Systems-Level Insights into Bronchopulmonary Dysplasia from Meta-Analysis of Genome-Scale Studies

Chris Happs[1,2]*, Prerna Khanna[1,2]*, Charlotte Scoynes[2], Nelly Muriungi[1], Akira Alexander[1], Josh Rogers[1], Elizabeth Lake[1,2], Maximilian Pickup[1,2], Nicholas Parkinson[1,3], Jonathan Millar[2], J. Kenneth Baillie[1,2], Sara Clohisey Hendry[1,2]

* These authors contributed equally

1. Roslin Institute, University of Edinburgh, Edinburgh, U.K.
2. Baillie-Gifford Pandemic Science Hub, Institute for Regeneration and Repair, University of Edinburgh, Edinburgh, U.K.
3. Royal (Dick) School of Veterinary Studies, University of Edinburgh, Edinburgh, U.K.

Supplementary Materials

Supplementary Table 1

Inclusion	Exclusion
Bronchopulmonary Dysplasia, Hyaline Membrane Disease, Respiratory Distress Disorder	Meta-analyses, *in-silico* analyses, or re-analysis of previously published data
Accepted methodologies	Candidate *in-vivo* or *in-vitro* transcriptomic or proteomic studies (defined as those investigating < 50 genes)
	Candidate gene association studies
Human	
In vivo, in vitro, primary human cells and tissues	Term neonates, Children, Adults
Any/all treatment administered to patients before sample collection	
Animal	
Mammals (non-human)	
In vivo studies	
Hyperoxia, induced IUGR, LPS treatment	

Supplementary Table 1: Inclusion and exclusion criteria for MAIC analysis

Supplementary Table 2

Accepted Methodologies	MAIC category
CRISPR screen	CRISPR
RNAi screen	RNAi
Protein-protein interaction study	Protein-protein
Genome-wide association study	GWAS
Transcriptomic study	RNAseq, scRNAseq, Microarray,
Proteomic study	Mass Spec
Selected gene-set screens	Geneset
Exome sequencing	Exomeseq
Epigenetic study (e.g. DNA methylation)	DNAMethylation

Supplementary Table 2: Methodologies accepted for inclusion and associated labels/categories for MAIC analysis.

Supplementary Table 3

Human MAIC analysis		Animal MAIC analysis	
Methodology	**Number of studies**	**Methodology**	**Number of studies**
Microarray	6	Microarray	11
ExomeSeq	4	RNAseq	18
RNAseq	5	GWAS	1
GWAS	4	scRNAseq	4
Mass Spec	2	DNA methylation	1

Supplementary Table 3: Methodologies used in included studies.

Supplementary Table 6

Dataset Comparison	Significance
ARDS human gross versus BPD human gross	-
ARDS human priority versus BPD human priority	***
BPD human gross versus BPD rodent gross	-
BPD human priority versus BPD rodent priority	***

Supplementary Table 6: Significance of overlaps between ranked gene lists.

Supplementary Methods

Search Strategy

The search strategy used to identify relevant literature for the systematic review:

1. "Bronchopulmonary Dysplasia*".ti,ab,kf,kw.

2. "Respiratory Distress Syndrome, Newborn*".ti,ab,kf,kw.

3. "Hyaline Membrane Disease*".ti,ab,kf,kw.

4. 1 or 2 or 3

5. "gene*".mp.

6. "genome*".mp.

7. "transcript*".mp.

8. "protein*".mp.

9. 5 or 6 or 7 or 8

10. 4 and 9

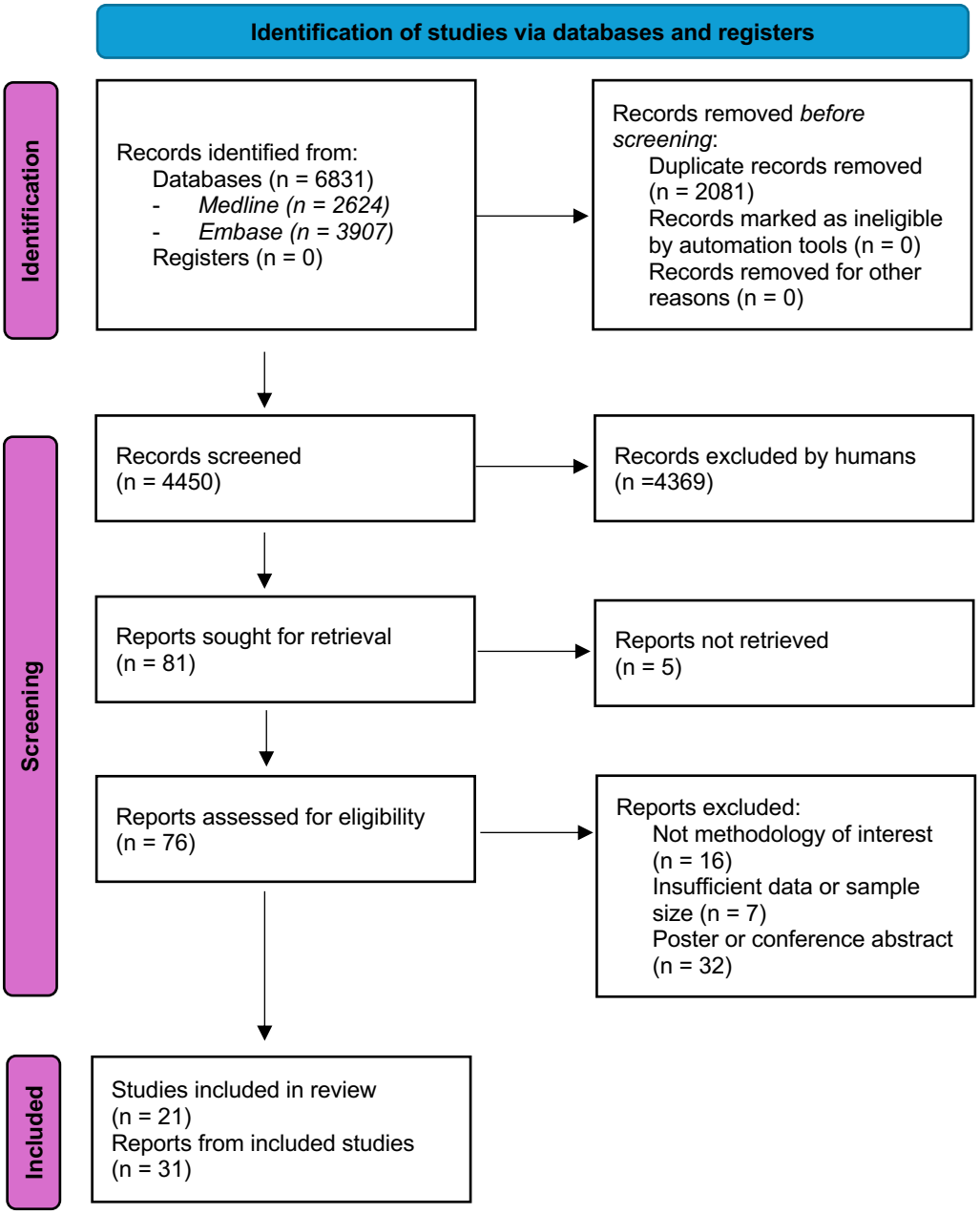
11. (Letter or Conference Abstract or Conference Paper or Conference Review or Editorial or Erratum or Review or Note or Tombstone).pt.

12. 10 not 11

Overlap Analysis of Ranked Gene Lists

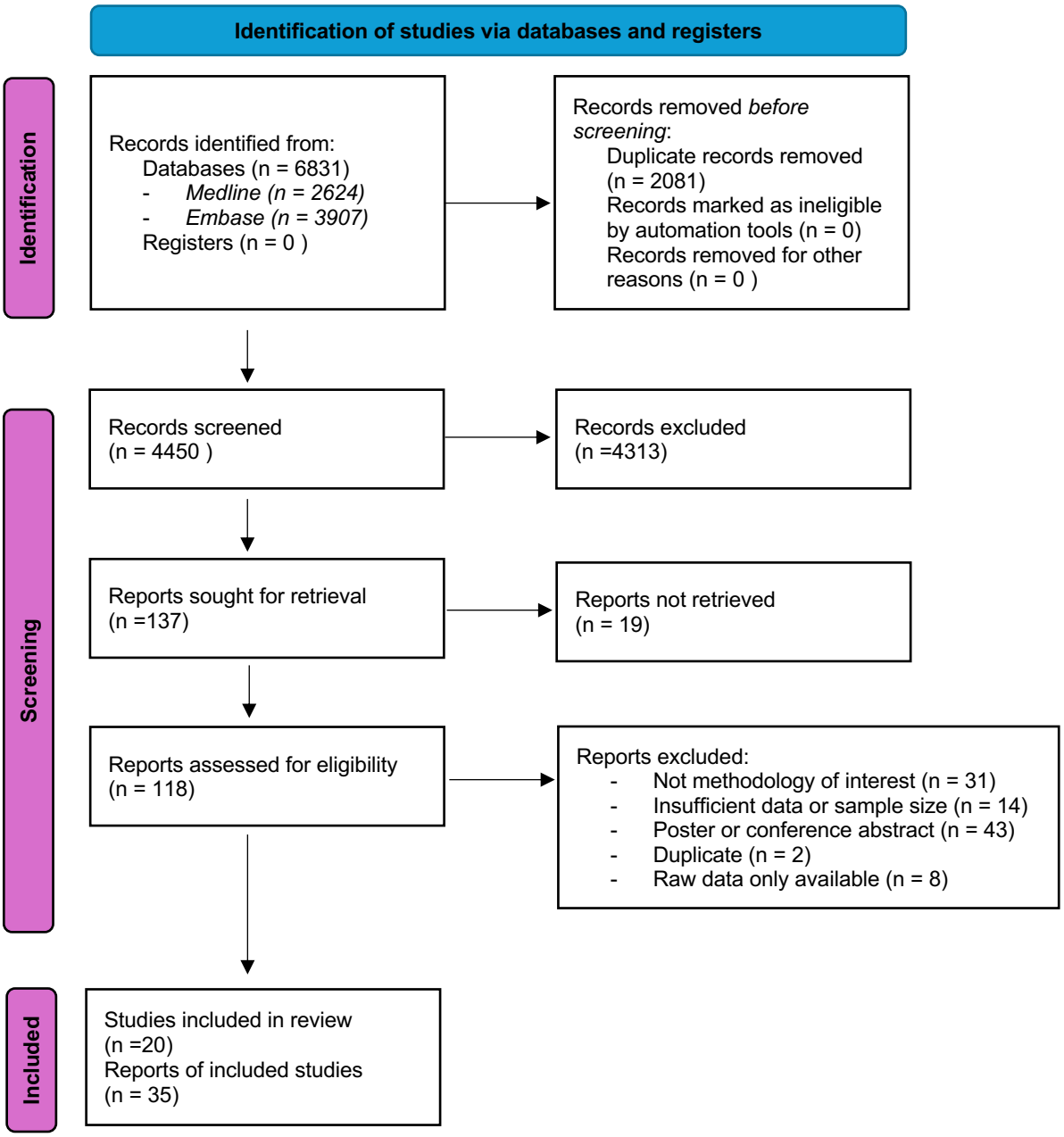
To assess the degree of similarity between ranked lists, we computed the percent overlap at incremental list lengths. Beginning with the top-ranked gene from each list, we iteratively increased the comparison window by one gene until reaching a maximum of n genes. At each step, the proportion of overlapping genes was calculated as the number of shared genes divided by the number of genes included at that step, expressed as a percentage.

Supplementary Figure 1:



From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

Supplementary Figure 2



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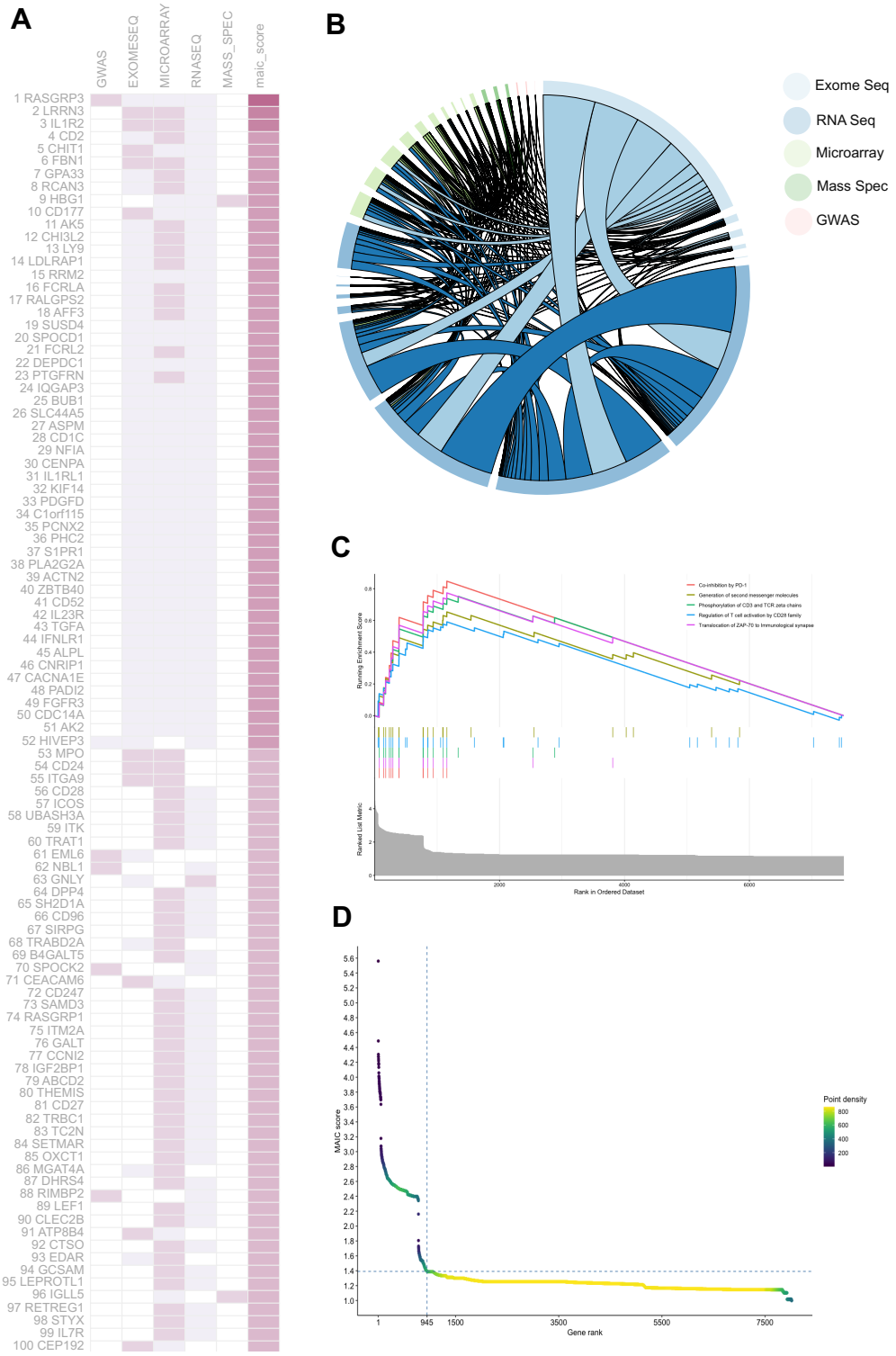
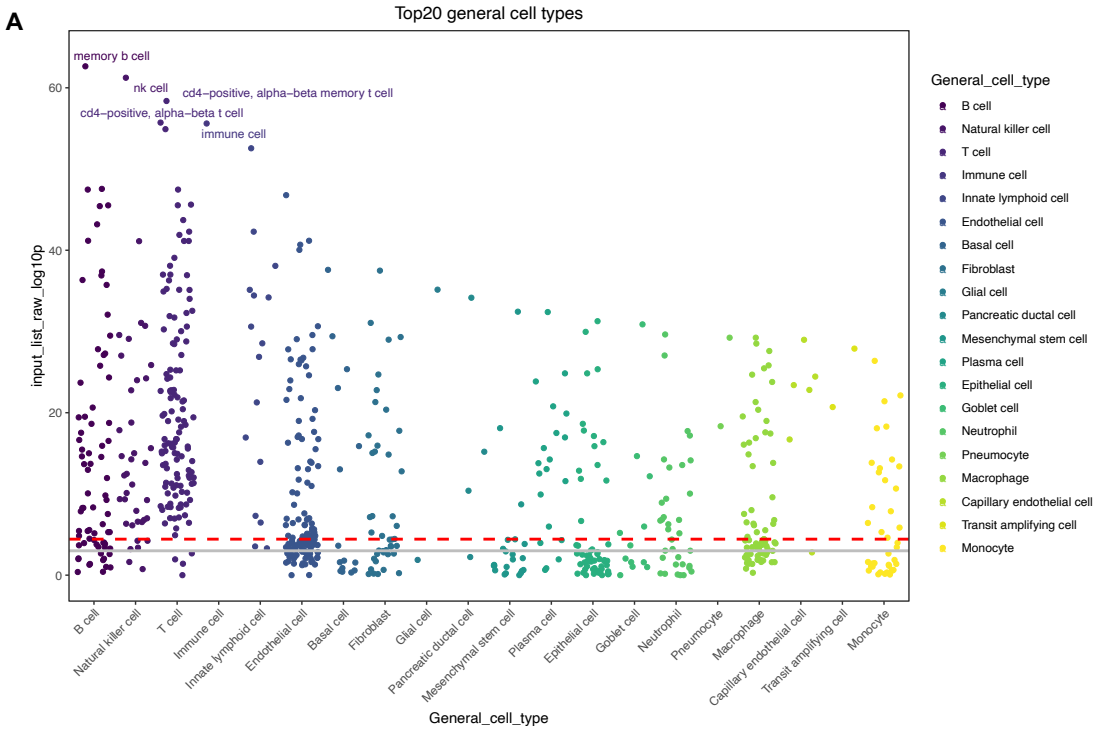
Supplementary Figure 3



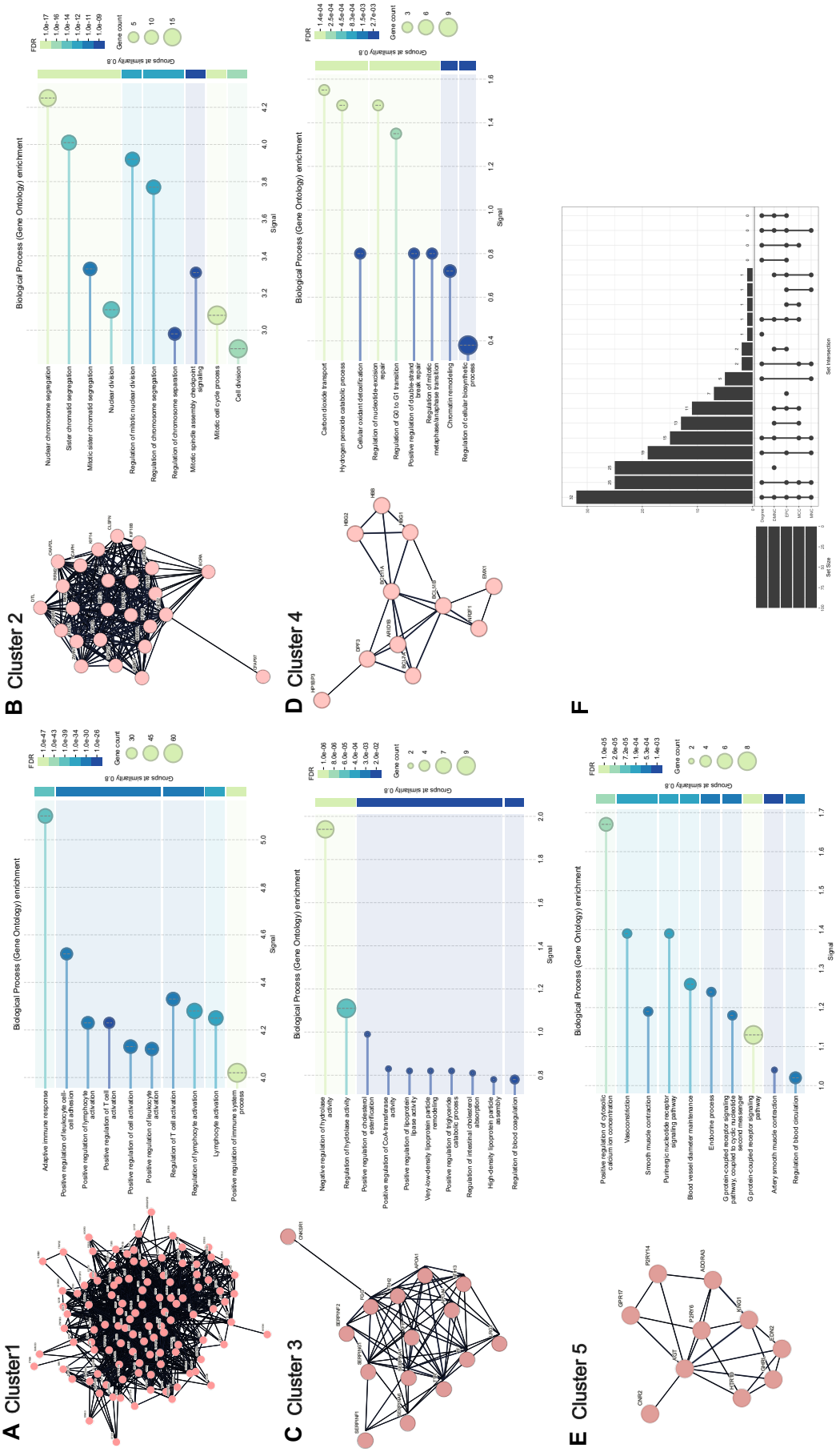
Supplementary Figure 3: A) Heatmap of top 100 human BPD genes ranked by MAIC score and indicating the source of the data. B) Circos representation of shared information content among data sources in the MAIC analysis. Each experiment or data source is represented by a block on the outer ring of the circle; the size of data source blocks is proportional to the summed information content of the input list—that is, the total contribution that this data source makes to the aggregate, calculated as the sum of the MAIC gene scores contributed by that list. Lines are coloured according to the dominant data source. Data sources within the same category share the same colour. C) Enrichment plot of top pathways in Figure 1 B. D) Gene prioritisation plot using the invariant knee method. The inflection point is indicated with a dotted line. 945 genes in the left upper quadrant of the knee threshold were prioritised for downstream analysis.

Supplementary Figure 4



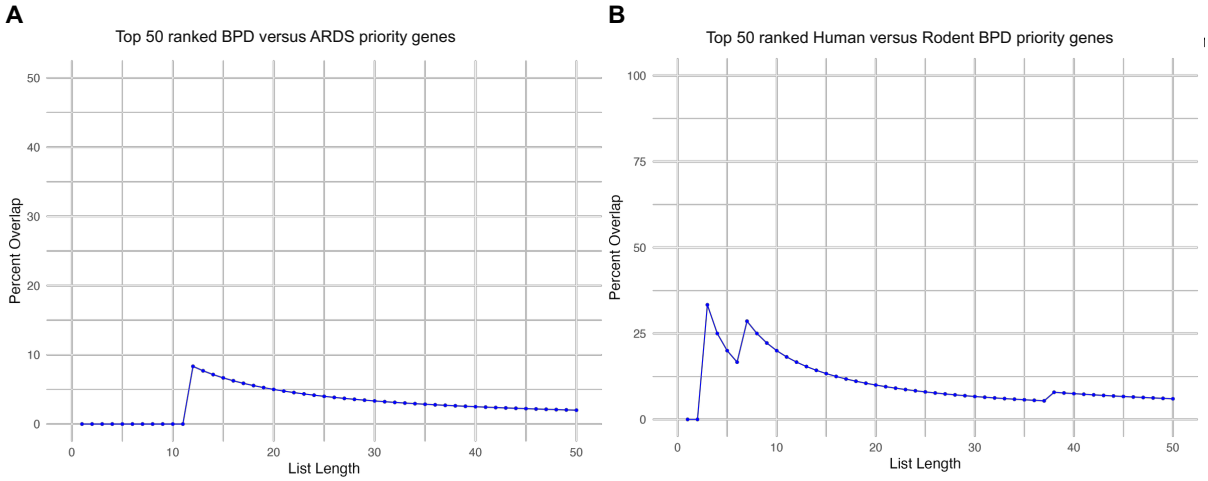
Supplementary Figure 4: Top 20 general cell types for the prioritised human BPD gene set, as indicated by WebCSEA.

Supplementary Figure 5



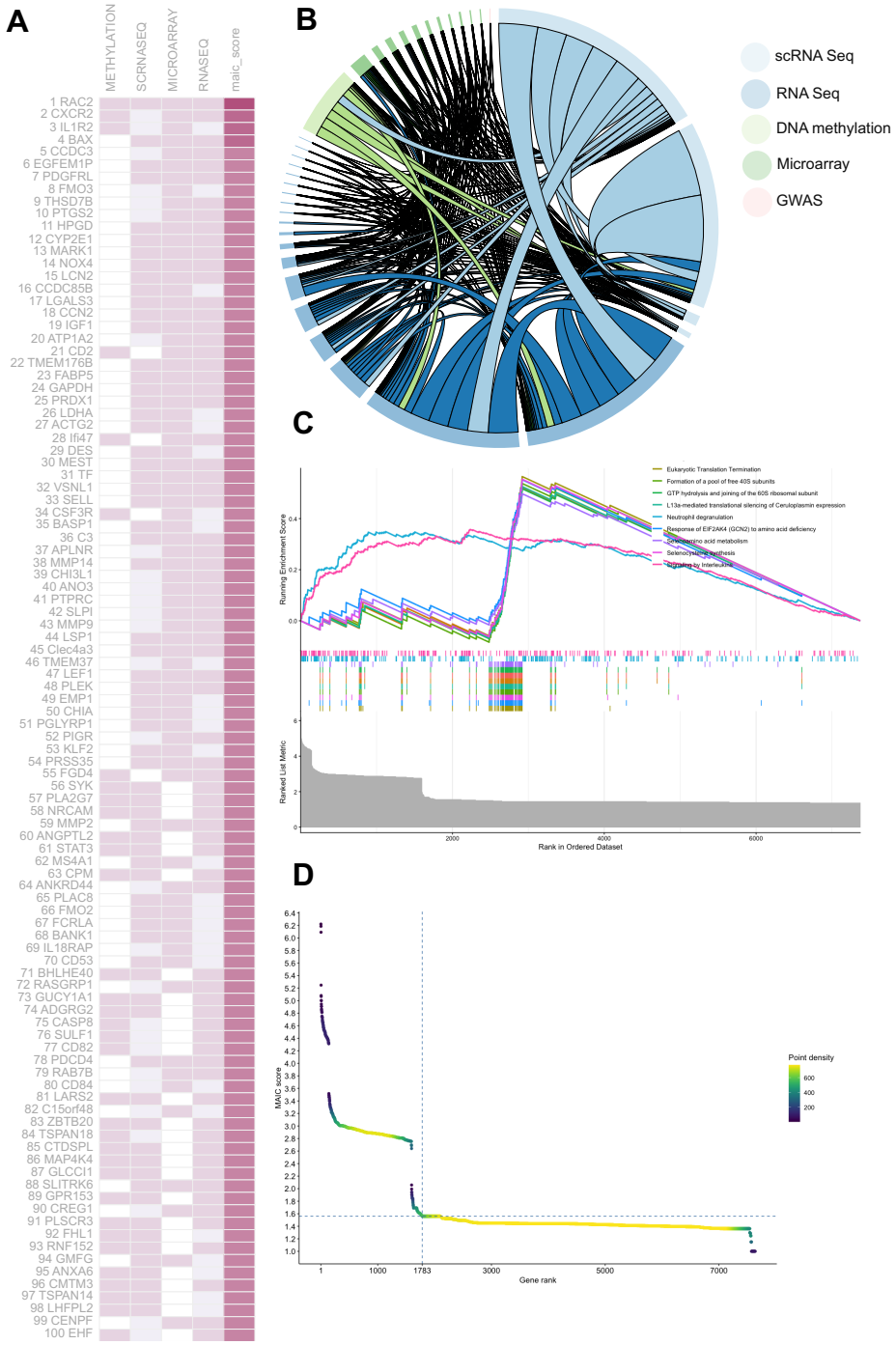
Supplementary Figure 5: A-E) Pathway analysis using String db of prioritised human BPD gene set. F) UpSet plot of overlapping proteins indicating hub proteins, identified by five methods: MNC - Maximum Neighbourhood Component, DMNC - Density of MNC, EPC - Edge Percolated Component, MCC - Maximal Clique Centrality.

Supplementary Figure 6



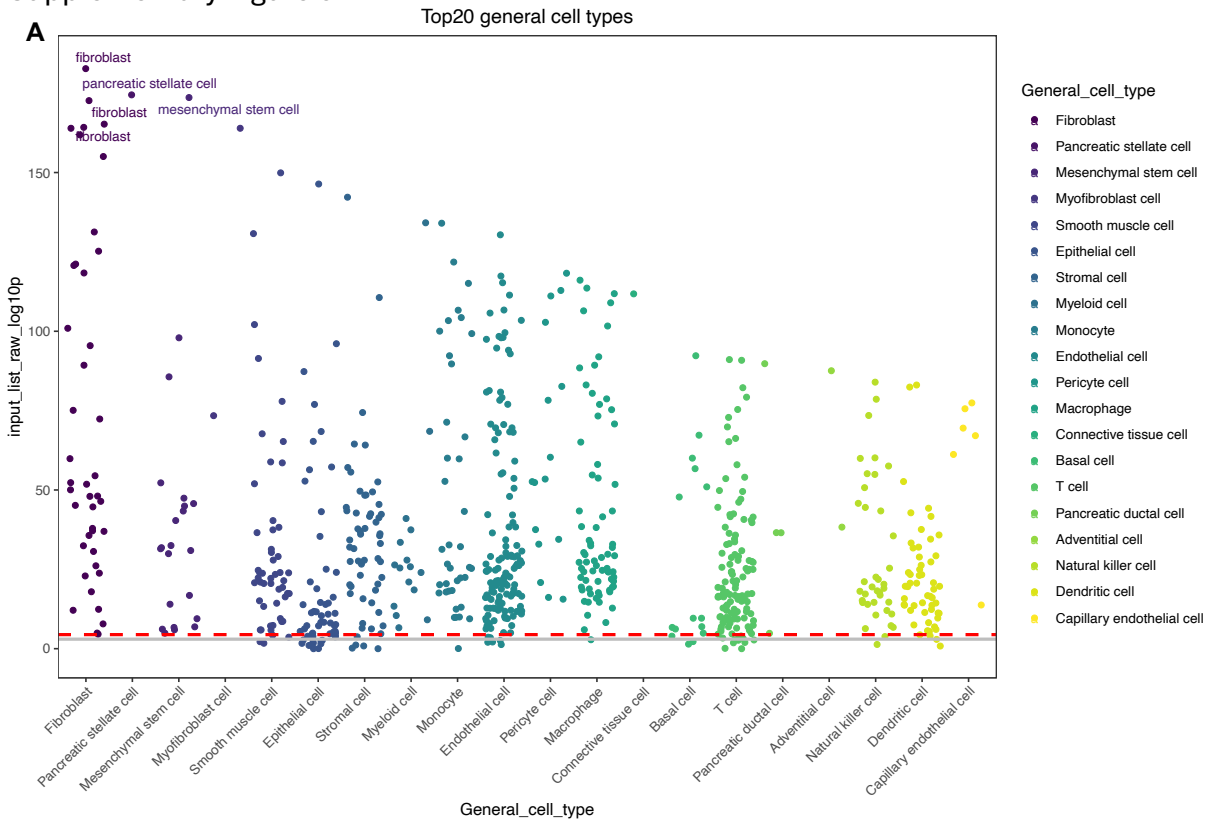
Supplementary Figure 6: A) Percent overlap between the top 50 MAIC-ranked Human ARDs genes versus the top 50 Human BPD genes. B) Percent overlap between the top 50 MAIC-ranked Human BPD genes versus the top 50 Rodent BPD genes.

Supplementary Figure 7



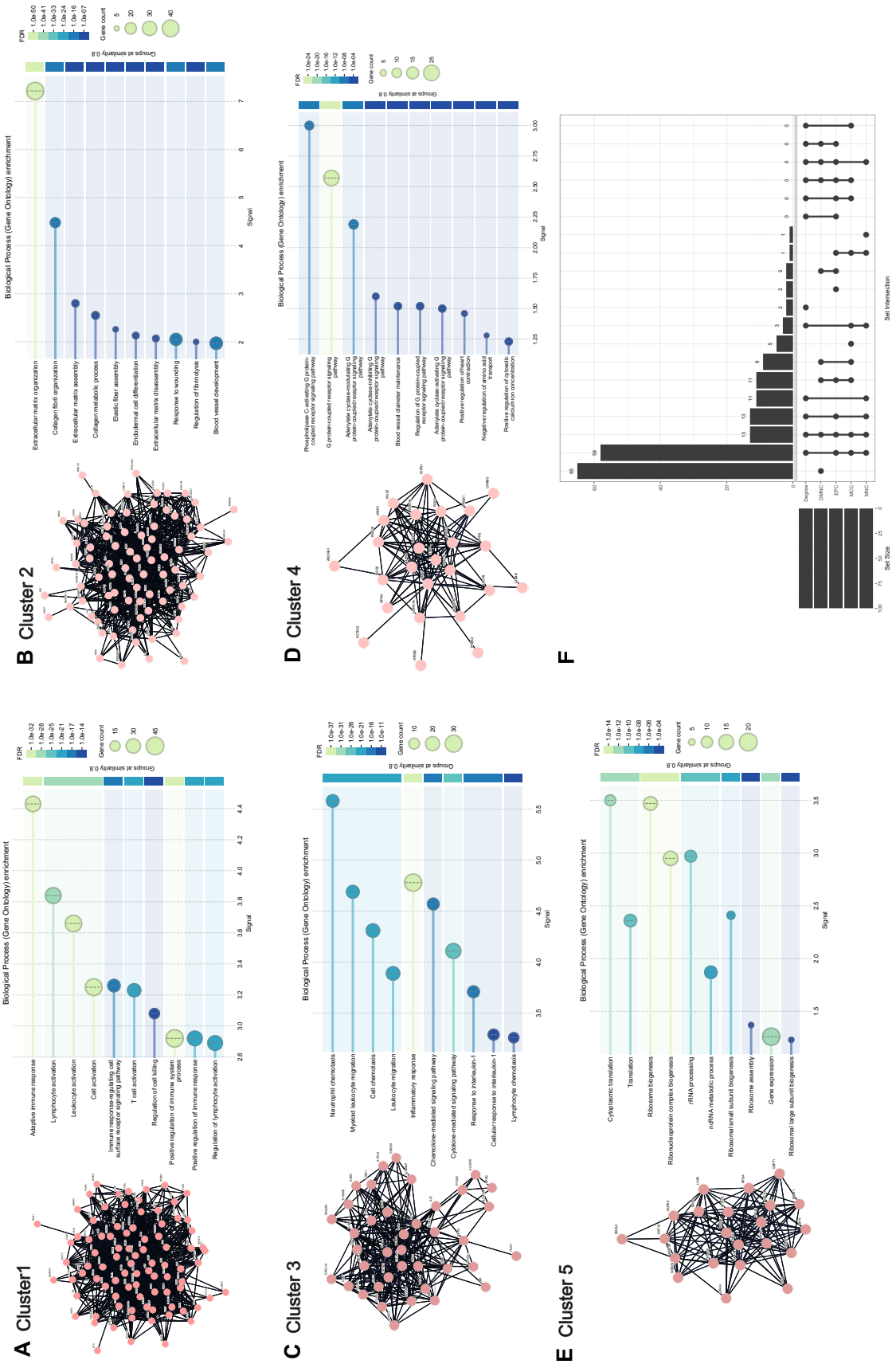
Supplementary Figure 7: A) Heatmap of top 100 rodent BPD genes ranked by MAIC score and indicating the source of the data. B) Representation of shared information content among data sources in the MAIC analysis. Each experiment or data source is represented by a block on the outer ring of the circle; the size of data source blocks is proportional to the summed information content of the input list—that is, the total contribution that this data source makes to the aggregate, calculated as the sum of the MAIC gene scores contributed by that list. Lines are coloured according to the dominant data source. Data sources within the same category share the same colour. C) Enrichment plot of top pathways in Figure 3 B. D) Gene prioritisation plot using the invariant knee method. The inflection point is indicated with a dotted line. 1783 genes in the left upper quadrant of the knee threshold were prioritised for downstream analysis.

Supplementary Figure 8



Supplementary Figure 8: Top 20 general cell types for the prioritised rodent BPD gene set, as indicated by WebCSEA.

Supplementary Figure 9



Supplementary Figure 9: A-E) Pathway analysis using String db of prioritised rodent BPD gene set. F) UpSet plot of overlapping proteins indicating hub proteins, identified by five methods: MNC - Maximum Neighbourhood Component, DMNC - Density of MNC, EPC - Edge Percolated Component, MCC - Maximal Clique Centrality.