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Lab resource: Stem cell line

Induced pluripotent stem cells (iPSCs) derived from a patient with frontotemporal dementia caused by a R406W mutation in microtubule-associated protein tau (MAPT)

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ABSTRACT

Skin fibroblasts were obtained from a 59-year-old woman diagnosed with frontotemporal dementia. The disease is caused by a R406W mutation in microtubule-associated protein tau (MAPT). Induced pluripotent stem cells (iPSCs) were established by electroporation with episomal plasmids containing *hOCT4*, *hSOX2*, *hKLF2*, *hL-MYC*, *hLIN-28* and *shP53*. iPSCs were free of genomically integrated reprogramming genes, contained the expected c.1216C > T substitution in exon 13 of the *MAPT* gene, expressed the expected pluripotency markers, displayed in vitro differentiation potential to the three germ layers and had normal karyotype. The iPSC line may be useful for studying hereditary frontotemporal dementia and TAU pathology in vitro.

1. Resource table

Name of Stem Cell construct	H237 C3
Institution	Bioneer A/S
Person who created resource	Mikkel Aabech Rasmussen, Bjørn Holst
Contact person and email	Bjørn Holst, bho@bioneer.dk
Date archived/stock date	July 1, 2012
Origin	Human skin fibroblasts
Type of resource	Biological reagent: induced pluripotent stem cell (iPS); derived from a MAPT R406W mutation carrier
Sub-type	Induced pluripotent stem cell
Key transcription factors	Episomal plasmids containing *hOCT4*, *hSOX2*, *hL-MYC*, *hKLF4*, *hLIN28* and *shP53* (Addgene plasmids 27077, 27078 and 27080; Okita et al., 2011)
Authentication	Identity and purity of cell line confirmed by integration analysis, sequencing of mutation, pluripotency analysis, karyotyping and in vitro differentiation (Fig. 1).
Link to related literature (direct URL links and full references)	http://onlinelibrary.wiley.com/doi/10.1111/-j.1468-1331.2008.02069.x/abstract;jsessionid=175DB65708CDD60137A0E1D39E93D3D6.f04t01 The MAPT R406W patient diagnosed with frontotemporal dementia is the mother of a pre-symptomatic carrier which is also heterozygous for the MAPT R406W mutation
Information in public databases	Link to any data or information about this resource in a database if applicable

2. Resource details

Fibroblasts were obtained from a 59-year old woman heterozygous for a R406W mutation in microtubule-associated protein tau (MAPT). The patient was clinically diagnosed with frontotemporal dementia at age 52, displaying atrophy of the temporal lobes on magnetic resonance imaging and reduction in glucose metabolism bilaterally in the temporal pole and adjacent lateral and medial temporal cortex including the anterior sections of the hippocampi and the amygdalae using 18-fluoro-deoxyglucose positron emission tomography (Lindquist et al., 2008). Reprogramming was performed by electroporation with three episomal plasmids containing *hOCT4* with or without a short hairpin to TP53 (*shp53*), *hSOX2* and *hKLF4*, and *hL-MYC* and *hLIN28* (Okita et al., 2011). This method had previously been used to establish integration-free iPSC from an 18-year old healthy male (Rasmussen et al., 2014). Four weeks after reprogramming, an average of 64 colonies per 1×10^5 fibroblasts (0.06%) emerged with the inclusion of *shp53*, whereas, no colonies were observed without *shp53*. Integration analysis with plasmid-specific primers showed that *hOCT4*, *hSOX2* and *hLIN28*, present on each of the three plasmids, had not integrated into the genome (Fig. 1A) and sequencing confirmed the presence of a c.1216C > T substitution in one of the alleles of exon 13 in the *MAPT* gene corresponding to a R406W mutation (Fig. 1B). Pluripotency analysis showed that transcription from the endogenous pluripotency genes *NANOG*, *POU5F1* (*OCT4*), *TDGF1*, *DNMT3B*, *GABRB3* and *GDF3* was between 100 and

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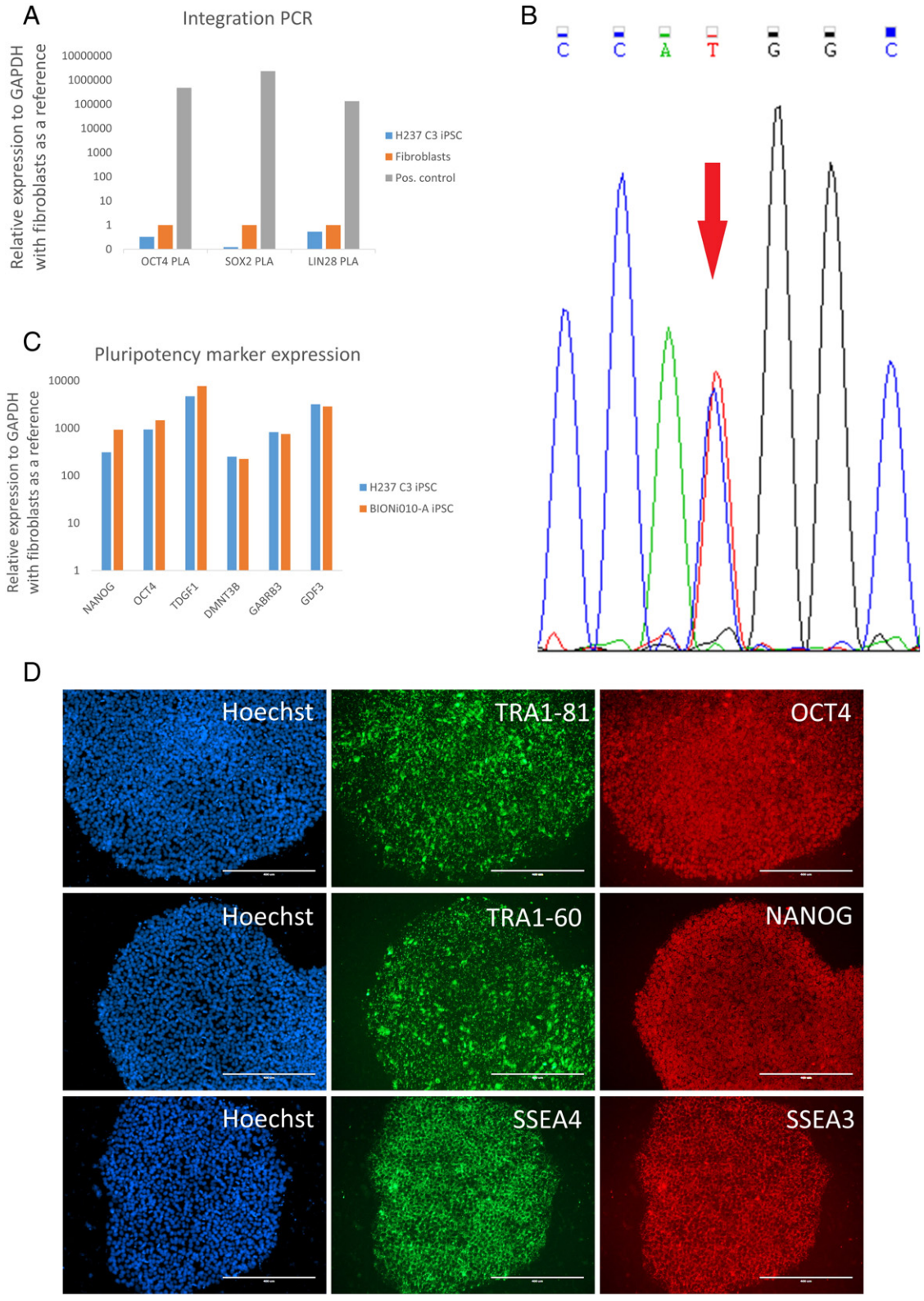

Fig. 1. A. Integration analysis. Quantitative PCR (qPCR) on genomic DNA from H237 C3 induced pluripotent stem cells (iPSC), fibroblasts and a pool of fibroblasts electroporated with episomal plasmids (positive control) with plasmid-specific primers of *hOCT4*, *hSOX2*, and *hLIN28*. Data is shown as the fold change ($2-\Delta\Delta Ct$) with *GAPDH* and fibroblasts as references. B. Sequencing of mutation. Sequencing of exon 13 of the *MAPT* gene in H237 C3 induced pluripotent stem cells showing a c.1216C > T substitution in one of the alleles marked with a red arrow. C. Pluripotency expression analysis. Quantitative reverse-transcriptase PCR (qRT-PCR) expression analyses on cDNA from H237 C3 induced pluripotent stem cells (iPSC), fibroblasts and the iPSC line BIONi010-A (Rasmussen et al., 2014) as a positive control with the endogenous pluripotency genes *NANOG*, *POU5F1* (*OCT4*), *TDGF1*, *DNMT3B*, *GABRB3* and *GDF3*. Relative expression is shown as the fold change ($2-\Delta\Delta Ct$) with *GAPDH* and fibroblasts as references. D. Immunofluorescence staining. Immunocytochemical detection of H237 C3 induced pluripotent stem cells with the pluripotency markers OCT3/4, TRA1-81, NANOG, TRA1-60, SSEA3, and SSEA4. Scale bars correspond to 400 μm. E. *In vitro* differentiation. Immunocytochemical staining of plated embryoid bodies (EBs) from H237 C3 induced pluripotent stem cells on day 28 with smooth muscle actin (SMA), alpha-fetoprotein (AFP) and betaIIItubulin (TUJI). Scale bars correspond to 100 μm. F. Karyotyping. Representative karyotype of H237 C3 induced pluripotent stem cells.