

14. Pre-symptomatic detection of cytoplasmic TDP-43 accumulation using tissue-engineered skin model derived from C9ORF72-FALS patients

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Amyotrophic lateral sclerosis (ALS) is an adult-onset disease characterized by the selective degeneration of motor neurons in the brain and spinal cord resulting in progressive paralysis and death. Current diagnosis of ALS is based on clinical assessment of related symptoms, which appear only late in the disease course after degeneration of a significant number of motor neurons. As a result, the identification and development of disease-modifying therapies is difficult, making ALS an incurable disease. Novel strategies for early diagnosis of ALS, to monitor disease progression and to assess response to existing and future treatments are urgently needed.

Many neurological disorders, including ALS, are accompanied by skin changes that often precede the onset of neurological symptoms. We have developed a unique ALS tissue-engineered skin model (ALS-TES), derived from the cells of ALS patients, in order to study the earliest stages of ALS-related skin pathology. For each participant, two skin biopsies were collected using a 6-mm diameter punch biopsy. Tissue-engineered skin was then generated from isolated keratinocytes and fibroblasts, and examined by routine histochemistry and immunohistochemistry, as well as by confocal microscopy. The ALS-TES model presents a number of striking features including altered epidermal differentiation, abnormal dermo-epidermal junction, delamination, keratinocyte infiltration, collagen disorganization and cytoplasmic TDP-43 inclusions, which are not seen in skin models derived from healthy subjects. The same abnormal skin model changes were detected in skin models derived from the cells of pre-symptomatic C9orf72-linked ALS patients carrying the GGGGCC DNA repeat expansion. Consequently, our ALS-TES skin model could represent a renewable source of human tissue to better understand the physiopathological mechanisms underlying this disease, including cytoplasmic TDP43 accumulation, and lead to better tools for early diagnosis and disease monitoring.

TITLES OF DIAGNOSTIC CASE PRESENTATIONS

1. Myxopapillary Ependymoma, multifocal

P.W. Schutz¹, G.R.W. Moore¹, R. Akagami², I.R. Mackenzie¹

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2. Phosphaturic mesenchymal tumor

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3. Secondary Gliosarcoma with Epithelial and Pseudoepithelial Differentiation

Claire I. Coire¹, And Warren P. Mason²

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4. Lymphomatosis cerebri

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5. Myopathy with Hexagonally Cross-Linked Crystalloid Inclusions

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6. Bilateral brain stem tegmental calcification

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