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Data Article

Electroretinography data from ovine models of CLN5 and CLN6 neuronal ceroid lipofuscinoses

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ABSTRACT

This article presents datasets associated with the research article entitled "Intravitreal gene therapy protects against retinal dysfunction and degeneration in sheep with CLN5 Batten disease" (Murray et al., [1]). The neuronal ceroid lipofuscinoses (NCL; Batten disease) are a group of fatal inherited diseases caused by mutations in a number of *CLN* genes that lead to degenerative and fatal encephalopathies in children. Naturally-occuring sheep models of NCL exist. Affected sheep share the clinical and pathological features of the human disease, including retinal degeneration. Electroretinography (ERG) was employed to characterise the physiological changes in the degenerating retina of CLN5 and CLN6 forms of ovine NCL. ERGs were performed every two months from 3 to 17 months of age in 11 NCL affected (6 $CLN5^{-/-}$ and 5 $CLN6^{-/-}$) sheep and 12 clinically normal heterozygous controls (6 $CLN5^{+/-}$ and 6 $CLN6^{+/-}$) under three different adaptation conditions. A-wave and b-wave amplitudes were collected from each eye using the Eickemeyer Veterinary ERG system. These are the first longitudinal datasets assessing the progression of retinal degeneration in ovine NCL, aiding in characterisation of the disease process and

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providing insight into optimal therapeutic windows for subsequent studies.

Specifications Table

Subject	Ophthalmology and Neuroscience
Specific subject area	Retinal physiology Neurodegeneration
Type of data	Graph Figure
How data were acquired	A-wave and B-wave ERG amplitudes were collected using the Eickemeyer Veterinary ERG system (Eickemeyer - Medizintechnik für Tierärzte KG, Tuttlingen, Germany).
Data format	Raw Analyzed
Parameters for data collection	Longitudinal ERG recordings were collected from 23 sheep, including 11 NCL affected (6 *CLN5*$^{-/-}$ and 5 *CLN6*$^{-/-}$) and 12 clinically normal heterozygous controls (6 *CLN5*$^{+/-}$ and 6 *CLN6*$^{+/-}$) between 3 and 17 months of age.
Description of data collection	Sheep were anaesthetized and their pupils were dilated. ERG recordings were collected initially under ambient light (light adaptation). The light was then turned off and a (zero minute) dark adaptation recording was performed immediately. After five minutes dark adaptation a third recording was performed.
Data source location	Institution: Lincoln University City/Town/Region: Lincoln, Canterbury Country: New Zealand
Data accessibility	Repository name: Data in Brief (DIB) DataVerse https://doi.org/10.7910/DVN/JOSWTD
Related research article	Murray, S.J., Russell, K.N., Melzer, T.R., Gray, S.J., Heap, S.J., Palmer, D.N., Mitchell, N.L., 2021. Intravitreal gene therapy protects against retinal dysfunction and degeneration in sheep with CLN5 Batten disease. Exp. Eye Res. 207, 108600. https://doi.org/10.1016/j.exer.2021.108600

Value of the Data

- These longitudinal datasets provide the first electroretinographic (ERG) characterisation of retinal degeneration in two ovine models of neuronal ceroid lipofuscinoses.
- The ERG datasets can be used for the study of normal retinal function in sheep as well as the assessment of therapeutic efficacy of ocular gene therapies in NCL sheep models.
- These datasets can be used to determine the optimal therapeutic window for ocular therapies for ovine NCL. The data can be reused to perform regression analyses to determine the rate of decline of ERG amplitudes in clinically normal and NCL affected sheep and to compare this to rates of decline in animals who have received an ocular treatment.

1. Data Description

Two full datasets have been deposited on a repository [2]. Each file consists of a Microsoft Excel Spreadsheet, containing six worksheets for the longitudinal a-wave and b-wave ERG amplitudes for each of the three light adaptation conditions (light-adapted, zero

minutes dark-adapted, and 5 minutes dark-adapted) respectively. The first spreadsheet, entitled CLN5 Full Dataset, has longitudinal ERG recordings from 6 CLN5 affected (*CLN5*$^{-/-}$) and 6 clinically normal CLN6 heterozygous (*CLN5*$^{+/-}$) sheep. The second spreadsheet, entitled CLN6 Full Dataset, has longitudinal ERG recordings from 5 CLN6 affected (*CLN6*$^{-/-}$) and 6 clinically normal CLN6 heterozygous (*CLN6*$^{+/-}$) sheep. For each animal in these datasets, the ERG recording for the left and right eye are shown, as well as the average for both eyes.

Four tagged image file format (tif) files are provided with this article. Two of these show graphs of the mean longitudinal a-wave and b-wave ERG amplitudes for each of the three light adaptation conditions for CLN5 and CLN6 sheep respectively (Graph 1 CLN5 ERG and Graph 2 CLN6 ERG). The other two tif files contain representative individual ERG traces from CLN5 and CLN6 sheep respectively at different ages under the three different lighting situations (Fig. 1 CLN5 Traces and Fig. 2 CLN6 Traces).

2. Experimental Design, Materials and Methods

2.1. Animals

This longitudinal investigation included a total of 23 sheep: 12 animals born in 2014 and 11 born in 2015. The first cohort of 12 (6 affected males, 6 female controls) were not enrolled until after 11 months of age whereas the second cohort of 11 (5 affected females, 6 female controls) were studied from 3 months of age. Each cohort contained *CLN6*$^{-/-}$ (n = 2-3) and *CLN6*$^{+/-}$ (n = 3) South Hampshire sheep and *CLN5*$^{-/-}$ (n = 3) and *CLN5*$^{+/-}$ (n = 3) Borderdale sheep. The heterozygous sheep (i.e. *CLN5*$^{+/-}$ and *CLN6*$^{+/-}$) were clinically normal and served as control animals. Sheep were maintained on outdoor pasture.

Prior to testing, the sheep were brought indoors, fasted for 18-24 h and weighed. 1% Tropicamide (Mydriacyl, 10 mg/mL; Alcon NZ Ltd, Auckland, NZ) was administered to achieve mydriasis during recordings. Sheep were anaesthetised by intravenous injection of 0.5 mg/kg live weight (LW) diazepam (Pamlin injection, Troy Laboratories NZ Pty Ltd, Auckland, NZ) and 10 mg/kg LW of ketamine hydrochloride (Phoenix Ketamine injection, Phoenix Pharm Distributors Ltd, Auckland, NZ). After intubation, they were maintained on inhalation anaesthesia, isoflurane in oxygen (1.5% - 3% v/v to effect).

2.2. Electroretinography (ERG)

Electroretinography was conducted using an Eickemeyer Veterinary ERG system (Eickemeyer - Medizintechnik für Tierärzte KG, Tuttlingen, Germany). The eye was kept open with a 40 mm Barraquer speculum, whilst a gold-plated ERG-Jet contact lens electrode (Fabrinal SA, La Chaux-De-Fonds, Switzerland), filled with sterile saline solution, was placed on the eye. Subdermal 12 mm, 29-gauge needle electrodes (LKC Technologies Inc., Gaithersburg, MD, USA) were placed approximately 1 cm lateral to the lateral canthus (reference), and onto the dorsal surface of the skull (earth) 1 cm lateral to the midline towards the eye that was being measured. The light stimulus was positioned within 1 cm of the eye and delivered four consecutive flashes of white light (2-3 cd/m^2) at an interval of 0.8 seconds. The first recording was performed with the ambient light turned on (light adaptation). The light was then turned off and a second recording (zero minutes dark adaptation) was performed immediately. Finally, following five minutes in the dark, the third recording (five minutes dark adaptation) was performed. A minimum of 10 minutes was allowed between eye recordings to allow the contralateral eye to become light adapted before its ERGs were conducted.

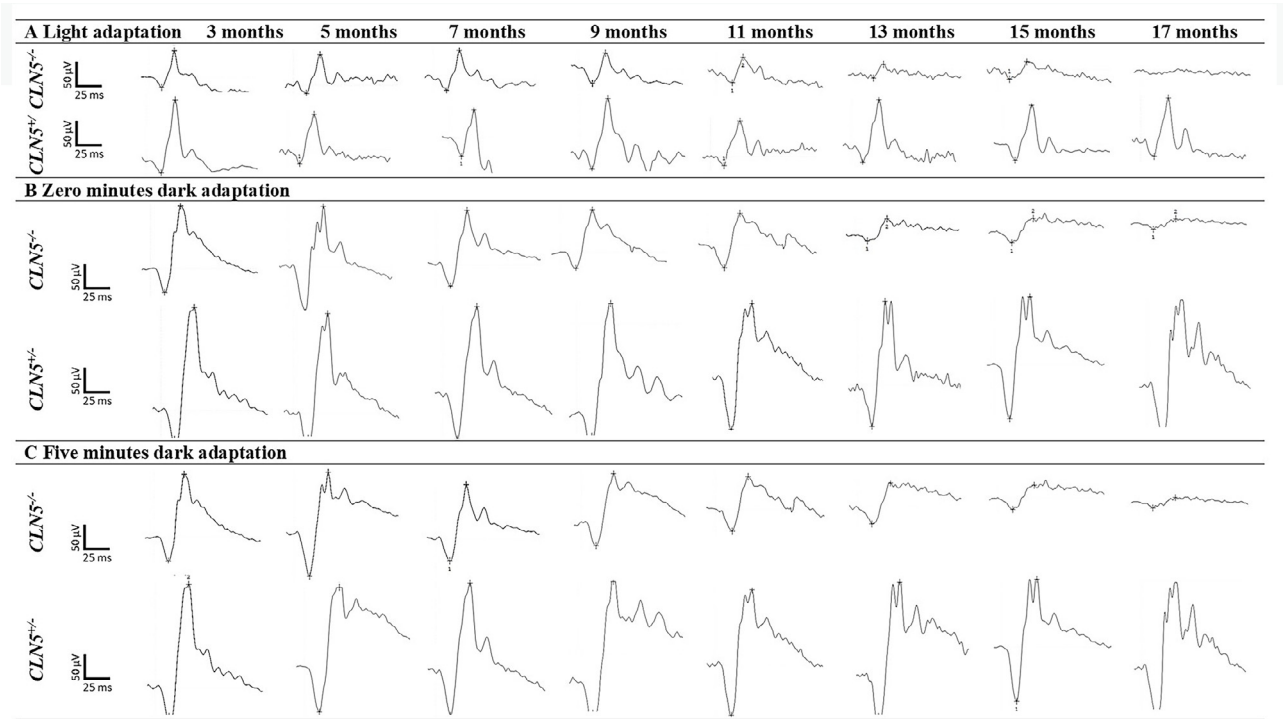
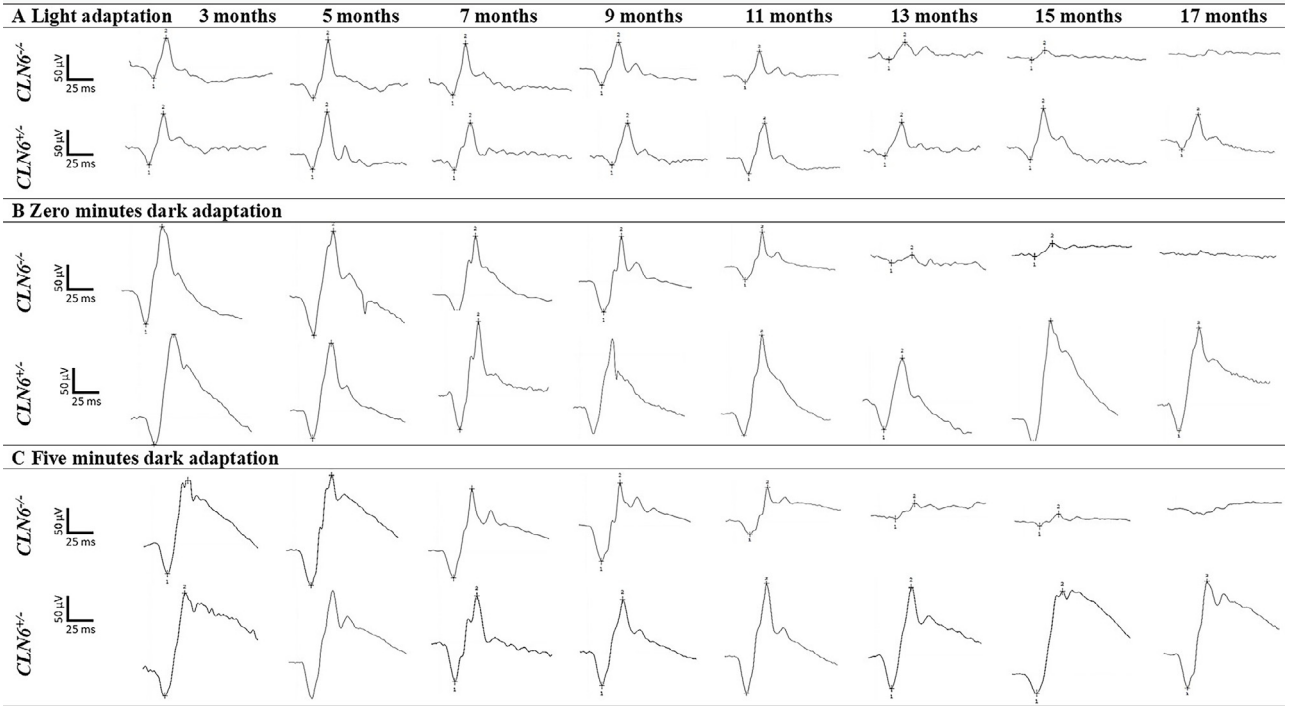


Fig. 1. Individual longitudinal electroretinography (ERG) traces from CLN5 animals. Representative individual ERG traces from CLN5 affected (CLN5-/-) and clinically normal heterozygous control (CLN5+/-) sheep at different ages in different lighting situations. (A) ERGs obtained in ambient lighting, (B) ERGs obtained immediately after light was turned off, (C) ERGs obtained five minutes after the light was turned off.



Graph 1. Mean amplitudes of electroretinography (ERG) a- and b-waves in CLN5 sheep.
Mean amplitudes (± SEM) from clinically normal heterozygous control (CLN5+/-) and CLN5 affected (CLN5-/-) sheep at different ages. Left column shows a-waves, right column shows b-waves. Light adapted ERGs were obtained first (A, B), followed by a measurement immediately after the light was turned off (C, D), and a third measurement after five minutes of dark adaptation (E, F). * indicates where $P < 0.05$ after a mixed effects model followed by Tukey's multiple comparisons test.

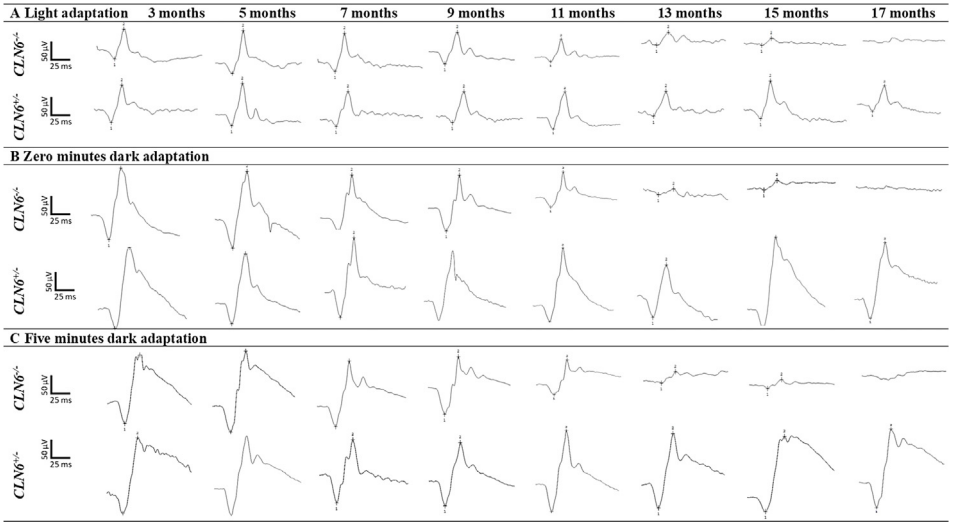


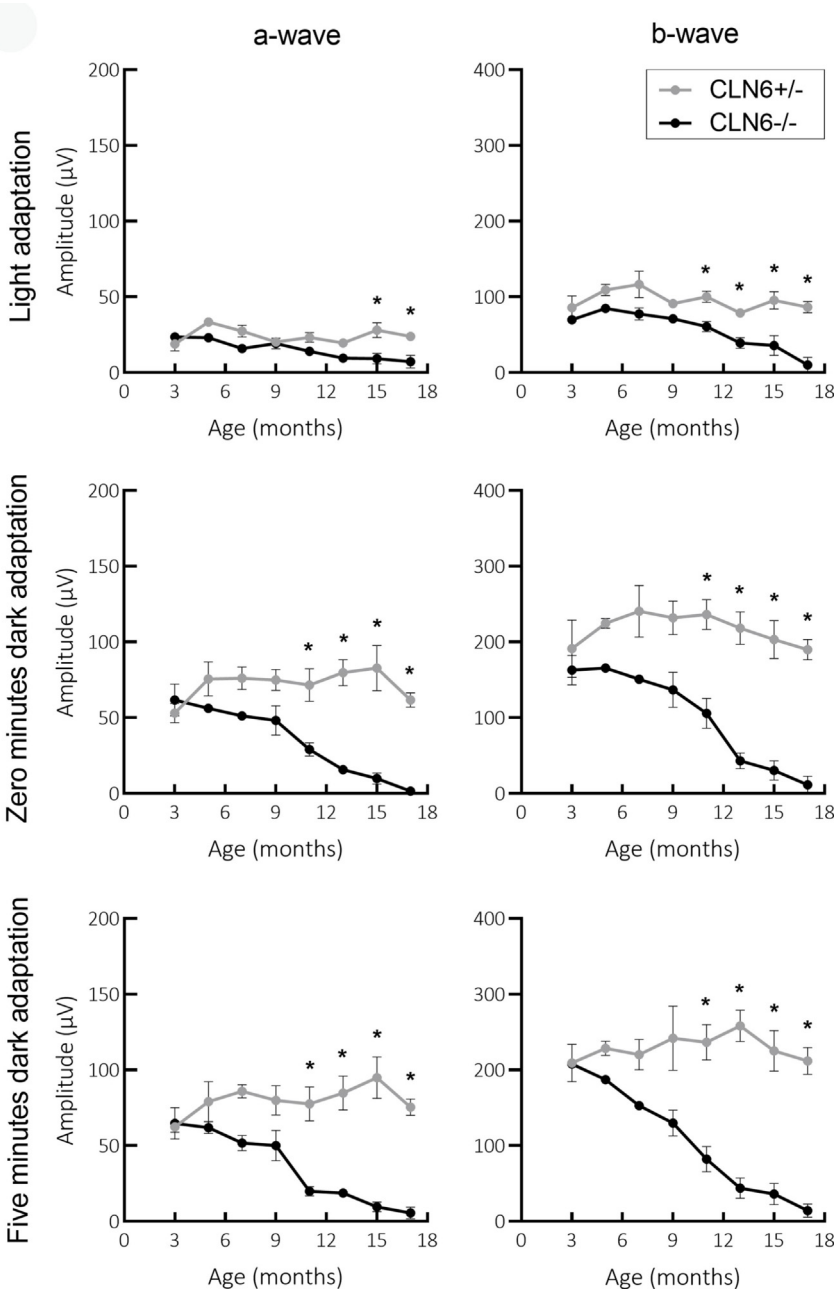
Fig. 2. Individual longitudinal electroretinography (ERG) traces from CLN6 animals. Representative individual ERG traces from CLN6 affected (CLN6-/-) and clinically normal heterozygous control (CLN6+/-) sheep at different ages in different lighting situations. (A) ERGs obtained in ambient lighting, (B) ERGs obtained immediately after light was turned off, (C) ERGs obtained five minutes after light was turned off.

2.3. Data processing and statistical analysis

ERG a- and b-wave amplitudes were determined for each eye for each type of adaptation at each age using the provided software (Eickemeyer). The a-wave amplitude was calculated as the distance from the centre line (or still position) to the trough of the a-wave whilst the b-wave amplitude was calculated from the trough of the a-wave to the peak of the b-wave. Average measures were then calculated from both eyes. Both raw and average data for each animal are presented in the datasets.

All statistical analyses were performed on GraphPad Prism (v 8.2.0, GraphPad Software

Animals were grouped by breed and genotype (*CLN5*$^{+/-}$, *CLN5*$^{-/-}$, *CLN6*$^{+/-}$ and *CLN6*$^{-/-}$) and the repeated measurements were allocated into age-groups (3, 5, 7, 9, 11, 13, 15 and 17 months). Means and corresponding standard error of the mean (SEM) values were calculated for each genotype for each measurement for each age. A mixed-effects model, fit using Restricted Maximum Likelihood (REML), followed by Tukey's multiple comparisons test was performed using GraphPad Prism version 8.2.0 for Windows (GraphPad Software, San Diego, CA, USA, www.graphpad.com) for each set of measurements to investigate the effects of time and disease status on the a- and b-wave amplitudes. Differences were regarded significant where $P < 0.05$.



Graph 2. Mean amplitudes of electroretinography (ERG) a- and b-waves in CLN6 sheep.
Mean amplitudes (± SEM) of clinically normal heterozygous control (CLN6+/-) and CLN6 affected (CLN6-/-) sheep at different ages. Left column shows a-waves, right column shows b-waves. Light adapted ERGs were obtained first (A, B), followed by a measurement immediately after the light was turned off (C, D), and a third measurement after five minutes of dark adaptation (E, F). * indicates where $P < 0.05$ after a mixed effects model followed by Tukey's multiple comparisons test.

Ethics Statement

All experiments were approved by the Lincoln University Animal Ethics Committee and performed in accordance with the National Institutes of Health guide for the care and use of Laboratory animals (NIH Publications No. 8023, revised 1978), the Lincoln University Code of Ethical Conduct for the Use of Animals and the New Zealand Animal Welfare Act 1999.

CRediT Author Statement

Katharina Russell: Conceptualization, Methodology, Data curation, Formal analysis, Investigation, Writing - original draft, Writing - review & editing; **Nadia Mitchell:** Conceptualisation, Methodology, Data curation, Formal analysis, Investigation, Writing - original draft, Writing - review & editing; **Martin Wellby:** Investigation; **Graham Barrell:** Conceptualization, Supervision, Writing - review & editing; **David Palmer:** Funding acquisition; Conceptualization, Supervision, Writing - review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships which have or could be perceived to have influenced the work reported in this article.

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References

[1] S.J. Murray, K.N. Russell, T.R. Melzer, S.J. Gray, S.J. Heap, D.N. Palmer, N.L. Mitchell, Intravitreal gene therapy protects against retinal dysfunction and degeneration in sheep with CLN5 Batten disease, Exp. Eye Res. 207 (2021) 108600, doi:10.1016/j.exer.2021.108600.

[2] K. Russell, N. Mitchell, M. Wellby, G. Barrell, D. Palmer, Electroretinography data from ovine models of CLN5 and CLN6 neuronal ceroid lipofuscinoses, Harvard Dataverse 1 (2021), doi:10.7910/DVN/JOSWTD.