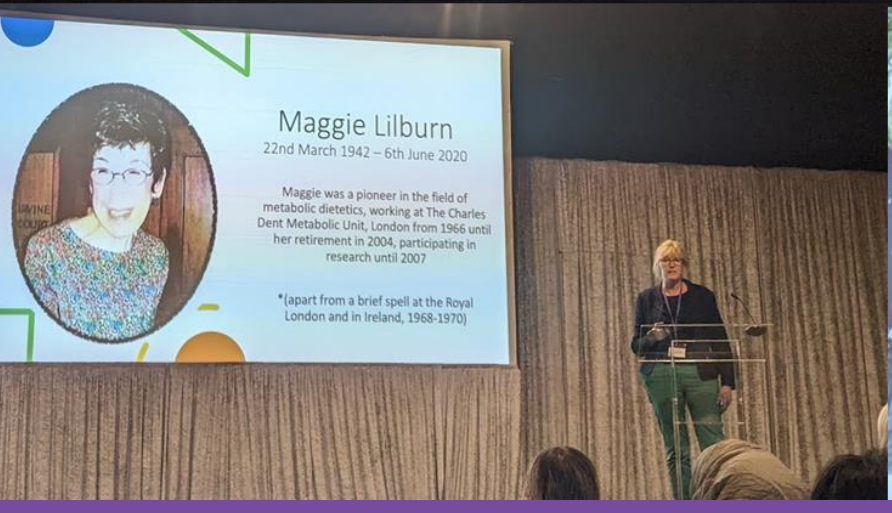
BIMDG Bulletin

British Inherited Metabolic Diseases Group



2022 Winter Edition

BIMDG Newcastle symposium

New Chair and Committee members

BIMDG
British Inherited Metabolic Disease Group

Message from the chair — By James Davison

This edition of the BIMDG Bulletin comes at an exciting if challenging time in metabolic medicine.

I'm grateful to Elaine Murphy who has led the BIMDG so effectively over the last few years, including cementing in place the required changes to ensure we are in good shape for the Charity Commission, establishing the national metabolic drug and dietetic formularies, and also completing the workforce survey which has highlighted some of the challenges faced in paediatric and adult branches of metabolic workforce.

2023 will continue to see BIMDG supporting a number of key workshops focusing on specific disease entities, as well as with a broader horizon as we continue to engage with seeking to develop the UK's newborn screening programme. Members of the BIMDG collaborate in the work of the National Screening Committee at various levels, and we are also engaging with Genomics England in the proposed pilot of Whole Genome Sequencing for newborn screening to ensure that the community's extensive experience in good practice in this area is used to guide the process.

It is exciting to see a number of innovative therapies including the first gene therapies for metabolic disorders coming from the research pipeline to routine clinical commissioning and use. NICE continues to have a lead role in the evaluation of these new therapies, but this does rely on clinical experts from the metabolic field being willing to support these processes and you will see requests coming from Committee to expand the pool of those supporting this work.

Education and training remains a key focus for the BIMDG, and showcasing metabolic medicine as a great career option is one part of addressing the workforce challenges that we know are an issue across the medical, laboratory, nursing, dietetic and allied health professions.

There are particular challenges facing those working in the devolved nations and their health care systems. If there are ways you think that the BIMDG can help in advocating and developing the service we provide to patients and families living with metabolic disorders please do get in touch with me.

The BIMDG Annual Meeting 2023 is being held in London, and I look forward to seeing as many as possible at the meeting 6-8th June 2023, following the great success of the 2022 Newcastle gathering.

James Davison

Chair, BIMDG Committee james.davison@gosh.nhs.uk

Message from the outgoing chair — By Elaine Murphy

Just a quick note from me to wish James and committee all the best with the next 3 years. My three year stint as chair did not turn out quite as expected – Covid and the pandemic soon saw to that – but was nonetheless very rewarding. Despite the incredible challenges that everyone in the NHS has faced over the last 3 years – I think we can be proud of all those working in IMD – the newborn screeners (clinical and laboratory) kept the programme going; the pharmacy group got the BIMDG formulary published (this is now being reviewed by the BNF and we

are hopeful that it will be endorsed); our nurses threw themselves into any role asked of them – from vaccinators, to ward work and ITU support; the dietitians also got their formulary published and provided invaluable support in contacting patients and ensuring the most vulnerable had access to all their prescriptions and emergency regimens throughout; the psychologists worked with Metabolic Support UK and the LSD Collaborative to produce webinars to support our patients and members in the pandemic.

We've found new ways of working – remote and virtual - and shown the remarkable adaptive capability of humans in general. Despite challenges the BH4 responsiveness programme is now up and running. We got to a successful end of our first managed access agreement for elsosulfase alfa. Best of all we managed our first in person annual conference since 2019 this year in Newcastle – a great programme, with really interesting aspects focusing on the bigger picture of sustainability and climate change in health services.

There are incredible challenges ahead – political, financial, environmental, for stability in Europe and for staffing and resourcing of the NHS. As ever we are asked to do 'more with less' and this is stretching the resilience of all of us to the limit (with a personal apology to my own team when I am snappy and irritable!). There is solidarity in facing difficulties together which seems a good time to thank all 'my' committee members with special named mention to Donna Fullerton (expert minute taker and organiser extraordinaire), Rob Barski (the hardest job – looking after our money and making sure we spend it wisely) and Greg Toulson (for all the hassle I gave him to get the bulletin together twice a year!).

Many thanks all and good luck BIMDG committee 2022-2025!

Introducing new BIMDG Committee members:

Incoming BIMDG Medical trainee's representative:

I am a Paediatric Registrar in the West Midlands, and am very much looking forward to starting Paediatric Inherited Metabolic Medicine sub-specialty training at Birmingham Children's Hospital in September 2022!

I'm delighted to be the new BIMDG Trainee Rep (Clinical), and look forward to working with the BIMDG Committee and other colleagues. If anyone has any ideas they'd like to discuss, please email me on shona.brothwell@nhs.net

Incoming BIMDG Scientific trainee's representative:

I'm Jennie, the new BIMDG Scientific Trainee representative. I have been part of the Nottingham Metabolic lab team for just over a year. Needless to say, the last year has been a huge metabolic learning curve!

It was lovely to meet, face-to-face, so many people at the BIMDG Conference in Newcastle in June, and I look forward to meeting many more during future training events. jennie.freestone@nhs.net

Incoming Adult metabolic clinician committee member:

Dr Nishan Guha, Consultant in chemical pathology and metabolic medicine at the John Radcliffe Hospital, Oxford.

BIMDG specialism updates

Psychologists' updates, CPD fund: By Lynne Aitkenhead

In recent years, there has been increasing recognitions of the neuropsychological consequences of many inherited metabolic disorders. These include neurodevelopmental disorders such as intellectual disability, autism spectrum disorder and ADHD, cognitive impairment, and mood, anxiety or adjustment disorders. Often more than one of these psychological comorbidities occur together, in the context of significant physical symptoms or disability, meaning that the needs of people who are affected are particularly complex. There is therefore increasing demand for neuropsychology within IMD services. In order to meet this demand, psychologists require a highly specialist set of skills.

We carried out consultations with members of the BIMDG Psychologist Group and with stakeholders including Metabolic Consultants, Dietitians, Nurses and Scientists, service users and parents/carers. These identified an extremely high rate of cognitive and behavioural difficulties (70% and 30% respectively). More than half of patients (56%) have not been able to access any support with these difficulties. Amongst Psychologists, funding for training fees stood as one of the main barriers to completing specialist training.

In response, the BIMDG Psychologists Group launched a new educational fund for members. The fund is now open for applications to support education and training for psychologists that will benefit the IMD community. Details of how to apply can be found on the BIMDG website.

Adult IMD Group: By Charlotte Dawson

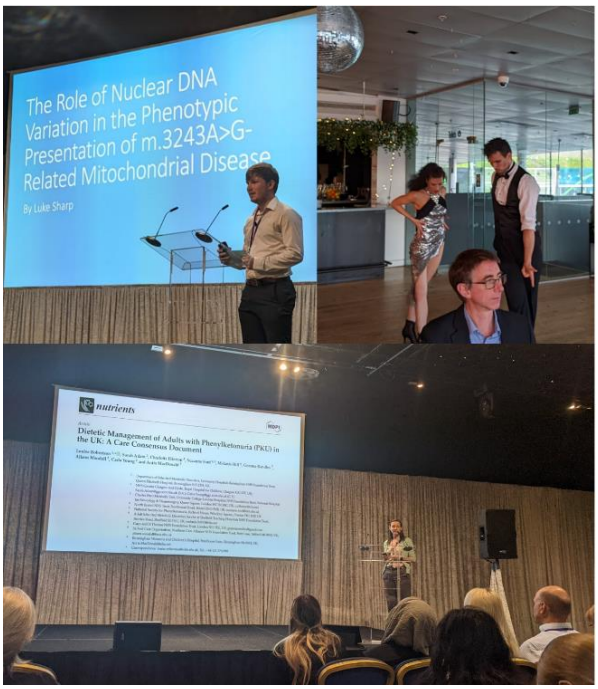
The adult IMD group now have their own You Tube channel where we will upload the lectures you've prepared on Adult IMD for the Chemical Pathology/Metabolic Medicine trainee. I will be in touch with you individually over the coming months to organise a time to record your lecture. Once all the lectures are available the BIMDG have kindly agreed to make the link available through the website.

BIMDG 2022: A Perspective By Ann Bowron

The invitation to host the 2021 BIMDG annual conference was met with enthusiasm from the Newcastle team and at a planning meeting in January 2020 there were enough suggestions to fill a week-long programme.

That was the first and last time the group met together as meetings in person were soon to be banned. A few weeks later the BIMDG committee took the decision to postpone the 2020 meeting to the following year, and to put back the Newcastle meeting to 2022. As time went on it appeared that restrictions would continue, so the 2021 conference was moved to an on-line platform. The BIMDG committee discussed the 2022 conference at length. Should the meeting go ahead in person? Would restrictions still be in place? Would we make a financial loss? Would anyone come?

In the meantime, Jacqui from JM Associates was looking for a venue to meet the complex requirements of the BIMDG, doing so virtually due to travel restrictions, and found the ideal conference hotel in a superb location overlooking the Tyne Bridge.



Registration opened in early 2022 at the same time as the number of covid cases was rising steeply. Jacqui dealt with registrations and abstracts, so we were unaware of how many were planning to attend or to present posters.

In the end, the conference exceeded our expectations. There was a buzz of excitement on the first afternoon when delegates started to arrive – for many our first in-person meeting for almost 3 years. The programme that had been planned so long ago was well-received, there were far more posters than expected, we had a lovely evening at The Baltic, over 20 people got up early for a walk or run along the Quayside the following morning and, for most of the time, the sun shone.

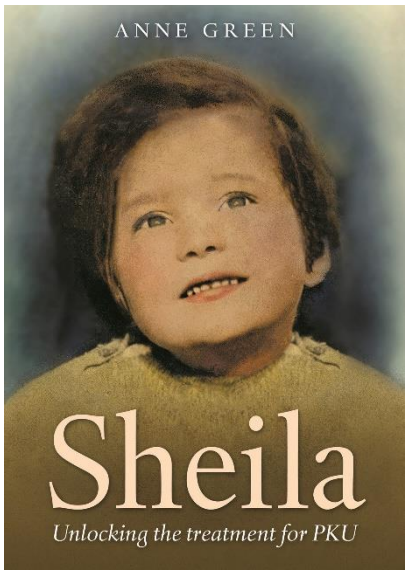
Thank you to the BIMDG for taking the risk to go ahead with the meeting, to the local team for the programme, to Jacqui taking on the challenge of organising a conference during a global pandemic but most of all to everyone who came and took part and helped create a memorable BIMDG reunion.

LEAF: The environmentally conscious laboratory — By Martin Farley

Laboratories are the workhorse space for science. They provide a tailored space for specialist equipment, consumables, and reagents to be utilised for more applications than one can count. Laboratories though can cost large sums of money to operate, and can have comparable impacts on the environment. The specialist lab equipment will result in significant energy consumption, the consumables are utilised in immense volumes and often eventually incinerated, and the reagents are produced and shipped from around the world. To address this, sustainable or green lab initiatives have sprung up around the world.

At UCL, we launched LEAF, which aimed to provide a standard approach to sustainable laboratories. The idea was to provide a standard akin to health and safety standards for safe lab operations, but for sustainability. LEAF contains actions around purchasing, managing, and disposing of lab equipment in a sustainable manner, as well as promoting reuse or recycling of consumables. Launched in 2021, it's quickly grown to the largest programme of its kind globally and is in 80+ institutions. In developing LEAF, we recognised that there was an opportunity to develop a version of LEAF specifically for diagnostic and clinical labs, as they presented comparable but distinct challenges to research and teaching laboratories. To address this, we've developed a version of LEAF specifically for clinical labs, and have just launched a pilot of this tool. The interest in this area has been growing tremendously, evidenced by the uptake in the newly launched Clinical Labs Susnet. If interested in joining our pilot, contact LEAF@ucl.ac.uk to learn more.

Book Review: Sheila — By Suzanne Ford



There is a brilliant combination in this book, of fascinating scientific detail and the moving family history that enable the successful trial of a very first treatment for PKU or phenylketonuria.

Many readers of this bulletin may know, Sheila Jones was found to have PKU when she was 17 months old, (on 14th April 1951), but no treatment was available. On 21st November 1951 Sheila was admitted to Birmingham Children's Hospital to trial a phenylalanine free mixture of amino acids.

The work over the summer and autumn of 1951 in the Birmingham biochemistry laboratory is retold in detail. This book is testimony to the love and persistence of Sheila's mother Mary in getting medics (Dr Horst Bickel and team alongside biochemist Evelyn Hickman and Great Ormond Street collaborator Louis Woolf) to develop a treatment. The tenacity of all involved is humbling – post war Birmingham is the context and resources are tight in Sheila's family - the NHS is just 3 years old.

Mary's extraordinary efforts to make the treatment work led to some very small success for her daughter who subsequently lived her adult life in NHS facilities for people with learning disabilities (a "mental hospital"). There are estimated to be half a million people across the world with PKU and those being treated owe their wellbeing to Sheila and Mary. This book describes a little of how the low phe diet was rolled out in the 1950s and 60s in the UK – so we get a sense of how diagnostics and amino acid treatment were both upscaled in these decades.

Professor Anne Green wrote this book following her retirement from her own distinguished IMD career (much of which was in Birmingham). In building this book Anne Green spoke in depth to Sheila's brothers, which gives an extra dimension to this account of pioneering metabolic medicine. Anne's writing is clear and evocative – Anne uses the language of the time to good effect – and the text is augmented by visuals such as amino acid chromatograms from Horst Bickel's notes, and period photographs of the protagonists in this work.

For an inspiring and accessible read over the winter evenings, or, maybe a high quality secret santa gift, or a present to give your loved ones some insights into your own work – look no further.

'This book movingly tells the story of a family and their contribution to the history of PKU'.

Professor Dame Sally Davies, Master of Trinity College Cambridge UK orders: https://store.bch.org.uk/ or ring 0121 333 8506

Non UK orders: https://www.brewinbooks.com/sheila - Price: £12.95 - ISBN: 978-1-85858-714-1

The Role of Nuclear DNA Variation in the Phenotypic Presentation of m.3243A>G-Related Mitochondrial Disease

Student: Luke Sharp; **Principal Investigator:** Dr Sarah Pickett; **Co-Investigator:** Professor Rob Taylor. Wellcome Centre for Mitochondrial Research, Institute for Translational and Clinical Research, Newcastle University, UK.

Introduction and Aims

Genetic variants in either the nuclear or mitochondrial genomes can cause mitochondrial disease; one of the most common pathogenic variants found within the mitochondrial genome is the m.3243A>G variant. Disease caused by m.3243A>G are phenotypically heterogeneous, and affected patients present with a wide range of clinical features. Two syndromes associated with the m.3243A>G variant are mitochondrial encephalopathy and lactic acidosis with stroke-like episodes (MELAS) and maternally inherited diabetes and deafness (MIDD)(1).

Many factors are believed to influence this phenotypic heterogeneity, including the m.3243A>G level and the patient's age. However, these factors don't explain all the phenotypic heterogeneity exhibited in patients; there is evidence to suggest that nuclear DNA variation could explain this heterogeneity(2). We hypothesised that variants in the nuclear genome give a patient a predisposition to a specific clinical feature, which is only exhibited clinically when in combination with the m.3243A>G variant(2).

The aim of this project was to identify potentially deleterious nuclear genetic variants that influence the phenotypic heterogeneity associated with m.3243A>G-related disease. We used data from whole genome sequencing and employed a gene-based burden analysis to test for association with disease phenotypes.

Methods

Clinically affected individuals carrying m.3243A>G were recruited from the UK Mitochondrial Disease Patient Cohort (Ethical approval:13/NE/0326 and 17/NE/0267), the German Network for Mitochondrial Diseases (Ethical approval: LMU Munich; 182-09), and the Exeter Centre of Excellence for Diabetes Research (Ethical approval: 17/WA/0327). We obtained whole genome sequences from 53 of these individuals and used an in-house variant calling pipeline to identify and annotate all genetic variants. This enabled us to filter the genetic variations using multiple variant effect predictors such as CADD (Combined Annotation Dependent Depletion) scores, retaining only variants that were potentially deleterious(3). We also limited our search to genes encoding proteins with evidence for mitochondrial function(4).

We divided the patients into two groups depending on whether they exhibited a certain clinical phenotype. For each gene, we compared the number of individuals within each patient group who carried at least one potentially deleterious variant. We plotted these results on a jittered-scatter plot and determined significance using a permutation test.

Results

Potentially deleterious variants in the *GPX1* gene are common in individuals affected with diabetes (~75%) than those without diabetes (~25%). Hypothesis testing using permutations returned a p-value of 0.005. The predominant variant identified within this gene in the patients from the diabetes symptomatic group was the rs1050450 variant.

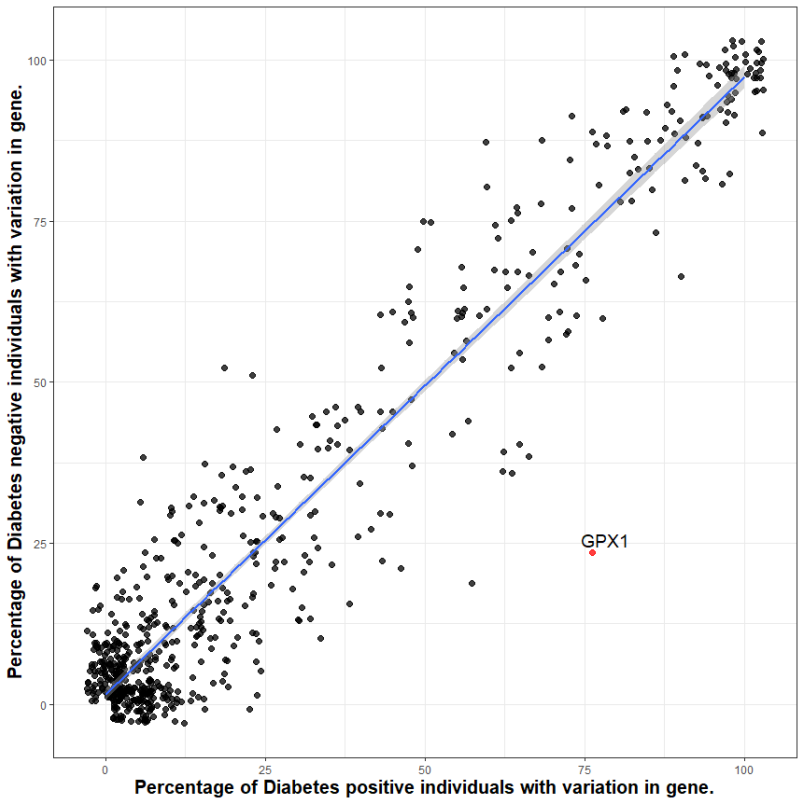


Figure 1 Diabetes gene-based burden jittered scatter plot: Gene-based burden results for diabetes plotted on a jittered scatter plot. Each point on the scatter plot represents a gene which contains at least one potentially deleterious variant. The outlier gene, *GPX1*, has been highlighted. This analysis was conducted using 53 individuals, 24 of which presented with the diabetes phenotype and 29 which did not.

Discussion

GPX1 encodes the glutathione peroxidase 1 protein, which plays a role in removing reactive oxygen species from the cell. The predominant variant identified within this gene, rs1050450, has previously been shown to cause a reduction in the enzyme's activity(5). These results provide evidence that the rs1050450 variant in *GPX1*, in combination with m.3243A>G, could contribute to the diabetes phenotype associated with m.3243A>G-related disease. Future work in this area should include repeating the gene-based burden test with a larger sample size and investigating other m.3243A>G-related phenotypes, such as the stroke-like episodes that define MELAS.

Acknowledgements

I would like to thank everybody at the Wellcome Centre for Mitochondrial Research who assisted me with my project with a special thanks to Dr Sarah Pickett and Prof Rob Taylor.

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Retirement: Peter Galloway — By Marianne Bar

Dr Peter Galloway made the decision to retire in April 2022 after dedicating 35 years to the NHS.

After training as a general medical registrar in Lothian, he completed a paediatric post prior to commencing training in Clinical biochemistry at Glasgow Royal Infirmary in 1993. After obtaining FRCPath, he joined the biochemistry department at Yorkhill Children's Hospital as a consultant in 1999. It was here he developed his interest and expertise in inherited metabolic disease (IMD). He initially started with 40 metabolic patients in his clinic and over the subsequent years built up this West of Scotland adult metabolic service at least ten fold. His kind and compassionate approach towards his patients and the dedication with which he looked after their health and interests will no doubt leave a huge void.

In 2015, Yorkhill Children's Hospital relocated to the new Royal Hospital for Children on the Queen Elizabeth University Hospital site. Alongside the new hospitals was a brand new purpose built laboratory building to accommodate the new South Glasgow Biochemistry department formed from the merger of the Southern General, Victoria and Yorkhill hospitals. Peter was closely involved in the planning, design and relocation of services and as one of the largest hospital complexes in Europe this was no small undertaking. Importantly he managed to secure a large combined space for the metabolic laboratory ensuring the capacity to expand and develop this service.

Apart from IMD another of Peter's principle interests was training and he was actively involved both locally and nationally. He was on the joint RCP/RCPath Scientific Advisory Committee in Metabolic Medicine right from the start and was instrumental in delivering the first accepted UK training scheme in the West of Scotland. More importantly, all Scottish trainees (both medical and scientific) now undergo a paediatric/metabolic training placement to broaden their awareness and understanding of IMD. For many years, he very much enjoyed being training programme director as well as senior examiner for the Royal College of Pathologists, which meant that candidates were regularly tested with some interesting metabolic questions.

Having recently relocated to the Highlands he is planning to spend his retirement in a more rural location enjoying long walks in the hills and countryside. We wish him all the very best for his retirement. The laboratory is a much quieter place without him!