR common chiffchaff[tiab] OR common chiffchaffs[tiab] OR garfishes[tiab] OR lesser whitethroat[tiab] OR lesser whitethroats[tiab] OR myoxidae[tiab] OR seabasses[tiab] OR spariformes[tiab] OR umbridae[tiab] OR yellow boxfish[tiab] OR anabantiformes[tiab] OR aotidae[tiab] OR common bleak[tiab] OR common bleaks[tiab] OR common rudd[tiab] OR common rudds[tiab] OR greater pipefish[tiab] OR hapale[tiab] OR nandiniidae[tiab] OR stone loaches[tiab] OR whinchat[tiab] OR whinchats[tiab] OR acanthuriformes[tiab] OR brotula barbata[tiab] OR common ling[tiab] OR common lings[tiab] OR common roaches[tiab] OR cottonrat[tiab] OR cottonrats[tiab] OR douroucoulis[tiab] OR dromaiidae[tiab] OR fitches[tiab] OR fitchew[tiab] OR galaxiiformes[tiab] OR laprine[tiab] OR saimiriinae[tiab] OR solenette[tiab] OR tarsii[tiab] OR tompot blenny[tiab] OR common dragonet[tiab] OR common dragonets[tiab] OR longspined bullhead[tiab] OR longspined bullheads[tiab] OR monotremate[tiab] OR monotremates[tiab] OR pempheriformes[tiab] OR perdicinae[tiab] OR presbytini[tiab] OR smegmamorpha[tiab] OR bighead gobies[tiab] OR carangaria incertae sedis[tiab] OR coiidae[tiab] OR fivebeard rockling[tiab] OR foulmart[tiab] OR foumart[tiab] OR grasskeet[tiab] OR greater pipefishes[tiab] OR ibices[tiab] OR millionfish[tiab] OR muguliformes[tiab] OR norwegian topknot[tiab] OR peewit[tiab] OR red sea sailfin tang[tiab] OR rupicapras[tiab] OR sheatfishes[tiab] OR tompot blennies[tiab] OR twait shad[tiab] OR yellow boxfishes[tiab]) NOT medline[sb]) |
| 6 | 4 AND 5 |
| 7 | ((systematic review[tiab] OR systematic reviews[tiab] OR meta-analyses[tiab] OR meta-analysis[tiab] OR metaanalyses[tiab] OR metaanalysis[tiab] OR systematic literature review[tiab] OR comprehensive literature review[tiab] OR Systematic survey[tiab] OR systematic overview[tiab] OR "Syst Rev"[Journal] OR meta-analysis[pt] OR Systematically review[tiab] OR Systematically searched[tiab] OR Systematic search[tiab] OR systematic-literature-search\*[tiab] OR Meta synthesis[tiab] OR PRISMA[tiab] OR ((electronic-database\*[tiab] OR databases-search\*[tiab] OR electronic-search\*[tiab] OR comprehensive-search\*[tiab] OR literature review[tiab] OR literature search[tiab] OR literature searches[tiab] OR literature searching[tiab] OR data collection[tiab]) AND (Pubmed[tiab] OR Medline[tiab] OR Embase[tiab] OR study-selection[tiab] OR selection-criteri\*[tiab] OR Web of Science[tiab] OR Google[tiab] OR Scopus[tiab] OR BIOSIS[tiab]))) NOT (letter[pt] OR newspaper article[pt] OR comment[pt])) |
| 8 | 6 AND 7 |

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| --- | --- |
| **Ovid Embase search strategy** | |
| **#** | **Search terms** |
| 1 | ((neurodevelop\* OR neurodevelop\* delay\* OR intellectual disabilit\* OR epilepsy OR ASD OR autis\*).ti,ab,kw.) |
| 2 | (("Fragile X Syndrome" OR "fragile x mental retardation protein" OR "FMR1" OR "Rett Syndrome" OR "Methyl-CpG-Binding Protein 2" OR MECP2).ti,ab,kw.) |
| 3 | ((CHD8 OR SCN2A OR SYNGAP1 OR ADNP OR FOXP1 OR POGZ OR ARID1B OR SUV420H1 OR DYRK1A OR SLC6A1 OR GRIN2B OR PTEN OR SHANK3 OR MED13L OR GIGYF1 OR CHD2 OR ANKRD11 OR ANK2 OR ASH1L OR TLK2 OR DNMT3A OR DEAF1 OR CTNNB1 OR KDM6B OR DSCAM OR SETD5 OR KCNQ3 OR SRPR OR KDM5B OR WAC OR SHANK2 OR NRXN1 OR TBL1XR1 OR MYT1L OR BCL11A OR RORB OR RAI1 OR DYNC1H1 OR DPYSL2 OR AP2S1 OR KMT2C OR PAX5 OR MKX OR GABRB3 OR SIN3A OR MBD5 OR MAP1A OR STXBP1 OR CELF4 OR PHF12 OR TBR1 OR PPP2R5D OR TM9SF4 OR PHF21A OR PRR12 OR SKI OR ASXL3 OR SPAST OR SMARCC2 OR TRIP12 OR CREBBP OR TCF4 OR CACNA1E OR GNAI1 OR TCF20 OR FOXP2 OR NSD1 OR TCF7L2 OR LDB1 OR EIF3G OR PHF2 OR KIAA0232 OR VEZF1 OR GFAP OR IRF2BPL OR ZMYND8 OR SATB1 OR RFX3 OR SCN1A OR PPP5C OR TRIM23 OR TRAF7 OR ELAVL3 OR GRIA2 OR LRRC4C OR CACNA2D3 OR NUP155 OR KMT2E OR NR3C2 OR NACC1 OR PTK7 OR PPP1R9B OR GABRB2 OR HDLBP OR TAOK1 OR UBR1 OR TEK OR KCNMA1 OR CORO1A OR HECTD4 OR NCOA1 OR DIP2A).ti,ab,kw.) |
| 4 | #1 OR #2 OR #3 |
| 5 | (exp animal experiment/ OR exp animal model/ OR exp experimental animal/ OR exp transgenic animal/ OR exp male animal/ OR exp female animal/ OR exp juvenile animal/ OR animal/ OR chordata/ OR vertebrate/ OR tetrapod/ OR exp fish/ OR amniote/ OR exp amphibia/ OR mammal/ OR exp reptile/ OR exp sauropsid/ OR therian/ OR exp monotreme/ OR placental mammal/ OR exp marsupial/ OR Euarchontoglires/ OR exp Afrotheria/ OR exp Boreoeutheria/ OR exp Laurasiatheria/ OR exp Xenarthra/ OR primate/ OR exp Dermoptera/ OR expGlires/ OR exp Scandentia/ OR Haplorhini/ OR exp prosimian/ OR simian/ OR exp tarsiiform/ OR Catarrhini/ OR exp Platyrrhini/ OR ape/ OR exp Cercopithecidae/ OR hominid/ OR exp hylobatidae/ OR exp chimpanzee/ OR exp gorilla/ OR exp orang utan/ OR exp cephalopod/) OR (rat OR rats OR animal OR animals OR mice OR "in vivo" OR mouse OR rabbit OR rabbits OR murine OR pig OR pigs OR dog OR dogs OR bovine OR fish OR vertebrate OR vertebrates OR cat OR cats OR rodent OR rodents OR mammal OR mammals OR chicken OR chickens OR monkey OR monkeys OR sheep OR canine OR canines OR porcine OR cattle OR bird OR birds OR hamster OR hamsters OR primate OR primates OR cow OR cows OR chick OR horse OR horses OR avian OR avians OR calf OR swine OR swines OR xenopus OR turkeys OR bear OR bears OR frog OR frogs OR zebrafish OR goat OR goats OR equine OR calves OR poultry OR macaque OR macaques OR mole OR moles OR ovine OR lamb OR lambs OR fishes OR diptera OR amphibian OR amphibians OR snake OR snakes OR ruminant OR ruminants OR henOR hens OR piglet OR piglets OR feline OR felines OR simian OR simians OR laevis OR trout OR trouts OR teleost OR teleosts OR salmon OR salmons OR seal OR seals OR bull OR bulls OR ewe OR ewes OR hedgehog OR hedgehogs OR macaca OR macacas OR proteus OR pigeon OR pigeons OR bat OR bats OR duck OR ducks OR chimpanzee OR chimpanzees OR baboon OR baboons OR deer OR deers OR rana OR ranas OR carp OR carps OR heifer OR swallow OR swallows OR lizard OR lizards OR canis OR sow OR sows OR cynomolgus OR quail OR quails OR reptile OR reptiles OR turtle OR turtles OR buffalo OR gerbil OR gerbils OR boar OR boars OR squirrel OR squirrels OR oncorhynchus OR mus OR toad OR toads OR fowl OR fowls OR rerio OR danio OR ara OR aras OR musculus OR tadpole OR tadpoles OR mulatta OR salmo OR ram OR eagle OR eagles OR ferret OR ferrets OR goldfish OR catfish OR whale OR whales OR fox OR foxes OR ape OR apes OR elephant OR elephants OR bos OR marmoset OR marmosets OR cod OR cods OR shark OR sharks OR wolf OR eel OR eels OR auratus OR rattus OR zebra OR zebras OR tilapia OR tilapias OR gilt OR camel OR camels OR squid OR gallus OR marsupial OR marsupials OR vole OR voles OR fascicularis OR ovis OR salmonid OR salmonids OR tiger OR tigers OR dolphin OR dolphins OR robin OR robins OR carpio OR opossum OR opossums OR cyprinus OR salamander OR salamanders OR felis OR mink OR minks OR swan OR swans OR norvegicus OR bufo OR torpedo OR bass OR lamprey OR lampreys OR sus OR python OR pythons OR tetrapod OR tetrapods OR shrew OR shrews OR lionOR lions OR hog OR hogs OR songbird OR songbirds OR oreochromis OR starling OR starlings OR caprine OR carassius OR owl OR owls OR newt OR newts OR papio OR scrofa OR hare OR hares OR gorilla OR gorillas OR flounder OR flounders OR goose OR herring OR herrings OR therian OR buffaloes OR canary OR sparrow OR sparrows OR microtus OR octopus OR troglodytes OR tuna OR amphibia OR chinchilla OR chinchillas OR ide OR oryzias OR cervus OR kangaroo OR kangaroos OR armadillo OR armadillos OR callithrix OR "pan troglodytes" OR saimiri OR cichlid OR cichlids OR donkey OR donkeys OR bream OR char OR chars OR finch OR raccoon OR raccoons OR bothrops OR anguilla OR perch OR cricetus OR seabird OR seabirds OR buck OR bucks OR naja OR coturnix OR salmonids OR geese OR minnow OR minnows OR raptor OR raptors OR merione OR meriones OR rodentia OR elaphus OR amniote OR amniotes OR elasmobranch OR emu OR emus OR peromyscus OR hominid OR hominids OR bubalus OR crotalus OR gull OR gulls OR anas OR anura OR lemur OR lemurs OR crow OR crows OR camelus OR gibbon OR gibbons OR waterfowl OR parrot OR parrots OR eels OR cob OR stickleback OR sticklebacks OR columba OR mesocricetus OR ambystoma OR raven OR ravens OR gadus OR penguin OR penguins OR orangutan OR orangutans OR sturgeon OR sturgeons OR cuniculus OR aves OR virginianus OR cephalopod OR cephalopods OR cebus OR sparus OR tortoise OR tortoises OR guttata OR morhua OR unguiculatus OR dogfish OR vulpes OR mallard OR mallards OR apodemus OR alligator OR alligators OR oryctolagus OR llama OR llamas OR reindeer OR mustela OR duckling OR ducklings OR wolves OR sander OR amazona OR zebu OR badger OR badgers OR dove OR doves OR ictalurus OR capra OR capras OR equus OR camelid OR camelids OR poecilia OR mule OR mules OR perciformes OR salvelinus OR labrax OR cyprinidae OR ariidae OR crocodile OR crocodiles OR fundulus OR dicentrarchus OR clarias OR cercopithecus OR chiroptera OR alpaca OR alpacas OR pike OR pikes OR paralichthys OR puma OR pumas OR didelphis OR pisces OR macropus OR triturusOR bison OR bisons OR epinephelus OR gasterosteus OR panthera OR acipenser OR mackerel OR mackerels OR tamarin OR tamarins OR ostrich OR anolis OR vervet OR vervets OR wallaby OR glareolus OR beaver OR beavers OR dromedary OR catus OR killifish OR pimephales OR promelas OR aotus OR phoca OR panda OR pandas OR porpoise OR porpoises OR myotis OR yak OR yaks OR agkistrodon OR vipera OR otter OR otters OR turbot OR turbots OR squamate OR carnivora OR mullet OR mullets OR hawk OR hawks OR taeniopygia OR seahorse OR seahorses OR "poecilia reticulata" OR falcon OR falcons OR prosimian OR prosimians OR parus OR perca OR fingerling OR fingerlings OR antelope OR antelopes OR tupaia OR passeriformes OR sepia OR saguinus OR coyote OR coyotes OR pongo OR meleagris OR reptilia OR lepus OR psittacine OR hagfish OR warbler OR warblers OR "russell s viper" OR "russell s vipers" OR smolt OR smolts OR budgerigar OR sardine OR sardines OR cavia OR cavias OR hyla OR pleurodeles OR siluriformes OR "great tit" OR "great tits" OR guppy OR bonobo OR bonobos OR rutilus OR trichosurus OR muridae OR phodopus OR channa OR squalus OR lynx OR sturnus OR petromyzon OR vitulina OR monodelphis OR cuttlefish OR adder OR adders OR lepomis OR canaria OR gambusia OR guppies  OR xiphophorus OR flatfish OR koala OR koalas OR labeo OR stingray OR stingrays OR chelonia OR lampetra OR spermophilus OR crocodilian OR "passer domesticus" OR sciurus OR artiodactyla OR ranidae OR corvus OR necturus OR platypus OR canaries OR bovid OR lagopus OR trimeresurus OR gariepinus OR marten OR martens OR drosophilidae OR mugil OR sunfish OR porcellus OR cypriniformes OR alouatta OR scophthalmus OR anser OR electrophorus OR putorius OR iguana OR iguanas OR lama OR lamas OR takifugu OR circus OR eptesicus OR flycatcher OR galago OR galagos OR trachemys OR lungfish OR characiformes OR shorebird OR shorebirds OR giraffe OR giraffes OR micropterus OR scyliorhinus OR cichlidae OR loligo OR porcupine OR porcupines OR chub OR chubs OR solea OR pleuronectes OR hylidae OR viperidae OR echis OR sorex OR anchovy OR lagomorph OR ostriches OR vulture OR vultures OR whitefish OR araneus OR jird OR jirds OR tern OR esox OR drake OR drakes OR elapidae OR gallopavo OR chordata OR myodes OR caretta OR serinus OR grouse OR misgurnus OR meles OR blackbird OR blackbirds OR coregonus OR bobwhite OR bobwhites OR heteropneustes OR mammoth OR mammoths OR turdus OR rhinella OR ateles OR characidae OR clupea OR bungarus OR brill OR "struthio camelus" OR sloth OR sloths OR pteropus OR sculpin OR anthropoids OR pollock OR pollocks OR morone OR "pan paniscus" OR litoria OR chipmunk OR chipmunks OR balaenoptera OR marmota OR melopsittacus OR hyrax OR lemming OR lemmings OR halibut OR hylobates OR lates OR caiman OR caimans OR sigmodon OR stenella OR barbel OR barbels OR sterna OR parakeet OR parakeets OR phocoena OR leptodactylus OR canidae OR buteo OR harengus OR gopher OR gophers OR marmot OR marmots OR gosling OR goslings OR platichthys OR gar OR gars OR sebastes OR marsupialia OR notophthalmus OR gazelle OR gazelles OR insectivora OR paridae OR felidae OR russula OR galliformes OR bombina OR colobus OR echidna OR echidnas OR seabass OR syncerus OR plaice OR "blue tit" OR "blue tits" OR pagrus OR catfishes OR cetacea OR barbus OR cygnus OR ficedula OR chamois OR colubridae OR perches OR coelacanth OR fitch OR urodela OR cynops OR martes OR halichoerus OR aix OR salmonidae OR leuciscus OR magpie OR magpies OR silurus OR whiting OR whitings OR anseriformes OR colinus OR rhea OR chlorocebus OR octodon OR acinonyx OR mouflon OR mouflons OR ibex OR tetraodon OR bufonidae OR equidae OR jackal OR cephalopoda OR dendroaspis OR glama OR muskrat OR muskrats OR sable OR sables OR wildebeest OR streptopelia OR albifrons OR vespertilionidae OR woodpecker OR woodpeckers OR muntjac OR muntjacs OR archosaur OR branta OR cricetulus OR megalobrama OR poeciliidae OR desmodus OR snakehead OR snakeheads OR tench OR teal OR teals OR bandicoot OR bandicoots OR apteronotus OR phyllostomidae OR crocidura OR buzzard OR buzzards OR larimichthys OR cercocebus OR pipistrellus OR erithacus OR impala OR impalas OR rousettus OR haddock OR haddocks OR tinca OR ratite OR calidris OR cynoglossus OR hypophthalmichthys OR bullock OR bullocks OR dromedaries OR alectoris OR filly OR salamandra OR cingulata OR bitis OR grus OR ammodytes OR macaw OR macaws OR hypoleuca OR sapajus OR cyprinodontiformes OR hippopotamus OR pelophylax OR capybara OR capybaras OR weasel OR weasels OR cairina OR cynomys OR lutra OR cockatoo OR cockatoos OR lachesis OR lagomorpha OR rupicapra OR daboia OR "orang utan" OR "orang utans" OR platyrrhini OR charadriiformes OR micrurus OR psittaciformes OR spalax OR loris OR mustelidae OR sylvilagus OR vitticeps OR cockatiel OR mustelus OR cottus OR erythrocebus OR dipodomys OR platessa OR callicebus OR loricariidae OR catostomus OR cuneata OR cyanistes OR cyprinodon OR sigmodontinae OR elasmobranchii OR trichechus OR sauropsid OR xenarthra OR dormouse OR perissodactyla OR nautilus OR cirrhinus OR gulo OR gulos OR tragelaphus OR merula OR numida OR sciaenidae OR cerastes OR sciuridae OR gibbosus OR octopuses OR eland OR elands OR phyllomedusa OR pogona OR walrus OR agamidae OR leptodactylidae OR ridibundus OR leontopithecus OR anteater OR anteaters OR pelodiscus OR cebidae OR columbianus OR "pelteobagrus fulvidraco" OR hominoidea OR mandrillus OR "zonotrichia leucophrys" OR agama OR gobiocypris OR "bearded dragon" OR "bearded dragons" OR sarotherodon OR talpa OR discoglossus OR hagfishes OR sphenodon OR gudgeon OR amphiuma OR aythya OR tenrec OR tenrec OR hominidae OR risoria OR salamandridae OR camelidae OR columbiformes OR latimeria OR plover OR plovers OR afrotheria OR "falco sparverius" OR polecat OR polecats OR crotalinae OR salvadora OR tarsier OR lucioperca OR anchovies OR lungfishes OR terrapin OR "dromaius novaehollandiae" OR lateolabrax OR eigenmannia OR pelamis OR theropithecus OR murinae OR gander OR gymnotus OR pseudacris OR gymnophiona OR gymnotiformes OR laticauda OR falconiformes OR dugong OR dugongs OR pintail OR pintails OR rook OR rooks OR lasiurus OR catshark OR catsharks OR micropogonias OR "red junglefowl" OR paddlefish OR ophiophagus OR hollandicus OR nymphicus OR pimelodidae OR aepyceros OR cobitidae OR strigiformes OR cobitis OR dormice OR alytes OR calloselasma OR guanaco OR guanacos OR phasianidae OR "round goby" OR trichogaster OR catarrhini OR eelpout OR eelpouts OR galaxias OR gaur OR pungitius OR suslik OR susliks OR flatfishes OR percidae OR caprinae OR todarodes OR osmerus OR ameiurus OR anthropoidea OR"castor canadensis" OR pouting OR poutings OR tetraodontiformes OR arvicolinae OR siamang OR siamangs OR "castor fiber" OR nomascus OR "red knot" OR "red knots" OR syngnathidae OR iguanidae OR eretmochelys OR ursidae OR callimico OR columbidae OR microhylidae OR anaxyrus OR menidia OR pipistrelle OR greylag OR pipidae OR scandentia OR bowfin OR bowfins OR dendrobatidae OR zenaida OR bushbaby OR harrier OR harriers OR macropodidae OR pygerythrus OR clupeidae OR odorrana OR corvidae OR jerboa OR jerboas OR canutus OR hylobatidae OR clupeiformes OR "great cormorant" OR "great cormorants" OR scorpaeniformes OR chondrostean OR garfish OR proboscidea OR psetta OR diapsid OR serotinus OR tetrao OR walruses OR carcharhiniformes OR leucoraja OR pumpkinseed OR dosidicus OR acipenseriformes OR daubentonii OR emberizidae OR gadiformes OR hyraxes OR stizostedion OR wolverine OR wolverines OR lissotriton OR acanthurus OR centrarchidae OR gloydius OR laurasiatheria OR limosa OR psittacula OR leporidae OR proteidae OR zander OR zanders OR arapaima OR bagridae OR cyprinodontidae OR mithun OR pandion OR jackdaw OR jackdaws OR procyonidae OR carus OR jaculus OR salmoniformes OR "common sole" OR "common soles" OR protobothrops OR calamita OR brachyteles OR trionyx OR turdidae ORboidae OR luscinia OR pugnax OR euarchontoglires OR saithe OR saithes OR symphalangus OR aardvark OR aardvarks OR oystercatcher OR oystercatchers OR arius OR corydoras OR poacher OR poachers OR aurochs OR cebuella OR crecca OR lemuridae OR sirenia OR lemmus OR perdix OR glires OR lepidosaur OR muskox OR deinagkistrodon OR pholidota OR holocephali OR cercopithecinae OR clariidae OR agapornis OR doryteuthis OR tyrannidae OR dicroglossidae OR godwit OR godwits OR monedula OR pongidae OR atheriniformes OR colobinae OR lophocebus OR atelidae OR cottidae OR leucopsis OR acanthuridae OR didelphimorphia OR elver OR elvers OR lapponica OR dermoptera OR "european hake" OR "european hakes" OR gerbillinae OR banteng OR hartebeest OR hartebeests OR hogget OR haematopus OR "anguis fragilis" OR "grey heron" OR "grey herons" OR "blue whiting" OR "blue whitings" OR furnariidae OR macrovipera OR esocidae OR lapwing OR lapwings OR mylopharyngodon OR wallabia OR beloniformes OR potoroo OR potoroos OR "athene noctua" OR pleuronectidae OR bushbabies OR muscicapidae OR alligatoridae OR fuligula OR "bush baby" OR guineafowl OR spoonbill OR spoonbills OR viverridae OR catostomidae OR zebrafishes OR ibexes OR vendace OR estrildidae OR monotremata OR sepiella OR ambystomatidae OR shelduck OR shelducks OR treeshrew OR treeshrews OR hoplobatrachus OR pochard OR hoolock OR hoolocks OR lynxes OR antilope OR antilopes OR blackbuck OR blackbucks OR cricetinae OR paramisgurnus OR skylark OR skylarks OR soleidae OR allobates OR "northern wheatear" OR "northern wheatears" OR pitheciidae OR takin OR theria OR vanellus OR galaxiidae OR lorisidae OR ostralegus OR palaeognathae OR "stone loach" OR alauda OR callitrichinae OR caniformia OR duttaphrynus OR ictaluridae OR osteoglossiformes OR poultries OR curema OR "ruddy turnstone" OR "ruddy turnstones" OR sheatfish OR sunfishes OR centropomidae OR hemachatus OR platalea OR thamnophilidae OR "song thrush" OR atherinopsidae OR siluridae OR tadorna OR chroicocephalus OR ermine OR ermines OR gavialis OR ruff OR tupaiidae OR diprotodontia OR hyaenidae OR antilopinae OR crocodylidae OR herpestidae OR hippopotamidae OR "northern shoveler" OR "round gobies" OR cheirogaleidae OR indriidae OR fundulidae OR pythonidae OR rhynchocephalia OR anodorhynchus OR "red-backed shrike" OR "red-backed shrikes" OR triakidae OR phalangeridae OR aoudad OR boreoeutheria OR "eurasian jay" OR "eurasian jays" OR feliformia OR haplorhini OR osteoglossidae OR paenungulata OR struthioniformes OR ferina OR sanderling OR sanderlings OR spheniscidae OR cuttlefishes OR cygnet OR dasycneme OR gadwall OR gadwalls OR "pelobates fuscus" OR wryneck OR wrynecks OR afrosoricida OR culaea OR "dover sole" OR "dover soles" OR paralichthyidae OR passeridae OR osteolaemus OR "song thrushes" OR bluethroat OR bluethroats OR hydrophiidae OR megrim OR mephitidae OR strepsirhini OR tomistoma OR epidalea OR osmeriformes OR "bush babies" OR tarsiiform OR atelinae OR bufotes OR "eurasian coot" OR "eurasian coots" OR galagidae OR geopelia OR philomachus OR tubulidentata OR bombinatoridae OR pelobatidae OR tachysurus OR ailuridae OR woodlark OR woodlarks OR alcelaphinae OR redshank OR redshanks OR salientia OR "sand smelt" OR "sand smelts" OR woodmice OR woodmouse OR dasyproctidae OR "eurasian wigeon" OR "eurasianwigeons" OR garganey OR garganeys OR "lemon sole" OR "lemon soles" OR "common dab" OR "common dabs" OR graylag OR graylags OR leucorodia OR osphronemidae OR bewickii OR "common moorhen" OR "common moorhens" OR decapodiformes OR gobbler OR gobblers OR odontophoridae OR paddlefishes OR eutheria OR salmonine OR esociformes OR "eurasian woodcock" OR "eurasian woodcocks" OR "european smelt" OR "european smelts" OR goldfishes OR tenches OR tyranni OR "common chaffinch" OR "common chaffinchs" OR "common redstart"OR "common redstarts" OR "common roach" OR "common roachs" OR "great knot" OR "great knots" OR potoroidae OR alytidae OR coregonine OR dipteral OR leveret OR "poeciliopsis gracilis" OR amphiumidae OR batrachoidiformes OR "bighead goby" OR heteropneustidaeOR lullula OR "norway pout" OR "norway pouts" OR sipunculida OR dogfishes OR sebastidae OR tarsiidae OR alethinophidia OR "common nase" OR "common nases" OR "common sandpiper" OR "common sandpipers" OR "eurasian blackcap" OR "eurasian blackcaps" OR pterocnemia OR syngnathiformes OR "common chaffinches" OR eupleridae OR octopodiformes OR phascolarctidae OR scophthalmidae OR "starry smooth-hound" OR "starry smooth-hounds" OR whitefishes OR cuniculidae OR "european sprat" OR "european sprats" OR "rosy bitterling" OR "rosy bitterlings" OR "common dace" OR "common daces" OR "lesser weever" OR "lesser weevers" OR scaldfish OR "water rail" OR "water rails" OR alouattinae OR centrarchiformes OR "common whitethroat" OR "common whitethroats" OR gavialidae OR "grey gurnard" OR "grey gurnards" OR lateolabracidae OR rheiformes OR "tub gurnard" OR "tub gurnards" OR "common chiffchaff" OR "common chiffchaffs" OR garfishes OR "lesser whitethroat" OR "lesser whitethroats" OR myoxidae OR seabasses OR spariformes OR umbridae OR "yellow boxfish" OR anabantiformes OR aotidae OR "common bleak" OR "common bleaks" OR "common rudd" OR "common rudds" OR "greater pipefish" OR hapale OR nandiniidae OR "stone loaches" OR whinchat OR whinchats OR acanthuriformes OR "brotula barbata" OR "common ling" OR "common lings" OR "common roaches" OR cottonrat OR cottonrats OR douroucoulis OR dromaiidae OR fitches OR fitchew OR galaxiiformes OR laprine OR saimiriinae OR solenette OR tarsii OR "tompot blenny" OR "common dragonet" OR "common dragonets"OR "longspined bullhead" OR "longspined bullheads" OR monotremate OR monotremates OR pempheriformes OR perdicinae OR presbytini OR smegmamorpha OR "bighead gobies" OR "carangaria incertae sedis" OR coiidae OR "fivebeard rockling" OR foulmart OR foumart ORgrasskeet OR "greater pipefishes" OR ibices OR millionfish OR muguliformes OR "norwegian topknot" OR peewit OR "red sea sailfin tang" OR rupicapras OR sheatfishes OR "tompot blennies" OR "twait shad" OR "yellow boxfishes").ti,ab,kw. |
| 6 | #4 AND #5 |
| 7 | (("systematic review" OR "meta-analysis" OR metaanalysis).ti. OR (((meta-analyses OR meta-analysis OR metaanalyses OR metaanalysis OR "systematic overview").ti,ab,de. OR "systematic reviews".jt. OR "meta analysis".jt. OR "Meta synthesis".ti,ab,de. OR (Systematic\* adj2 (Review OR literature OR Reviews OR survey OR search\*)).ti,ab,de.) and ("Data collection" OR "Data extraction" OR "Inclusion Criteria" OR "Exclusion criteria" OR Search\* OR Literature OR Pubmed OR Medline OR Embase OR selection OR Web of Science OR Google OR Scopus OR BIOSIS).ti,ab,de.)) |
| 8 | #6 AND #7 |

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| **Web of Science search strategy** | |
| **#** | **Search terms** |
| 1 | (TS=( neurodevelop\* OR neurodevelop\* delay\* OR intellectual disabilit\* OR epilepsy OR ASD OR autis\*)) |
| 2 | (TS=("Fragile X Syndrome" OR "fragile x mental retardation protein" OR "FMR1" OR "Rett Syndrome" OR "Methyl-CpG-Binding Protein 2" OR MECP2)) |
| 3 | (TS=( CHD8 OR SCN2A OR SYNGAP1 OR ADNP OR FOXP1 OR POGZ OR ARID1B OR SUV420H1 OR DYRK1A OR SLC6A1 OR GRIN2B OR PTEN OR SHANK3 OR MED13L OR GIGYF1 OR CHD2 OR ANKRD11 OR ANK2 OR ASH1L OR TLK2 OR DNMT3A OR DEAF1 OR CTNNB1 OR KDM6B OR DSCAM OR SETD5 OR KCNQ3 OR SRPR OR KDM5B OR WAC OR SHANK2 OR NRXN1 OR TBL1XR1 OR MYT1L OR BCL11A OR RORB OR RAI1 OR DYNC1H1 OR DPYSL2 OR AP2S1 OR KMT2C OR PAX5 OR MKX OR GABRB3 OR SIN3A OR MBD5 OR MAP1A OR STXBP1 OR CELF4 OR PHF12 OR TBR1 OR PPP2R5D OR TM9SF4 OR PHF21A OR PRR12 OR SKI OR ASXL3 OR SPAST OR SMARCC2 OR TRIP12 OR CREBBP OR TCF4 OR CACNA1E OR GNAI1 OR TCF20 OR FOXP2 OR NSD1 OR TCF7L2 OR LDB1 OR EIF3G OR PHF2 OR KIAA0232 OR VEZF1 OR GFAP OR IRF2BPL OR ZMYND8 OR SATB1 OR RFX3 OR SCN1A OR PPP5C OR TRIM23 OR TRAF7 OR ELAVL3 OR GRIA2 OR LRRC4C OR CACNA2D3 OR NUP155 OR KMT2E OR NR3C2 OR NACC1 OR PTK7 OR PPP1R9B OR GABRB2 OR HDLBP OR TAOK1 OR UBR1 OR TEK OR KCNMA1 OR CORO1A OR HECTD4 OR NCOA1 OR DIP2A)) |
| 4 | #1 OR #2 OR #3 |
| 5 | TS=(rat OR rats OR animal OR animals OR mice OR "in vivo" OR mouse OR rabbit OR rabbits OR murine OR pig OR pigs OR dog OR dogs OR bovine OR fish OR vertebrate OR vertebrates OR cat OR cats OR rodent OR rodents OR mammal OR mammals OR chicken OR chickens OR monkey OR monkeys OR sheep OR canine OR canines OR porcine OR cattle OR bird OR birds OR hamster OR hamsters OR primate OR primates OR cow OR cows OR chick OR horse OR horses OR avian OR avians OR calf OR swine OR swines OR xenopus OR turkeys OR bear OR bears OR frog OR frogs OR zebrafish OR goat OR goats OR equine OR calves OR poultry OR macaque OR macaques OR mole OR moles OR ovine OR lamb OR lambs OR fishes OR diptera OR amphibian OR amphibians OR snake OR snakes OR ruminant OR ruminants OR hen OR hens OR piglet OR piglets OR feline OR felines OR simian OR simians OR laevis OR trout OR trouts OR teleost OR teleosts OR salmon OR salmons OR seal OR seals OR bull OR bulls OR ewe OR ewes OR hedgehog OR hedgehogs OR macaca OR macacas OR proteus OR pigeon ORpigeons OR bat OR bats OR duck OR ducks OR chimpanzee OR chimpanzees OR baboon OR baboons OR deer OR rana OR ranas OR carp OR carps OR heifer OR swallow OR swallows OR lizard OR lizards OR canis OR sow OR sows OR cynomolgus OR quail OR quails OR reptile OR reptiles OR turtle OR turtles OR buffalo OR gerbil OR gerbils OR boar OR boars OR squirrel OR squirrels OR oncorhynchus OR mus OR toad OR toads OR fowl OR fowls OR rerio OR danio OR ara OR aras OR musculus OR tadpole OR tadpoles OR mulatta OR salmo OR ram OR eagle OR eagles OR ferret OR ferrets OR goldfish OR catfish OR whale OR whales OR fox OR foxes OR ape OR apes OR elephant OR elephants OR bos OR marmoset OR marmosets OR cod OR cods OR shark OR sharks OR wolf OR eel OR eels OR auratus OR rattus OR zebra OR zebras OR tilapia OR tilapias OR gilt OR camel OR camels OR squid OR gallus OR marsupial OR marsupials OR vole OR voles OR fascicularis OR ovis OR salmonid OR salmonids OR tiger OR tigers OR dolphin OR dolphins OR robin OR robins OR carpio OR opossumOR opossums OR cyprinus OR salamander OR salamanders OR felis OR mink OR minks OR swan OR swans OR norvegicus OR bufo OR torpedo OR bass OR lamprey OR lampreys OR sus OR python OR pythons OR tetrapod OR tetrapods OR shrew OR shrews OR lion OR lions OR hogOR hogs OR songbird OR songbirds OR oreochromis OR starling OR starlings OR caprine OR carassius OR owl OR owls OR newt OR newts OR papio OR scrofa OR hare OR hares OR gorilla OR gorillas OR flounder OR flounders OR goose OR herring OR herrings OR therianOR buffaloes OR canary OR sparrow OR sparrows OR microtus OR octopus OR troglodytes OR tuna OR amphibia OR chinchilla OR chinchillas OR ide OR oryzias OR cervus OR kangaroo OR kangaroos OR armadillo OR armadillos OR callithrix OR "pan troglodytes" OR saimiri OR cichlid OR cichlids OR donkey OR donkeys OR bream OR char OR chars OR finch OR raccoon OR raccoons OR bothrops OR anguilla OR perch OR cricetus OR seabird OR seabirds OR buck OR bucks OR naja OR coturnix OR salmonids OR geese OR minnow OR minnows ORraptor OR raptors OR merione OR meriones OR rodentia OR elaphus OR amniote OR amniotes OR elasmobranch OR emu OR emus OR peromyscus OR hominid OR hominids OR bubalus OR crotalus OR gull OR gulls OR anas OR anura OR lemur OR lemurs OR crow OR crows OR camelus OR gibbon OR gibbons OR waterfowl OR parrot OR parrots OR eels OR cob OR stickleback OR sticklebacks OR columba OR mesocricetus OR ambystoma OR raven OR ravens OR gadus OR penguin OR penguins OR orangutan OR orangutans OR sturgeon OR sturgeons OR cuniculus OR aves OR virginianus OR cephalopod OR cephalopods OR cebus OR sparus OR tortoise OR tortoises OR guttata OR morhua OR unguiculatus OR dogfish OR vulpes OR mallard OR mallards OR apodemus OR alligator OR alligators OR oryctolagus OR llama OR llamas OR reindeer OR mustela OR duckling OR ducklings OR wolves OR sander OR amazona OR zebu OR badger OR badgers OR dove OR doves OR ictalurus OR capra OR capras OR equus OR camelid OR camelids OR poecilia OR mule OR mules OR perciformes OR salvelinus OR labrax OR cyprinidae OR ariidae OR crocodile OR crocodiles OR fundulus OR dicentrarchus OR clarias OR cercopithecus OR chiroptera OR alpaca OR alpacas OR pike OR pikes OR paralichthys OR puma OR pumas OR didelphis OR pisces OR macropus OR triturus OR bison OR bisons OR epinephelus OR gasterosteus OR panthera OR acipenser OR mackerel OR mackerels OR tamarin OR tamarins OR ostrich OR anolis OR vervet OR vervets OR wallaby OR glareolus OR beaver OR beavers OR dromedary OR catus OR killifish OR pimephales OR promelas OR aotus OR phoca OR panda OR pandas OR porpoise OR porpoises OR myotis OR yak OR yaks OR agkistrodon OR vipera OR otter OR otters OR turbot OR turbots OR squamate OR carnivora OR mullet OR mullets OR hawk OR hawks OR taeniopygia OR seahorse OR seahorses OR "poecilia reticulata" OR falcon OR falcons OR prosimian OR prosimians OR parus OR perca OR fingerling OR fingerlings OR antelope OR antelopes OR tupaia OR passeriformes OR sepia OR saguinus OR coyote OR coyotes OR pongo OR meleagris OR reptilia OR lepus OR psittacine OR hagfish OR warbler OR warblers OR "russell s viper" OR "russell s vipers" OR smolt OR smolts OR budgerigar OR sardine OR sardines OR cavia OR cavias OR hyla OR pleurodeles OR siluriformes OR "great tit" OR "great tits" OR guppy OR bonobo OR bonobos OR rutilus OR trichosurus OR muridae OR phodopus OR channa OR squalus OR lynx OR sturnus OR petromyzon OR vitulina OR monodelphis OR cuttlefish OR adder OR adders OR lepomis OR canaria OR gambusia OR guppies OR xiphophorus OR flatfish OR koala ORkoalas OR labeo OR stingray OR stingrays OR chelonia OR lampetra OR spermophilus OR crocodilian OR "passer domesticus" OR sciurus OR artiodactyla OR ranidae OR corvus OR necturus OR platypus OR canaries OR bovid OR lagopus OR trimeresurus OR gariepinus ORmarten OR martens OR drosophilidae OR mugil OR sunfish OR porcellus OR cypriniformes OR alouatta OR scophthalmus OR anser OR electrophorus OR putorius OR iguana OR iguanas OR lama OR lamas OR takifugu OR circus OR eptesicus OR flycatcher OR galago OR galagos OR trachemys OR lungfish OR characiformes OR shorebird OR shorebirds OR giraffe OR giraffes OR micropterus OR scyliorhinus OR cichlidae OR loligo OR porcupine OR porcupines OR chub OR chubs OR solea OR pleuronectes OR hylidae OR viperidae OR echis OR sorex OR anchovy OR lagomorph OR ostriches OR vulture OR vultures OR whitefish OR araneus OR jird OR jirds OR tern OR esox OR drake OR drakes OR elapidae OR gallopavo OR chordata OR myodes OR caretta OR serinus OR grouse OR misgurnus OR meles OR blackbird OR blackbirds OR coregonus OR bobwhite OR bobwhites OR heteropneustes OR  mammoth OR mammoths OR turdus OR rhinella OR ateles OR characidae OR clupea OR bungarus OR brill OR "struthio camelus" OR sloth OR sloths OR pteropus OR sculpin OR anthropoids OR pollock OR pollocks OR morone OR "pan paniscus" OR litoria OR chipmunk OR chipmunks OR balaenoptera OR marmota OR melopsittacus OR hyrax OR lemming OR lemmings OR halibut OR hylobates OR lates OR caiman OR caimans OR sigmodon OR stenella OR barbel OR barbels ORsterna OR parakeet OR parakeets OR phocoena OR leptodactylus OR canidae OR buteo OR harengus OR gopher OR gophers OR marmot OR marmots OR gosling OR goslings OR platichthys OR gar OR gars OR sebastes OR marsupialia OR notophthalmus OR gazelle OR gazelles OR insectivora OR paridae OR felidae OR russula OR galliformes OR bombina OR colobus OR echidna OR echidnas OR seabass OR syncerus OR plaice OR "blue tit" OR "blue tits" OR pagrus OR catfishes OR cetacea OR barbus OR cygnus OR ficedula OR chamois OR colubridae OR perches OR coelacanth OR fitch OR urodela OR cynops OR martes OR halichoerus OR aix OR salmonidae OR leuciscus OR magpie OR magpies OR silurus OR whiting OR whitings OR anseriformes OR colinus OR rhea OR chlorocebus OR octodon OR acinonyx OR mouflon OR mouflons OR ibex OR tetraodon OR bufonidae OR equidae OR jackal OR cephalopoda OR dendroaspis OR glama OR muskrat OR muskrats OR sable OR sables OR wildebeest OR streptopelia OR albifrons OR vespertilionidae OR woodpecker OR woodpeckers OR muntjac OR muntjacs OR archosaur OR branta OR cricetulus OR megalobrama OR poeciliidae OR desmodus OR snakehead OR snakeheads OR tench OR teal OR teals OR bandicoot OR bandicoots OR apteronotus OR phyllostomidae OR crocidura OR buzzard OR buzzards OR larimichthys OR cercocebus OR pipistrellus OR erithacus OR impala OR impalas OR rousettus OR haddock OR haddocks OR tinca OR ratite OR calidris OR cynoglossus OR hypophthalmichthys OR bullock OR bullocks OR dromedaries OR alectoris OR filly OR salamandra OR cingulata OR bitis OR grus OR ammodytes OR macaw OR macaws OR hypoleuca OR sapajus OR cyprinodontiformes OR hippopotamus OR pelophylax OR capybara OR capybaras OR weasel OR weasels OR cairina OR cynomys OR lutra OR cockatoo OR cockatoos OR lachesis OR lagomorpha OR rupicapra OR daboia OR "orang utan" OR "orang utans" OR platyrrhini OR charadriiformes OR micrurus OR psittaciformes OR spalax OR loris OR mustelidae OR sylvilagus OR vitticeps OR cockatiel OR mustelus OR cottus OR erythrocebus OR dipodomys OR platessa OR callicebus OR loricariidae OR catostomus OR cuneata OR cyanistes OR cyprinodon OR sigmodontinae OR elasmobranchii OR trichechus OR sauropsid OR xenarthra OR dormouse OR perissodactyla OR nautilus OR cirrhinus OR gulo OR gulos OR tragelaphus OR merula OR numidaOR sciaenidae OR cerastes OR sciuridae OR gibbosus OR octopuses OR eland OR elands OR phyllomedusa OR pogona OR walrus OR agamidae OR leptodactylidae OR ridibundus OR leontopithecus OR anteater OR anteaters OR pelodiscus OR cebidae OR columbianus OR "pelteobagrus fulvidraco" OR hominoidea OR mandrillus OR "zonotrichia leucophrys" OR agama OR gobiocypris OR "bearded dragon" OR "bearded dragons" OR sarotherodon OR talpa OR discoglossus OR hagfishes OR sphenodon OR gudgeon OR amphiuma OR aythya OR tenrec OR tenrec OR hominidae OR risoria OR salamandridae OR camelidae OR columbiformes OR latimeria OR plover OR plovers OR afrotheria OR "falco sparverius" OR polecat OR polecats OR crotalinae OR salvadora OR tarsier OR lucioperca OR anchovies OR lungfishes OR terrapin OR "dromaius novaehollandiae" OR lateolabrax OR eigenmannia OR pelamis OR theropithecus OR murinae OR gander OR gymnotus OR pseudacris OR gymnophiona OR gymnotiformes OR laticauda OR falconiformes OR dugong OR dugongs OR pintail OR pintails OR rook ORrooks OR lasiurus OR catshark OR catsharks OR micropogonias OR "red junglefowl" OR paddlefish OR eutheria OR ophiophagus OR hollandicus OR nymphicus OR pimelodidae OR aepyceros OR cobitidae OR strigiformes OR cobitis OR dormice OR alytes OR calloselasma OR guanaco OR guanacos OR phasianidae OR "round goby" OR trichogaster OR catarrhini OR eelpout OR eelpouts OR galaxias OR gaur OR pungitius OR suslik OR susliks OR flatfishes OR percidae OR caprinae OR todarodes OR osmerus OR ameiurus OR anthropoidea OR "castor canadensis" OR pouting OR poutings OR tetraodontiformes OR arvicolinae OR siamang OR siamangs OR "castor fiber" OR nomascus OR "red knot" OR "red knots" OR syngnathidae OR iguanidae OR eretmochelys OR ursidae OR callimico OR columbidae OR microhylidaeOR anaxyrus OR menidia OR pipistrelle OR greylag OR pipidae OR scandentia OR bowfin OR bowfins OR dendrobatidae OR zenaida OR bushbaby OR harrier OR harriers OR macropodidae OR pygerythrus OR clupeidae OR odorrana OR corvidae OR jerboa OR jerboas OR canutus OR hylobatidae OR clupeiformes OR "great cormorant" OR "great cormorants" OR scorpaeniformes OR chondrostean OR garfish OR proboscidea OR psetta OR diapsid OR serotinus OR tetrao OR walruses OR carcharhiniformes OR leucoraja OR pumpkinseed OR dosidicus OR acipenseriformes OR daubentonii OR emberizidae OR gadiformes OR hyraxes OR stizostedion OR wolverine OR wolverines OR lissotriton OR acanthurus OR centrarchidae OR gloydius OR laurasiatheria OR limosa OR psittacula OR leporidae OR proteidae OR zander ORzanders OR arapaima OR bagridae OR cyprinodontidae OR mithun OR pandion OR jackdaw OR jackdaws OR procyonidae OR carus OR jaculus OR salmoniformes OR "common sole" OR "common soles" OR protobothrops OR calamita OR brachyteles OR trionyx OR turdidae OR boidae OR luscinia OR pugnax OR euarchontoglires OR saithe OR saithes OR symphalangus OR aardvark OR aardvarks OR oystercatcher OR oystercatchers OR arius OR corydoras OR poacher OR poachers OR aurochs OR cebuella OR crecca OR lemuridae OR sirenia OR lemmus OR perdix OR glires OR lepidosaur OR muskox OR deinagkistrodon OR pholidota OR holocephali OR cercopithecinae OR clariidae OR agapornis OR doryteuthis OR tyrannidae OR dicroglossidae OR godwit OR godwits OR monedula OR pongidae OR atheriniformes OR colobinae OR lophocebus OR atelidae OR cottidae OR leucopsis OR acanthuridae OR didelphimorphia OR elver OR elvers OR lapponica OR dermoptera OR "european hake" OR "european hakes" OR gerbillinae OR banteng OR hartebeest OR hartebeests OR hogget OR haematopus OR "anguis fragilis" OR "grey heron" OR "grey herons" OR "blue whiting" OR "blue whitings" OR furnariidae OR macrovipera OR esocidae OR lapwing OR lapwings OR mylopharyngodon OR wallabia OR beloniformes OR potoroo OR potoroos OR "athene noctua" OR pleuronectidae OR bushbabies OR muscicapidae OR alligatoridae OR fuligula OR "bush baby" OR guineafowl OR spoonbill OR spoonbills OR viverridae OR catostomidae OR zebrafishes OR ibexes OR vendace OR estrildidae OR monotremata OR sepiella OR ambystomatidae OR shelduck OR shelducks OR treeshrew OR treeshrews OR hoplobatrachus OR pochard OR hoolock OR hoolocks OR lynxes OR antilope OR antilopes OR blackbuck OR blackbucks OR cricetinae OR paramisgurnus OR skylark OR skylarks OR soleidae OR allobates OR "northern wheatear" OR "northern wheatears" OR pitheciidae OR takin OR theria OR vanellus OR galaxiidae OR lorisidae OR ostralegus OR palaeognathae OR "stone loach" OR alauda OR callitrichinae OR caniformia OR duttaphrynus OR ictaluridae OR osteoglossiformes OR poultries OR curema OR "ruddy turnstone" OR  "ruddy turnstones" OR sheatfish OR sunfishes OR centropomidae OR hemachatus OR platalea OR thamnophilidae OR "song thrush" OR atherinopsidae OR siluridae OR tadorna OR chroicocephalus OR ermine OR ermines OR gavialis OR ruffe OR tupaiidae OR diprotodontia OR hyaenidae OR antilopinae OR crocodylidae OR herpestidae OR hippopotamidae OR "northern shoveler" OR "round gobies" OR cheirogaleidae OR indriidae OR fundulidae OR pythonidae OR rhynchocephalia OR anodorhynchus OR "red-backed shrike" OR "red-backed shrikes" OR triakidae OR phalangeridae OR aoudad OR boreoeutheria OR "eurasian jay" OR "eurasian jays" OR feliformia OR haplorhini OR osteoglossidae OR paenungulata OR struthioniformes OR ferina OR sanderling OR sanderlings OR spheniscidae OR cuttlefishes OR cygnet OR dasycneme OR gadwall OR gadwalls OR "pelobates fuscus" OR wryneck OR wrynecks OR afrosoricida OR culaea OR "dover sole" OR "dover soles" OR paralichthyidae OR passeridae OR osteolaemus OR "song thrushes" OR bluethroat OR bluethroats OR hydrophiidae OR megrim OR mephitidae OR strepsirhini OR tomistoma OR epidalea OR osmeriformes OR "bush babies" OR tarsiiform OR atelinae OR bufotes OR "eurasian coot" OR "eurasian coots" OR galagidae OR geopelia OR philomachus OR tubulidentata OR bombinatoridae OR pelobatidae OR tachysurus OR ailuridae OR woodlark OR woodlarks OR alcelaphinae OR redshank OR redshanks OR salientia OR "sand smelt" OR "sand smelts" OR woodmice OR woodmouse OR dasyproctidae OR "eurasian wigeon" OR "eurasian wigeons" OR garganey OR garganeys OR "lemon sole" OR "lemon soles" OR "common dab" OR "common dabs" OR graylag OR graylags OR leucorodia OR osphronemidae OR bewickii OR "common moorhen" OR "common moorhens" OR decapodiformes OR gobbler OR gobblers OR odontophoridae OR paddlefishes OR salmonine OR esociformes OR "eurasian woodcock" OR "eurasian woodcocks" OR "european smelt" OR "european smelts" OR goldfishes OR tenches OR tyranni OR "common chaffinch" OR "common chaffinchs" OR "common redstart" OR "common redstarts" OR "common roach" OR "common roachs" OR "great knot" OR "great knots" OR potoroidae OR alytidae OR coregonine OR dipteral OR leveret OR "poeciliopsis gracilis" OR amphiumidae OR batrachoidiformes OR "bighead goby" OR heteropneustidae OR lullula OR "norway pout" OR "norway pouts" OR sipunculida OR dogfishes OR sebastidae OR tarsiidae OR alethinophidia OR "common nase" OR "common nases" OR "common sandpiper" OR "common sandpipers" OR "eurasian blackcap" OR "eurasian blackcaps" OR pterocnemia OR syngnathiformes OR "common chaffinches" OR eupleridae OR octopodiformes OR phascolarctidae OR scophthalmidae OR "starry smooth-hound" OR "starry smooth-hounds" OR whitefishes OR cuniculidae OR "european sprat" OR "european sprats" OR "rosy bitterling" OR "rosy bitterlings" OR "common dace" OR "common daces" OR "lesser weever" OR "lesser weevers" OR scaldfish OR "water rail" OR "water rails" OR alouattinae OR centrarchiformes OR "common whitethroat" OR "common whitethroats" OR gavialidae OR "grey gurnard" OR "greygurnards" OR lateolabracidae OR rheiformes OR "tub gurnard" OR "tub gurnards" OR "common chiffchaff" OR "common chiffchaffs" OR garfishes OR "lesser whitethroat" OR "lesser whitethroats" OR myoxidae OR seabasses OR spariformes OR umbridae OR "yellow boxfish" OR anabantiformes OR aotidae OR "common bleak" OR "common bleaks" OR "common rudd" OR "common rudds" OR "greater pipefish" OR hapale OR nandiniidae OR "stone loaches" OR whinchat OR whinchats OR acanthuriformes OR "brotula barbata" OR "common ling" OR "common lings" OR "common roaches" OR cottonrat OR cottonrats OR douroucoulis OR dromaiidae OR fitches OR fitchew OR galaxiiformes OR laprine OR saimiriinae OR solenette OR tarsii OR "tompot blenny" OR "common dragonet" OR "common dragonets" OR "longspinedbullhead" OR "longspined bullheads" OR monotremate OR monotremates OR pempheriformes OR perdicinae OR presbytini OR smegmamorpha OR "bighead gobies" OR "carangaria incertae sedis" OR coiidae OR "fivebeard rockling" OR foulmart OR foumart OR grasskeet OR "greater pipefishes" OR ibices OR millionfish OR muguliformes OR "norwegian topknot" OR peewit OR "red sea sailfin tang" OR rupicapras OR sheatfishes OR "tompot blennies" OR "twait shad" OR "yellow boxfishes") |
| 6 | #5 AND #6 |
| 7 | (TS=((=(("systematic review" OR "systematic reviews" OR "meta-analyses" OR "meta-analysis" OR "metaanalyses" OR "metaanalysis" OR "systematic literature review" OR "Systematic survey"[tiab] OR "systematic overview" OR "Systematically review" OR "Systematically searched" OR "Systematic search" OR "Meta synthesis" OR "literature search" OR "literature searches" OR "literature searching" OR "data collection" OR "electronic-database\*" OR "databases-search\*" OR "electronic-search\*" OR "comprehensive-search\*" OR "literature search" OR "literature searches" OR "literature searching" OR "data collection") AND (Pubmed OR Medline OR Embase OR selection OR Web of Science OR Google OR Scopus OR BIOSIS))) |
| 7 | #6 AND #7 |

## Appendix 2: Checklist to assess the state of reporting within preclinical systematic reviews

This checklist is taken from Hunniford et al., 2021.

|  |  |  |
| --- | --- | --- |
| **Section** | **#** | **Item** |
| **Title** | 1 | Identify the report as systematic review in title |
| 2 | Identify that the report contains animal data in title (preclinical, *in vivo* or synonym) |
| **Intro** | 3 | Describe the human condition being modelled (e.g. describe what is already known) |
| 4 | Describe the biological rationale for testing the intervention (e.g. how would the intervention affect the condition) |
| 5 | Provide an explicit statement of the question(s) the review addresses (specify the main objectives of the review, ideally in PICO format) |
| **Methods** | 6 | Indicate whether a review protocol was registered *a priori* |
| a | Where can the protocol be accessed and indicate the name of the protocol registry OR state that it is not available |
| b | Indicate any deviations from the protocol OR that there were no deviations |
| 7 | Eligibility criteria: Describe the animal species to be included in the review (e.g. only mice, vertebrates, large animals) |
| 8 | Eligibility criteria: Describe the animal model to be included in the review (methods of disease induction, age, sex, etc.) |
| 9 | Eligibility criteria: Describe the intervention/exposure of interest |
| 10 | Eligibility criteria: Describe the comparators and/or control population |
| 11 | Eligibility criteria: Describe the primary outcomes of interest (what is being measured/assessed in primary studies) |
| 12 | Eligibility criteria: Describe the timing (prevention vs rescue) of intervention, IF applicable |
| 13 | Indicate where a full search strategy of all data bases OR representative search strategy can be accessed |
| 14 | Describe inclusion limits (years conducted, language, AND publication type) |
| 15 | Describe the study screening/selection process |
| a | Report the platform used to screen and select studies (Excel, Access, DistillerSR, SyRF) |
| 16 | State the number of independent screeners |
| 17 | Describe methods for extracting numerical data from reports (e.g. data in bar graph, or non-text presentation), IF applicable \* |
| a | Report the platform and tools used to extract numerical data (Graph2data, Engauge) |
| 18 | Report number of independent reviewers extracting data |
| 19 | Describe methods and tool used to measure study quality/risk of bias in individual studies (e.g. SYRCLE tool, CAMARADES tool) |
| 20 | Describe methods to assess construct validity in individual studies |
| 21 | Describe methods for assessing publication bias of included studies, IF applicable |
| 22 | Describe methods for synthesizing the quantitative effect measures of included studies (e.g. risk ratio, mean difference), IF applicable \* |
| 23 | Describe methods for any data transformation needed to make extracted data suitable for analysis (e.g. only sample size range), IF applicable \* |
| 24 | Describe methods for handling shared control groups (common issue in analysis of preclinical studies), IF applicable \* |
| 25 | Describe methods for assessing heterogeneity between individual studies, IF applicable \* |
| 26 | Describe methods for handling effect sizes over multiple time points (e.g. used all time points or latest time point), IF applicable \* |
| 27 | Describe methods for sub-group and sensitivity analysis, IF applicable \* |
| **Results** | 28 | Report the number of included reports (individual references/publication) included in the review |
| a | Provides a list or table of individual studies with data or references |
| 29 | Report the number of eligible experiments included in the analysis (eligible animal experiments in individual reports) |
| 30 | Include a PRISMA flow diagram (or equivalent) of study selection process |
| 31 | Study characteristics: Report animal species |
| 32 | Study characteristics: Report animal model details (e.g. method of disease induction, age, sex) |
| 33 | Study characteristics: Report a measure of the sample size (e.g. total number or mean number of animals) |
| 34 | Study characteristics: Report intervention/exposure details (timing, dose) |
| 35 | Study characteristics: Report study design/intention (pharmakinetic, mechanistic, efficacy) |
| 36 | Report the risk of bias of the primary studies (individual studies/across outcomes) |
| 37 | Report the outcome effects of primary studies (forest plot if applicable), IF applicable \* |
| 38 | Report the confidence intervals of outcomes for the included studies, IF applicable \* |
| 39 | Report any measure of heterogeneity between studies, IF applicable \* |
| 40 | Report the results of sub-group and sensitivity analysis, IF applicable \* |
| 41 | Report the results of publication bias, OR report that it was not possible/done |
| **Discussion** | 42 | Discuss the impact of the risk of bias of the primary studies |
| 43 | Discuss the limitations (i.e. limitation of primary studies and/or outcomes included) |
| 44 | Discuss the limitations of the systematic review |
| **Other** | 45 | Include the funding source(s) of the systematic review |
| 46 | Report any data sharing, OR that there was no data sharing |
| **\* Reporting item is not applicable to systematic reviews that did not perform a quantitative synthesis. For reviews that did not perform a quantitative synthesis, these items receive an NA.** | | |

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