Institution: University College London

Unit of Assessment: 5 - Biological Sciences

Title of case study: Improving the diagnosis and understanding of Batten Disease

1. Summary of the impact

Research at UCL into the genetics of neuronal ceroid lipofuscinoses (NCL) – also known as Batten Disease – has had a global impact on the diagnosis and understanding of this group of diseases. The identification of genes and mutations has led to new diagnostic tests, which inform clinical management in terms of expected disease course and choice of the most effective drugs; prenatal and pre-implantation diagnoses for prevention are also possible. The group has established a new classification of diseases according to gene-based nomenclature. Information about all genes that underlie NCL has been collated in the NCL Mutation Database, which is freely available on the NCL Resource website. The group has also engaged closely with professionals and affected families to maximise the reach and understanding of research.

2. Underpinning research

NCL is a rare, progressive, inherited neurodegenerative disease affecting all ages, but mainly children. There is visual failure, epilepsy and a progressive loss of cognitive and motor functions, leading to premature death. The incidence varies across populations and is between 1 in 12,500 and 1 in 100,000, with approximately 10 new patients diagnosed each year in the UK.

Many of the impacts derive from work that began in the 1990s and continues to the present day on the identification of genes that cause NCL (1995 to date: genes *CLN3, CLN2, CLN4, CLN6, CLN7, CLN8, CLN11, CLN12, CLN13, CLN14*) and the identification of many mutations in these genes that cause both typical and atypical NCL disease **[1-5]**. This has changed perceptions of the some of the NCLs, since some, including the most common type (juvenile CLN3 disease, 2008), are mutation-specific phenotypes. The methodology used has changed over time, as genetic approaches have advanced and technology has changed. The new genetic information was continually incorporated into fresh diagnostic algorithms. As more genetic details emerged, discussions began in 2009 on the nomenclature of the disease, which had been based on age of onset for many years, leading to the decision to change to one that was gene-based. A patient cohort was audited and the results published in 2012 **[6]**.

The UCL-hosted and curated NCL Mutation Database was launched in 1998 to provide a freely accessible list of identified mutations to aid mutation diagnosis of patients, and also carrier and prenatal diagnosis. This was later incorporated into an expanded website in 2005 – the NCL Resource – as it had become clear that there was a need for an unbiased and clear summary of research and clinical information for this rare disease for both clinical, research, health, social and education professionals, industry and families. This established UCL as an international centre for NCL and provided a unique resource that is highly valued by the international community. The mutation database was significantly upgraded again in 2011 and 2012 with the addition of data on all published cases to allow better understanding of the genotype-phenotype relationship of NCL, and more detailed genomic information (2013). This underlies the continued development of diagnostics based on new DNA technologies as well as biochemistry. There continues a commitment to understanding the molecular basis of the NCL, and work has begun towards gene therapy for the visual failure, and the identification of new therapeutic tools for the most common NCL, juvenile CLN3 disease.

Key UCL researchers involved in this work are: Dr Sara E Mole, Reader, MRC Laboratory for Molecular Cell Biology (from 1992); Professor Robin Ali, Institute of Ophthalmology (from 2011); Dr Nicholas Lench, Director NE Thames Regional Genetics Service, Head of GOSH DNA and Cytogenetics diagnostic laboratories (from 2011); Professor Simon Heales, Head of Chemical Pathology/Director of Newborn Screening at Great Ormond Street Hospital and UCL Institute of

Child Health (from 2011); Mr Glenn Anderson, Clinical Electron Microscopist, Great Ormond Street Hospital for Children (from 1993); Dr Jose Bras, Research Fellow, UCL Institute of Neurology (from 2010); Dr Rita Guerreiro, Research Fellow, UCL Institute of Neurology (from 2010).

3. References to the research

These publications include those first reporting identification of a new gene or mutations that change our perception of the disease, or introduce new possibilities for diagnostics.

[1] The International Batten Disease Consortium (TL Lerner, R-MN Boustany, JW Anderson, KL D'Arigo, K Schlumpf, AJ Buckler, JF Gusella, JL Haines; G Kremmidiotis, IL Lensink, GR Sutherland, DF Callen; PEM Taschner, N de Vos, G-JB van Ommen, MH Breuning; NA Doggett, LJ Meincke, Z-Y Liu, LA Goodwin, JG Tesmer; HM Mitchison, AM O'Rawe, PB Munroe, IE Järvelä, RM Gardiner, SE Mole). Isolation of a novel gene underlying Batten disease, CLN3. Cell. 1995 Sep 22;82(6):949-57. http://doi.org/cd6nq5

[2] Munroe PB, Rapola J, Mitchison HM, Mustonen A, Mole SE, Gardiner RM, Jarvela I. Prenatal diagnosis of Batten's disease. Lancet. 1996 Apr 13;347(9007):1014-5. http://doi.org/fjq5tp

[3] Mitchison HM, Hofmann SL, Becerra CH, Munroe PB, Lake BD, Crow YJ, Stephenson JB, Williams RE, Hofman IL, Taschner PE, Martin JJ, Philippart M, Andermann E, Andermann F, Mole SE, Gardiner RM, O'Rawe AM. Mutations in the palmitoyl-protein thioesterase gene (PPT; CLN1) causing juvenile neuronal ceroid lipofuscinosis with granular osmiophilic deposits. Hum Mol Genet. 1998 Feb;7(2):291-7. http://doi.org/fvmb8j

[4] Ranta S, Zhang Y, Ross B, Lonka L, Takkunen E, Messer A, Sharp J, Wheeler R, Kusumi K, Mole S, Liu W, Soares MB, Bonaldo MF, Hirvasniemi A, de la Chapelle A, Gilliam TC, Lehesjoki AE. The neuronal ceroid lipofuscinoses in human EPMR and mnd mutant mice are associated with mutations in CLN8. Nat Genet. 1999 Oct;23(2):233-6. http://doi.org/c374jw

[5] Wheeler RB, Sharp JD, Schultz RA, Joslin JM, Williams RE, Mole SE. The gene mutated in variant late-infantile neuronal ceroid lipofuscinosis (CLN6) and in nclf mutant mice encodes a novel predicted transmembrane protein. Am J Hum Genet. 2002 Feb;70(2):537-42. http://doi.org/d39jhf

[6] Williams RE, Mole SE. New nomenclature and classification scheme for the neuronal ceroid lipofuscinoses. Neurology. 2012 Jul 10;79(2):183-91. http://doi.org/njd

Major Funding:

- EU FP7. 281234. A Treatment-Oriented Research Project of NCL Disorders as a Major Cause of Dementia in Childhood (DEM-CHILD). 2011-2014, 36 mo. €2,998,795 to DEM-CHILD Consortium (Coordinator A.Schulz, Hamburg). €401,347 to UCL (Mole and Ali).
- PhD studentship. Gene therapy to treat the visual failure of Batten disease. 2011-4. UCL Impact Award £31,627 / Batten Disease Family Association UK £80,928. SE Mole.
- EU FP6. 503051. Dissecting neuronal degeneration: Neuronal ceroid lipofuscinoses from genes to function (NCL-models). 2004-6, 36 mo. Coordinator (Prof Anu Jalanko). €321,966 to UCL (Mole).
- The Wellcome Trust. 054606. Molecular genetic analyses of the neuronal ceroid lipofuscinoses. 1998–2002. £239,973. SE Mole, R Williams, RM Gardiner.
- Medical Research Council. G9606970. Genetic analysis of the Batten disease gene, CLN3. 1996-1999. £284,584. SE Mole, HM Mitchison, RM Gardiner.
- Medical Research Council G9325438. Study of the molecular genetic analysis of Batten

Disease. 1994-7. £152,156. SE Mole, RM Gardiner.

4. Details of the impact

New diagnostic tests

The impact of our research on diagnosis and clinical management of NCL has been global. Laboratories around the world now offer comprehensive testing for the NCLs **[a]**. The diagnostic applications of this work include prenatal and pre-implantation diagnosis for prevention, predictive testing for pre-symptomatic diagnosis (important as experimental therapies become available), as well as the definitive diagnosis of symptomatic disease and determination of carrier status for relatives. For patients and their families the most significant impact has been the improvement in the time taken to reach a definite diagnosis, which had taken several years for some families but can now be as short as a few months or even weeks.

UCL now offers diagnostic biochemical tests for CLN1, CLN2, and CLN10 enzyme analysis and DNA-based mutation tests for CLN1, CLN2, CLN3, CLN5, CLN6, CLN7, CLN8 and CLN10. Great Ormond Street Hospital (GOSH) performs c.100 gene tests each year, for diagnostic, carrier or prenatal testing, and 450 enzyme assays. Pathological examination of skin biopsies using electron microscopy has long been offered (now around 100 per year), and because of UCL's position at the forefront of genetic discovery this is also extended to research cases with international collaboration. Five hundred blood tests for vacuolated lymphocytes that are characteristic for CLN3 disease, are also performed each year **[b]**.

New diagnostic algorithms

The identification of genes and mutations underlying different types of NCL has led to diagnostic algorithms being displayed on the NCL Resource website **[c]**. These have been viewed 1,970 times. Mole also offers personal consultations on a diagnostic pathway approximately six times per year. Algorithms are updated as new genes are discovered, and are also published in hard copy. As a result of our work, accurate genetic diagnosis now underpins disease nomenclature. This provides the essential information required for any clinical therapeutic intervention and ensures that families know exactly what their disease is. This new nomenclature is also summarised on the NCL Resource website (viewed 1,874 times) and published in hard copy.

NCL Resource

Since monitoring began in mid-2009, the NCL Resource website has received more than 15,000 unique visits from 121 countries. It is a unique resource which is used: by families to learn about NCL after a new diagnosis and particularly to keep up to date with the development of therapies **[d]**; by clinicians to learn how and where to access specialised tests for diagnosis, and which ones to request; by researchers to be updated about the wider aspects of NCL, recent gene identification and mutation data; by other professionals to link to international groups including the UK Batten Disease Professional Development Group. The website is also used by the media and is often cited in publications, particularly the mutation database.

Expert advice

Mole is Scientific Advisor to the UK Batten Disease Family Association (BDFA) **[e]**. This lay association represents and supports affected families and professionals (medical, social, educational) involved with them. Mole advises on the content of leaflets and phone response protocols, ensuring accuracy in terms of genetic, diagnostic, or research information. She has spoken about her research at many meetings over the last ten years. In 2008, Mole organised a meeting at UCL with BDFA entitled 'From bench to bedside.' This meeting gathered together scientists, clinicians, social scientists and nurses to discuss ways of speeding the future availability of therapy in the UK. From this, the BDFA developed their 'top ten priorities' for strategic support of research **[f]**.

Public Engagement work

In 2012, Mole organised a two-day conference for families and professionals that was integrated with the 13th International Conference on Neuronal Ceroid Lipofuscinoses (Batten Disease) **[g]**. The scientific conference was co-organised with colleagues from King's College London and the Evelina Children's Hospital, and covered all aspects of Batten disease research. The public engagement event was co-organised with BDFA. Events included: specialised workshops and training events; broader workshops on science relevant to Batten Disease families, such as on clinical trials or specialist education; a UK networking event for different professionals who would otherwise not meet; 'lay summary sessions' to help families benefit from the research being presented. Over 260 people attended overall, including nearly 100 family members. One family member commented: *"Really like your effort to make complicated science available for parents of persons with NCL."* Then *"I must say that today's session for parents in the afternoon was even better than yesterday (I now know there is something called a cell :-)). We do appreciate these efforts to educate the parents*" **[h]**.

Sara Mole won the UCL Provost's Award for Public Engagement (senior staff) 2013 for the integration of science and public involvement at NCL2012. She is also a member of the NIHR UCL Hospitals Biomedical Research Centre (BRC) Strategy Board as representative for Patient and Public Involvement, and especially advice on public engagement, from 2013.

5. Sources to corroborate the impact

[a] A full list is given on the NCL website: http://www.ucl.ac.uk/ncl/diaglabs.shtml

[b] Great Ormond Street and UCL specialist services:
- pathology of lysosomal storage disorders including pre-natal diagnosis. http://www.labs.gosh.nhs.uk/laboratory-services/histopathology/tests/electron-microscopy
- diagnostic, carrier and predictive testing. http://www.labs.gosh.nhs.uk/laboratory-services/genetics/molecular-genetics-service/molecular-genetics-tests
- The Chemical Pathology Laboratory hosts and supports the National Specialist Commissioning Group (NSCG) Service for Lysosomal Storage Disorders that includes testing for CLN1/PPT1, CLN2/TPP1 and ALN10/CTSD enzymes activities. http://www.labs.gosh.nhs.uk/laboratory-services/chemical-pathology
- UKGTN www.ukgtn.nhs.uk
- Corroboration of numbers of tests can be obtained from Director of NE Thames Regional Genetics Service. Contact details provided.

[c] NCL Resource: www.ucl.ac.uk/ncl

[d] Email sent to Mole in 2009: "*After scouring the internet for the past few weeks and sifting through scientific journals, personal testimonies, and clinical studies, I continue to return to your NCL website. At least for me, it is by far the most accessible, user-friendly, and informative site for the layperson that I have found and subsequently used.*" And another in 2012: *"I thought your Batten webpage was fantastic*". Copies available on request.

[e] All details can be corroborated by Chief Executive of the UK Batten Disease Family Association. Contact details provided.

[f] Documents "*WAY FORWARD from the Research Workshop – Bringing Therapy to Batten Disease March 2008 Sponsored by the BDFA*" and "*Bringing Therapy to Batten Disease – Top 10 priorities*" available upon request.

[g] http://www.ncl2012.org. See Programme for details of Patient Organisation sessions.

[h] Copies of emails available on request.