The gut microbiota is altered in *CRB1*-related retinopathies

Ana Catalina Rodriguez-Martinez[1,2], Neelima Nair[1,3], Jane Skinner[4], Ailsa A. Welch[4], Samantha Malka[2], Mariya Moosajee[1,2,3]

1 : UCL Institute of Ophthalmology, London EC1V 9EL, UK, 2: Moorfields Eye Hospital NHS Foundation Trust, London EC1V 2PD, UK, 3: The Francis Crick Institute, London NW1 1AT, UK, 4: Department of Public Health & Primary Care, Norwich Medical School, Norfolk, United Kingdom.

Background

The *CRB1* gene encodes the CRB1 protein, primarily expressed in retinal Müller cells and photoreceptors.

It is essential for retinal development and maintenance, playing a key role in apical-basal polarity, adherence junctions, and maintaining the outer limiting membrane barrier.

When disrupted it leads to a range of phenotypes including LCA/EOSRD, RP, CRD and MD with few systemic implications reported.

Studies suggest that disrupted Crb1 expression in the gastrointestinal (GI) epithelium of rd8 mouse models (Crb1$^{-/-}$) results in gut barrier dysfunction, allowing bacterial translocation to the retina causing retinal degeneration.

Whole metabolomic analysis in patients can provide insights into disease pathophysiology and help identify potential systemic biomarkers.

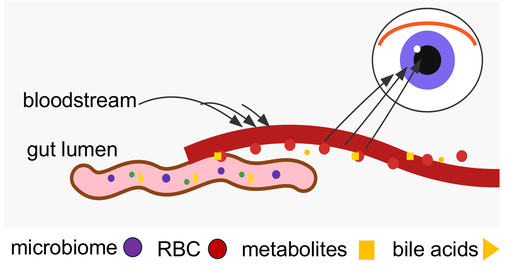
Methods:

Blood plasma from 25 molecularly confirmed *CRB1*-retinopathy patients from Moorfields Eye Hospital with 25 age- and gender-matched healthy controls underwent ultra-performance liquid chromatography-mass spectrometry (UPLC-MS).

Biochemicals were subjected to MetaboLync pathway analysis to identify relevant affected metabolic pathways.

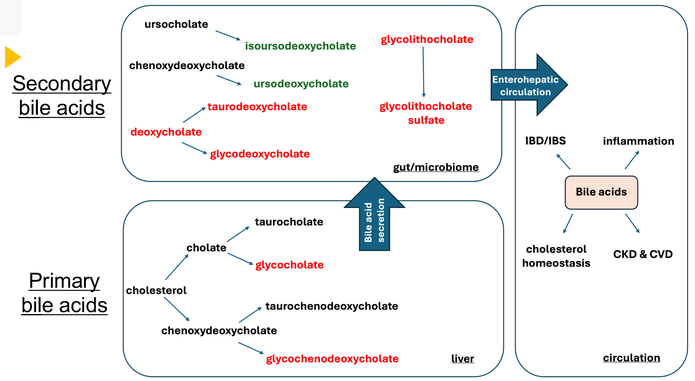
Results:

Of 872 identified compounds, 244 were significantly abnormal in *CRB1* patients (141 elevated, 103 reduced).

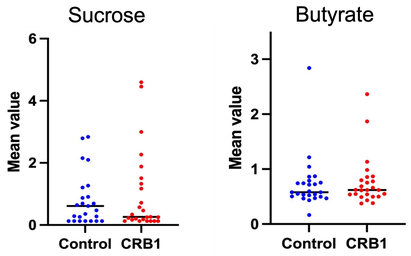


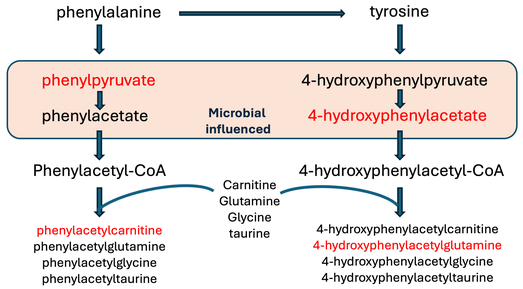
CRB1 patients showed elevated primary and secondary bile acids alongside increased gut microbial phenylalanine pathway metabolites, indicative of altered gut microbiome.

CRB1 patients exhibited no evidence of gut epithelial barrier dysfunction

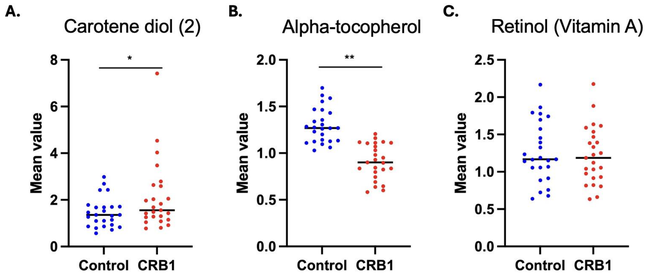


Gut epithelial barrier markers

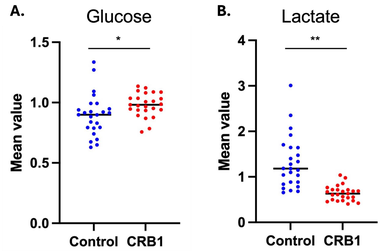




Antioxidants



Energetics



Significant reductions in key antioxidants and neuroprotective agents were found in CRB1 patients alongside energy metabolism dysregulation.

Key findings

- Metabolic dysregulation was found in *CRB1*-retinopathy, including potential gut microbiome alterations, despite no evidence of gut barrier dysfunction.
- The reductions in antioxidants, energy pathways and neuroprotective agents highlight potential therapeutic targets to delay disease progression.
- Further investigation into gut microbiome composition and intestinal permeability in humans with *CRB1* retinopathies is warranted.

ana.rodriguezmartinez@nhs.net