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

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**Running title:** MAIC analysis of Bronchopulmonary Dysplasia

**ABSTRACT**

**Background**

Despite marked improvements in survival following preterm birth, the incidence of bronchopulmonary dysplasia (BPD) continues to rise. BPD remains the most prevalent complication of prematurity and carries the risk of long-term morbidity. Characterising the cellular and molecular mechanisms driving disease progression is critical for informing clinical management and improving outcomes. To this end, we conducted a meta-analysis of genome-scale studies to identify molecular pathways implicated in BPD progression in both human cohorts and animal models.

**Methods**

Gene lists associated with bronchopulmonary dysplasia in humans and in rodent models were obtained from systematically identified genome-scale studies. These lists were then analysed using the meta-analysis by information content (MAIC) algorithm, which integrates multiple datasets to produce a single aggregated, ranked gene list based on the cumulative strength of evidence for each gene.

**Results**

**Conclusions**

**Key words:** Bronchopulmonary Dysplasia; adaptive immunity, T cells,

**Background**

Bronchopulmonary dysplasia (BPD), a chronic lung disease, is one of the most common complications of preterm birth, affecting up to 30% of preterm infants born before 32 weeks post-menstrual age (PMA).(*Neonatal Data Analysis Unit (NDAU). Neonatal Health Intelligence Tool. 2021. Available: Https://Www.Imperial.Ac.Uk/Neonatal-Data-Analysis-Unit/Neonatal-Data-Analysis-Unit/Neonatal-Data-Visualisations/*, n.d.),(Isayama et al., 2017; Jensen et al., 2019) Antenatal and postnatal factors disrupt the developing lung leading to decreased alveolarisation, larger alveoli, irregular pulmonary vessels, and fibrotic tissue.(Gilfillan et al., 2021; Thébaud et al., 2019) The effects of BPD can be life-long; individuals with BPD are more likely to require rehospitalisation during their childhood and to have limited lung function compared to those born preterm without BPD.(Dassios & Greenough, 2021; Greenough, 2000, 2006; Sun et al., 2023)

The heterogeneity of the disease has hampered efforts to identify reliable, consistent biomarkers. Understanding the molecular mechanisms that contribute to BPD could aid in risk prediction, targeted therapies, and understanding disease mechanisms. Alongside evidence from twin studies pointing to a possible heritable component in BPD (Bhandari et al., 2006; Lavoie et al., 2008) some candidates have been identified (e.g. SPOCK2, CRP). Though no gene has been significantly associated with the development of BPD via Genome Wide Association Studies (GWAS) or exome sequencing.(Ambalavanan et al., 2015; Hadchouel et al., 2011; Mahlman et al., 2017; Torgerson et al., 2018; H. Wang et al., 2013) Recently, transcriptomic data has been used to identify four endotypes of BPD, distinguished by T helper cell and T cell signalling.(Moreira et al., 2023)

Comparative transcriptomic analyses across species can provide valuable insights into common mechanisms while also highlighting potential species-specific responses. Rodent models, particularly murine models, have been widely employed to study the pathophysiology of BPD. Anatomical and physiological differences have prevented in-depth research of ventilator induced lung injury in this model and research has concentrated primarily on hyperoxia-induced lung injury, mimicking the impaired alveolar development and inflammation observed in preterm infants.(Hurskainen et al., 2021)

Integrating results from heterogenous sources can allow for novel insights. In this study we incorporate insights from genome-scale research to complement the longstanding emphasis on clinical studies in the field. We conducted two concurrent systematic reviews of the BPD literature, focusing on genome-scale studies in humans and rodents. Results were extracted from identified studies, where possible, and analysed using Meta Analysis by Information Content (MAIC) algorithm. MAIC is a previously described algorithm that uses data-driven gene list weightings to produce a comprehensive ranked list of genes associated with the trait of interest.(Millar et al., 2024; Parkinson et al., 2020; The GenOMICC Investigators et al., 2021; B. Wang et al., 2022)

Our findings show that BPD is a multifaceted disease characterised by disruptions in adaptive immune signalling and extracellular matrix organisation. Of note, genes associated with development and maintenance of adaptive immunity feature prominently, suggesting that adaptive-lineage cells may play a larger role in BPD pathogenesis, and a wider role in ventilator associated lung injury, than previously appreciated.

**Results**

*Systematic review*

We first conducted a systematic review of studies that reported associations between genes, transcripts, or proteins, and the development of BPD in humans or the study of BPD in non-human mammalian models. We did not restrict the search to a specific definition of BPD; however, the timeline of genome-scale studies results in an indirect emphasis on ‘new BPD’. Our search yielded 4450 unique citations that were evaluated for inclusion [Supplementary Figures 1 and 2]. For full text evaluation we retrieved 76 articles for human studies and 118 for mammalian studies, without overlap. Although large mammal models are used to explore BPD,(Eiby et al., 2013; Rozance et al., 2011) we did not identify any that met our inclusion criteria (Supplementary Tables 1 and 2) and the analysis therefore focused on rodents(mice and rats).

*Meta-Analysis by Information Content of human studies*

From the 81 human studies, 21 met our eligibility criteria[Supplementary Figure 1, Table 1]. This yielded 31 gene lists, 23 ranked and 8 unranked, employing 5 experimental techniques. (Supplementary Table 3,) The included studies represented 4358 infants (cases = 2247, controls = 2111). While the definition of BPD varied between studies, over two-thirds of studies, (71.4%, 15/21), used receipt of respiratory support at 36 weeks PMA.(Jensen et al., 2019) All but a single study used primary tissue or blood (Table 1). MAIC collated and ranked 8017 unique genes across the datasets [Supplmentary Table 4, Figure1A], and only a single gene was supported by evidence from all 5 experimental techniques (*RASGRP3*, rank = 1). Few genes (n = 53 genes, 0.6%) were supported by >=3 methods while 745 genes (9.74%) were supported by more than 1 method. Genes associated with immune processes (*RASGRP3, IL1R2, CD2, CHIT1, GPA33, CD177, RCAN3)* and extracellular structure *(LRRN3, FBN1)* are heavily represented within the top 10 ranked genes. Additionally, a subunit of foetal haemoglobin, *HGB1,* features,. We prioritised 945 genes for further investigation [Figure 1B], as previously described (Millar et al., 2024) and of these 310 (38%) were identified as druggable using the Druggable Genome.

*Over representation and enrichment analyses*

We first performed Over Representation Analysis (ORA), on the prioritised list of 945 genes. The ORA results from the Gene Ontology database (encompassing all ontologies) were grouped first based on semantic similarity and then based on function [Figure 1C]. Our analysis reveals a significant over-representation of immune system processes asscoaited with adaptive immunity and lymphoid cells, with a prominent emphasis on T cell differentiation and regulation, and cell-cell adhesion. This is further supported by ORA using the KEGG and Reactome databases [Supplementary Tables 5-8]. T cell development was further highlighted when we carried out gene set enrichment analysis (GSEA) of the human BPD MAIC dataset [Figure 1D, E]. We then created a protein-protein interaction (PPI) network using the prioritised set of genes. MCL clustering identified 25 clusters with >=5 members. The 7 largest clusters contained >=10 members [Supplementary Figures shows the top 5 clusters]. Using previously reported methods (Millar et al., 2024), we identified 32 hub genes proposed to play central roles in the broader network [Figure 1F]. MCL clustering of this hub revealed three major clusters related to lymphocytes, corresponding to activation (red, blue), receptors (blue), and immunoglobulins (green) (Figure 1G).

*ARDS dataset*

Acute lung injury caused or worsened by mechanical ventilation during treatment is a feature of BPD in neonates and Acute Respiratory Distress Syndrome (ARDS) in adults (paediatric ARDS in children). We wished to characterise, as a first step firstly, the shared of effects mechanical ventilation may have on the developed and the developing lung, and to understand distinct factors that may underlie each syndrome. We evaluated the human BPD MAIC dataset against our previously generated ARDS MAIC analysis.(Millar et al., 2024)

Over Representation Analysis focusing on the prioritised genes from both datasets highlighted shared pathology relating to adaptive immunity with pathways associated with positive regulation of T cell activation [Figure2A]. While NF-kappa signal transduction is associated with ARDS, it does it is not evident in our BPD dataset, suggesting a divergence in the underlying pathologies. We then sought the overlap between both datasets, to find the genes most likely to be associated with both syndromes from the literature. There were 112 genes that overlapped in the prioritised sets from both datasets, [Figure2B] and this overlap was found to be significant using a hypergeometric test using the protein-coding genome as the background set (p<0.005). We assessed the degree of similarity between ranked lists and found much of the overlap occurred toward the top of the lists. [Figure 2C]. Over representation analysis found leukocyte mediated immunity, lymphocyte mediated immunity, and positive regulation of both T cells and type II interferon were highlighted [Figure2D] in the overlapping genes. A PPI network focused on the overlap between datasets identifies a hub consisting of 5 genes with roles in IL8 signalling (*CXCL8, MMP9*) and lymphocyte surface receptors (*CD4, CD40, CD2*). [Figure 2E].

*Meta-Analysis by Information Content of rodent studies*

From 20 eligible rodent BPD studies [Supplementary Figure 2, Table 2] we extracted 35 gene lists for MAIC analysis (28 ranked and 7 unranked), employing 5 experimental techniques (Supplementary Table 3). Of these studies, 13 used mice models and 7 used rat models. The study therefore reflects primarily a rodent dataset rather than the broader non‑human mammalian dataset originally intended. The majority (17/20; 85%) of studies modelled BPD by exposing neonatal pups to a hyperoxic environment, though the approaches differed; there was variation in the timeframe of hyperoxia (from 3 days to 14 days), recovery in room air (0 days to 57 days), continuous versus intermittent hyperoxia, and the percent oxygen (70 – 100%) used across the studies. Other methods to model BPD in rodent models included lipopolysaccharide (LPS) treatment (1 study) and induced IUGR through maternal diet (1 study). All but one included study used lung tissue for analyses. MAIC collated 7637 genes across all datasets [Figure 3A, Supplementary table 5] and 3 genes were supported by evidence from >=4 experimental techniques (*RAC2*, *CXCR2*, *IL1R2*). One in five genes were supported by more than 1 method (n = 1597, 20.91%), with 141 genes (1.85%) supported by >=3 methods. Immune processes are again represented within the top ten genes (*RAC2*, *CXCR2*, *IL1R2*, *CCDC3*, *PTGS2*). Interestingly, *IL1R2* is shared between the top 10 lists of both analyses. We prioritised 1783 genes for further investigation [Figure 3B].

*Rodent functional enrichment*

Gene ontology ORA revealed a significant overrepresentation of pathways related to myeloid cells and development of muscle tissue and extracellular matrix organisation [Figure 3C]. Regulation of T cell activation is also observed though is less prominent than seen in the human results. We created a protein-protein interaction (PPI) network. MCL clustering identified 55 clusters with >=5 members [Supplementary Figure]. The 21 largest clusters contained >=10 members. Among these, we found programs associated with the adaptive immune response and mitosis. We used the PPI network to identify 13 hub genes, including FC gamma receptors [*FCGR1A, FCGR2A, FCGR2B*] and lymphocyte markers [*CD3E, CD2*], suggested as being central to the wider network [*Figure 3D*].

*Comparison of human and rodent datasets*

Ontology ORA showed that while the adaptive immune signal observed in humans above was seen in the rodent dataset, the rodent dataset also highlights the role of the extracellular matrix and wound healing [Figure 4A]. The gross overlap between the two parallel MAIC analyses carried out in this study was not shown to be significant by hypergeometric test (p>0.5). However, focusing on the prioritised genes from both datasets indicated the overlap of 163 genes [Figure 4B] was significant [Supplementary Table 6]. The similarity between ranked lists occurred predominantly toward the top of the prioritised lists. [Figure 4C]

Focusing on the overlapping genes,

**Discussion**

The clinical and biological heterogeneity of BPD presents challenges for identifying the molecular processes that drive progression of the disease. To address this, we applied a validated *in silico* approach to systematically integrate and prioritise existing genome-scale BPD datasets from both human and rodent studies. Further to this, we compared our human BPD MAIC results to previously generated similar output for ARDS generated within our lab.

Processes associated with lymphocytic cell development and activation are strongly represented throughout our results. Cell-type specific enrichment analysis of genes (Dai et al., 2022) in our prioritised human dataset (supplementary figure 5) reinforce this, as B-cells, NK cells and T-cells are the most over-represented cell types observed. Our findings prioritise specific elements of the T cell immune response, in particular development and adhesion. This is not without foundation within the literature. A recent study of potential transcriptomic endotypes in BPD focused on the Pietrzyk dataset included in our analysis.(Moreira et al., 2023; Pietrzyk et al., 2013) and identified 4 potential endotypes underlying BPD progression. T helper 17 (Th17) differentiation emerged as the most significant pathway distinguishing the BPD endotypes. CD4+ T-cells were shown to be reduced in infants who develop BPD.(‘Lymphocyte Subpopulations in Bronchopulmonary Dysplasia’, 2003) While, a lower CD4/CD8 ratio has been observed in adults with a history of BPD.(Um-Bergström et al., 2022) These taken together suggest a central role for lympohoid cells in the progression of BPD, though do not calarify the potential role that B cells may play.

Some evidence for the role of B-cells is that the top hit in the human dataset is Ras guanyl-releasing protein 3, RASGRP3, a guanyl nucleotide exchange factor. This gene acts downstream of the B-Cell Receptor to activate RAS and RAP1,(Rebhun et al., 2000) playing an analogous role to its family member RASGRP1 (rank = 75) which enables positive selection of thymocytes and activation of T cells. (Fuller et al., 2012)

ARDS results

IL8 signalling

Lymphocytes

We don’t see the cholesterol pathways.

Rodent results

The rodent results are

There is a focus on fibroblast processes and pathways associated with extra cellular matrix remodelling in the rodent dataset, perhaps reflecting the more common use of lung tissue over blood samples in genome-scale analysis (supplementary figure 6) or species-specific differences.

The Interleukin-1 Receptor Type 2 (IL1R2) gene was identified as a significant locus in both human (rank =) and rodent (rank = ) datasets, a finding that anchors the disease in the context of the perinatal hypoxic-inflammatory environment. IL1R2 is upregulated in acute hypoxia.(Johnson et al., 2007) and functions as a decoy receptor, acting as a crucial endogenous brake on the potent pro-inflammatory signalling cascade initiated by Interleukin-1 (IL-1) (Peters et al., 2013). The preterm lung is uniquely vulnerable to hypoxia, which can trigger a dangerous, self-amplifying cycle of injury and inflammation.(Eltzschig & Carmeliet, 2011) IL-1 antagonism has been shown to confer protection in rodent models of BPD (Bui et al., 2019; Nold et al., 2013), suggesting that IL1R2 may exert a protective role as an anti-inflammatory ‘brake’ protein. Insufficient upregulation of this gene would leave the preterm lung defenceless against unchecked IL-1-driven inflammation, leading to the severe and progressive lung damage that defines BPD.

This study is based on the published literature and is intended to capture the current state of genome-wide BPD research. It is subject to several limitations. Firstly, blood is among the least invasive and most practical biological samples to collect in the NICU setting. Over half of the gene lists from human studies were derived from primary blood samples (11/21, 52.4%). Gene regulation and expression is often context and tissue specific, consequently, our human results are likely indicative of circulating biomarkers and may not entirely reflect the extent of tissue injury at its origin. Conversely, blood samples are not commonly taken in rodent studies of BPD, where whole lung tissue is preferred. This may have contributed to the different gene signatures observed between the two analyses. Secondly, due to experimental methodologies, the rodent models of BPD included in this analysis may not accurately reflect the human disease as a whole but summarise the effects of hypoxia induced during disease. Thirdly, due to key developmental differences - such as timing of alveolarisation and immune system maturation – the results may not be directly comparable between species. It is difficult to determine if some uncommon, enriched pathways reflect rodent-specific responses to experimental injury rather than universally conserved disease mechanisms. Finally, MAIC does not accommodate direction of effect.

In conclusion, ...

**Methods**

***Systematic review***

The systematic review and meta-analysis protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO; CRD42022306270, CRD42024550229). The review is reported in compliance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.(Page et al., 2021)

***Search strategy and selection criteria***

A detailed description of our search strategy and eligibility criteria is provided in the Supplementary Methods. Briefly, we searched MEDLINE, Embase without language restrictions on 24/05/2024. We included human genome-wide studies reporting associations between genes, transcripts, or proteins. For human studies we accepted any contemporaneous BPD definition. For rodent studies, definitions of BPD study groups were accepted as hyperoxic exposure and induced low birth weight. We excluded candidate in vivo or in vitro studies (< 50 genes/proteins), candidate gene associations, and studies with <5 patients per arm. Following deduplication, titles were initially screened using Screenatron.(Clark et al., 2020)

Abstracts were then screened against eligibility criteria, this included organising the studies into separate collections of human and animal studies, with an independent author resolving inconsistencies. Full texts were retrieved and analysed for inclusion before extraction of gene lists for inclusion in MAIC. Input lists were processed as previously described.(Li et al., 2020; Millar et al., 2024; Parkinson et al., 2020) Briefly, lists were considered ranked if metrics of statistical significance (p-value) and/or fold change (FC) were reported. These lists were ordered by p-value/false discovery rate (low to high) then, where applicable, by absolute fold change or effect size (high to low). Gene names were converted to HGNC gene symbols (or Ensembl/Refseq symbols if no HGNC symbol). Rodent data was mapped to human ortholog symbols using custom scripts to allow for comparison with the human MAIC results.

***MAIC***

The MAIC algorithm has previously been described in detail.(Li et al., 2020; Millar et al., 2024; Parkinson et al., 2020; The GenOMICC Investigators et al., 2021; B. Wang et al., 2022) A full description and the source code is available at https://baillielab.net/maic. We implemented pymaic v0.2 in Python v3.9 and used Technique to categorise input lists. MAIC combines both ranked and unranked lists, of unknown quality, to build a comprehensive ranked list of entities according to 4 basic assumptions.1. There is a set of true positives (genes implicated in BPD), 2. A gene is more likely to be a true positive if it appears in datasets from more than one source, 3. A gene is more likely to be a true positive if it appears in datasets with a higher proportion of replicated genes. 4. A gene is more likely to be a true positive if it appears in datasets from multiple methods or modalities.

***Functional analyses and tissue expression***

All enrichment and over representation analyses were implemented using clusterProfiler (v4.0)(Wu et al., 2021) in R (v4.4.0) and visualised using functions in that package. Redundancy of enriched GO terms was removed using the simplify function. Hypergeometric tests were implemented with the 1-phyperfunction in R. Gene overlaps were visualised using ggvenn. We conducted cell-type specific enrichment analysis using WebCSEA{Dai} and extracted the top 20 general cell types for each query.

***Protein Interaction Network***

Prioritised genes were analysed using the online tool STRING (https:// string-db.org) to determine potential protein-protein interactions. For humans 919 genes were mapped, for rodents 1726. A PPI network was constructed using the MCL (Markov Clustering) algorithm, with an inflation parameter of 3 and focused on high confidence (interaction score of >= 0.7) interactions. The network was exported and hub genes subsequently identified using CytoHubba 0.1 implemented in CytoScape 3.10.3. The overlap of the top 100 ranked genes, ranked using 5 common algorithms (MCC, MNC, Degree, EPC and DMNC), was used to evaluate hub genes, apart from overlaps between MAIC analyses where the top 10 ranked genes were used.

**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.

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**CONFLICT OF INTEREST**

All authors report no conflicts of interest.

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**DATA AVAILABILITY**

The MAIC output is included as supplementary material. All code is available at https://github.com/baillielab/bpd\_maic.

**CONTRIBUTIONS**

SCH, JKB and JEM conceived the study. SCH, PK, CH, JAR, NM, AA, NP, EL, MP manually reviewed abstracts for inclusion. SCH, PK, CH and CS curated the data. SCH, PK and CH did the formal analysis. SCH supervised the study. SCH, PK and CH wrote the original draft of the manuscript. All authors reviewed and edited the manuscript. SCH validated the study data. SCH, PK and CH had access to the raw data. The corresponding author had full access to all the data and final responsibility for the decision to submit for publication.