Spontaneous ATM Gene Reversion in A-T iPSC to Produce an Isogenic Cell Line

Lucy Lin[1], Mavis R. Swerdel[1], Michael P. Lazaropoulos[1], Gary S. Hoffman[1], Alana J. Toro-Ramos[1], Jennifer Wright[2], Howard Lederman[2], Jianmin Chen[1], Jennifer C. Moore[2] and Ronald P. Hart[1]*

[1]Department of Cell Biology & Neuroscience, Rutgers University, Piscataway, NJ 08854 USA

[2]A-T Clinic, Johns Hopkins University School of Medicine, Baltimore, MD USA

[3]Department of Genetics, Rutgers University, Piscataway, NJ 08854 USA

***Email of Presenting Author: rhart@rutgers.edu**

A spontaneously reverted iPSC line was identified from an A-T subject with heterozygous ATM truncation mutations. The reverted iPSC line expressed ATM protein and was capable of radiation-induced phosphorylation of Chk2 and H2A.X. Genome-wide SNP analysis confirmed a match to source T-cells and also to a distinct, non-reverted iPSC line from the same subject. Rearranged T-cell receptor sequences predict that the iPSC culture originated as several independently reprogrammed cells that resolved into a single major clone, suggesting that gene correction likely occurred early in the reprogramming process. Gene expression analysis comparing ATM-/- iPSC lines to unrelated ATM+/- cells identifies a large number of differences but comparing only the isogenic pair of A-T iPSC lines reveals that the primary pathway affected by loss of ATM is a diminished expression of p53-related mRNAs. Gene reversion in culture, while likely a rare event, provided a novel, reverted cell line for studying ATM function.