Further insights into Allan-Herndon-Dudley syndrome: a novel SLC16A2 splice site variant

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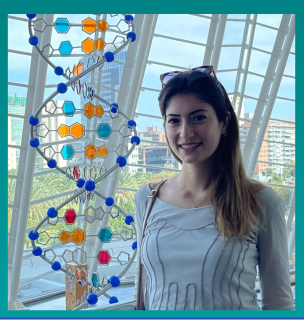

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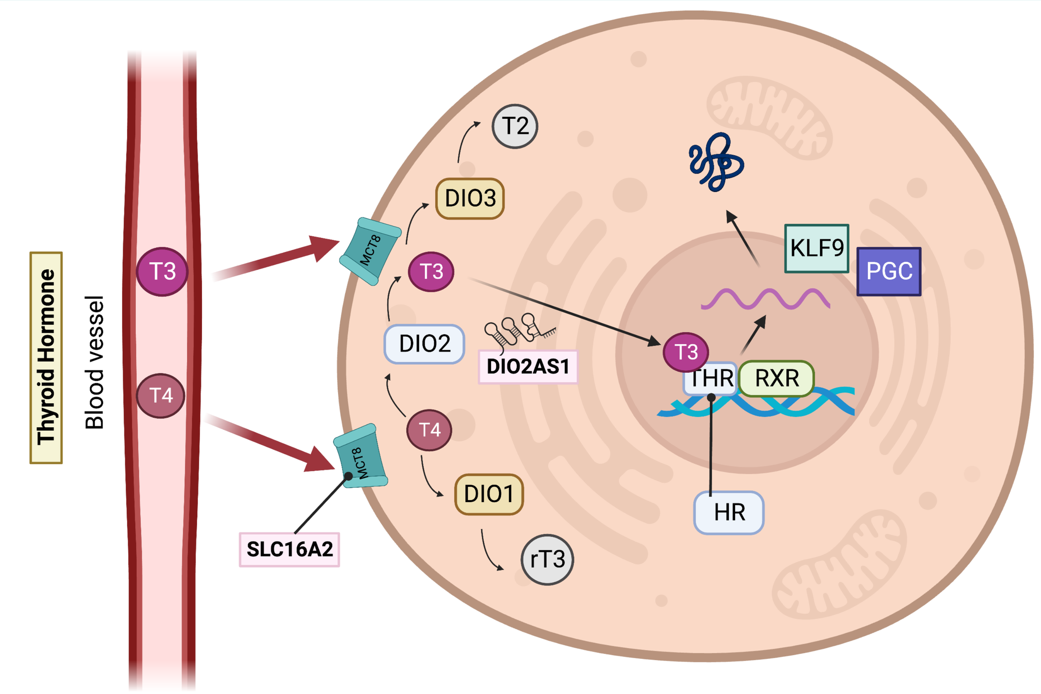
Introduction

Genetics variants in *SLC16A2* gene encoding for the monocarboxylate transporter 8 (MCT8) cause a severe X-linked intellectual deficit and neurological impairment known as Allan-Herndon-Dudley syndrome (AHDS). MCT8 promotes cellular uptake and efflux of thyroid hormone and its mutations provoke elevated serum T3 levels in children. Iodothyronine deiodinases (DIO) 1 and 2 are implicated in the conversion of T4 into biologically active T3, while DIO3 converts T4 into the inactive hormone reverse T3 (rT3). Active T3 and retinoid X receptors (RXR) can form heterodimer complexes which bind to hormone response elements (HREs) that leads to activate or repress transcription.



Representative figure of thyroid homone signaling pathway.
Created with BioRender.com.

Methods

- Real time PCR
- Western blot
- Live and dead assay
- MTT assay
- Oil Red O staining

Aim of the study

Our aim is to investigate the impact of mutations in *SLC16A2* gene on the pathogenetic mechanisms of AHDS.

Results

Figure 1. The identified variant in the *SLC16A2* gene causes the breakup of the wild type donor splice site, possibly leading to exon 1 skipping, affecting cell viability. Created with BioRender.com.

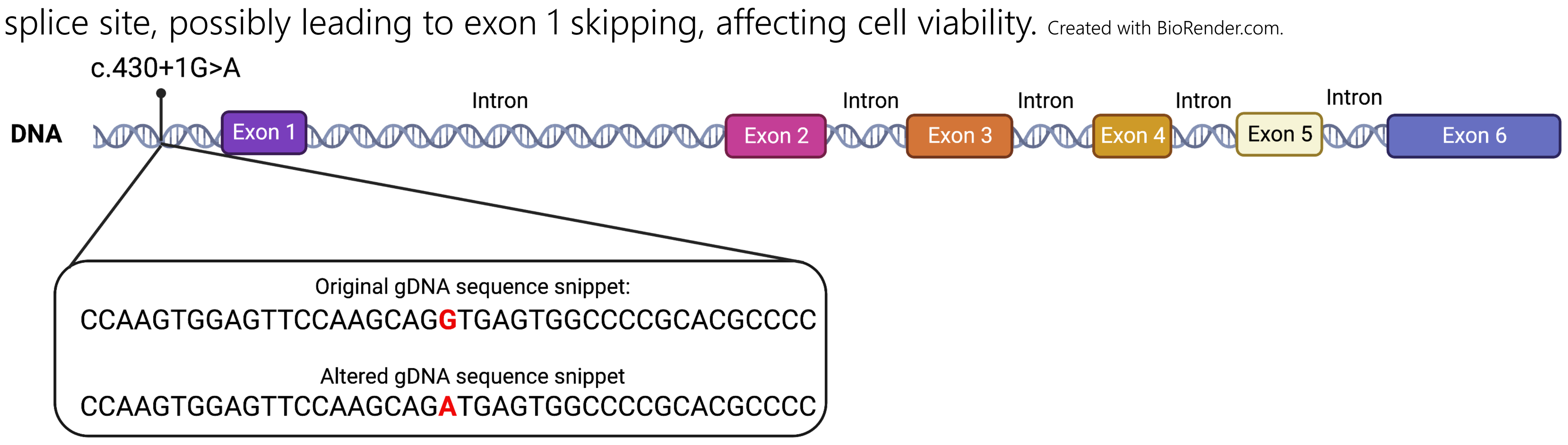


Figure 2. MTT assay after 24-48-72 hours (**p<0.01 vs CTR).

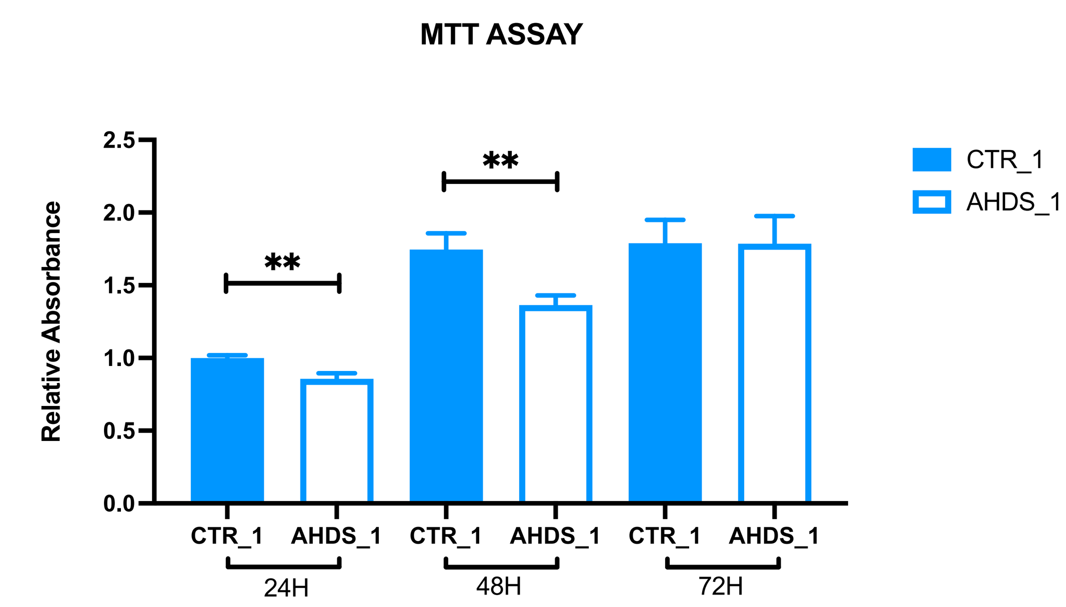


Figure 3. Live and Dead assay revealed a decrease in live cell populations (n=3, *p<0.05 vs CTR).

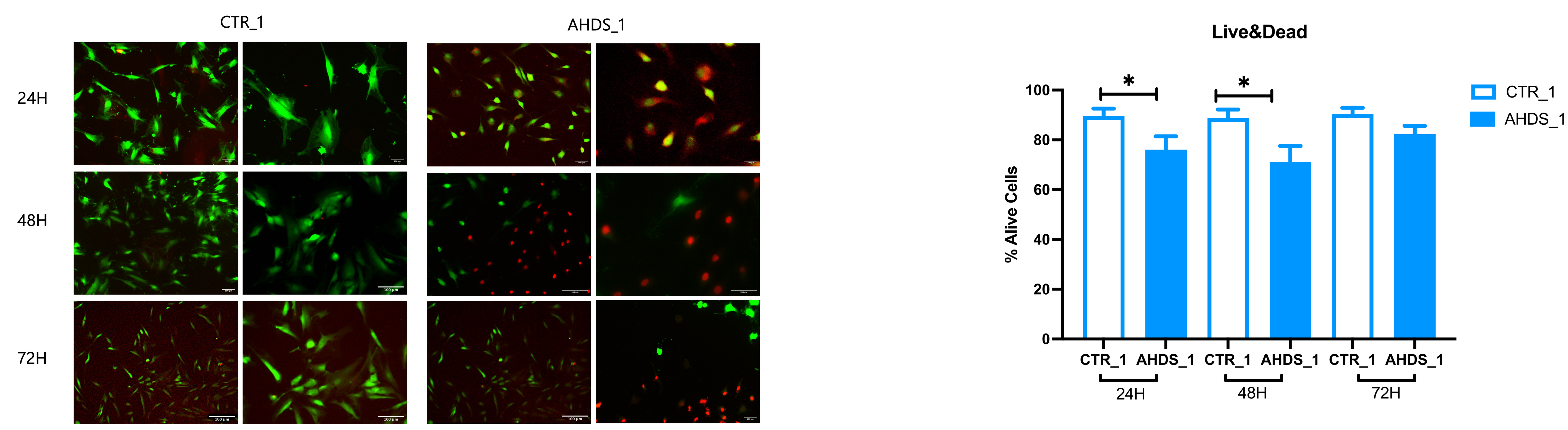


Figure 4. RT-qPCR Analysis of both *SLC16A2* and thyroid hormone signalling pathway genes expression (n=3, *p<0.05, **p<0.01, ****p<0.0001 vs CTR).

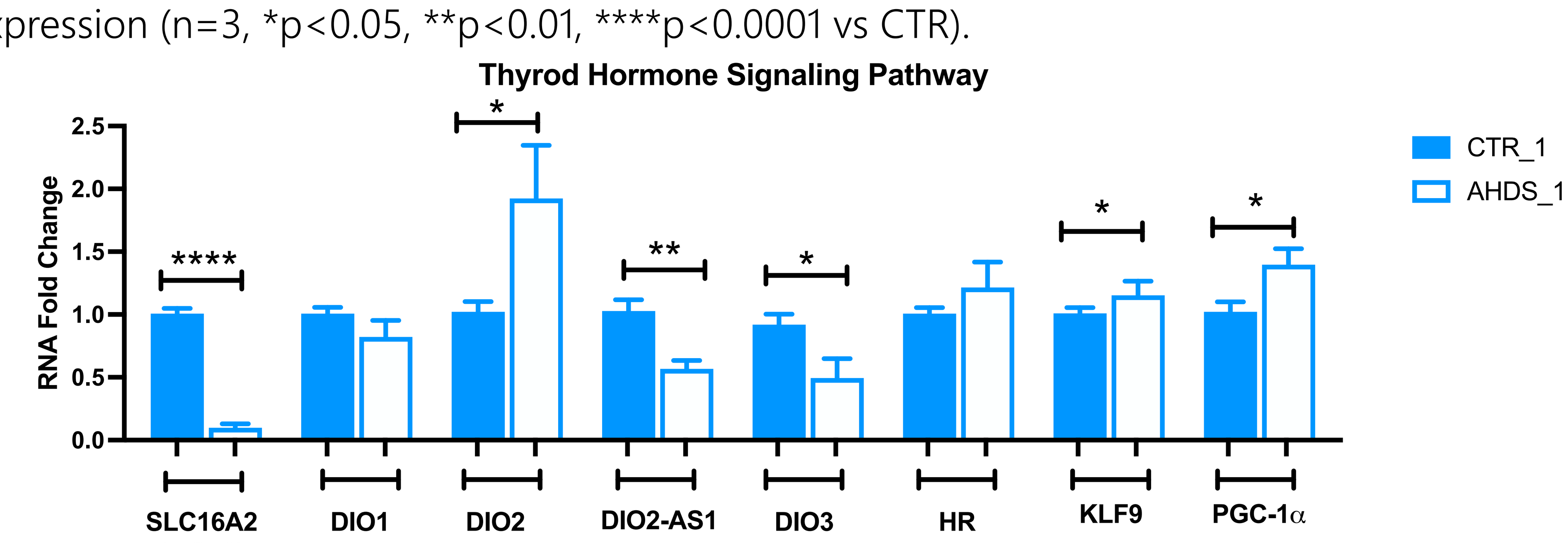


Figure 5. Western blot analysis to evaluate HR protein expression (n=3, *p<0.05 vs CTR).

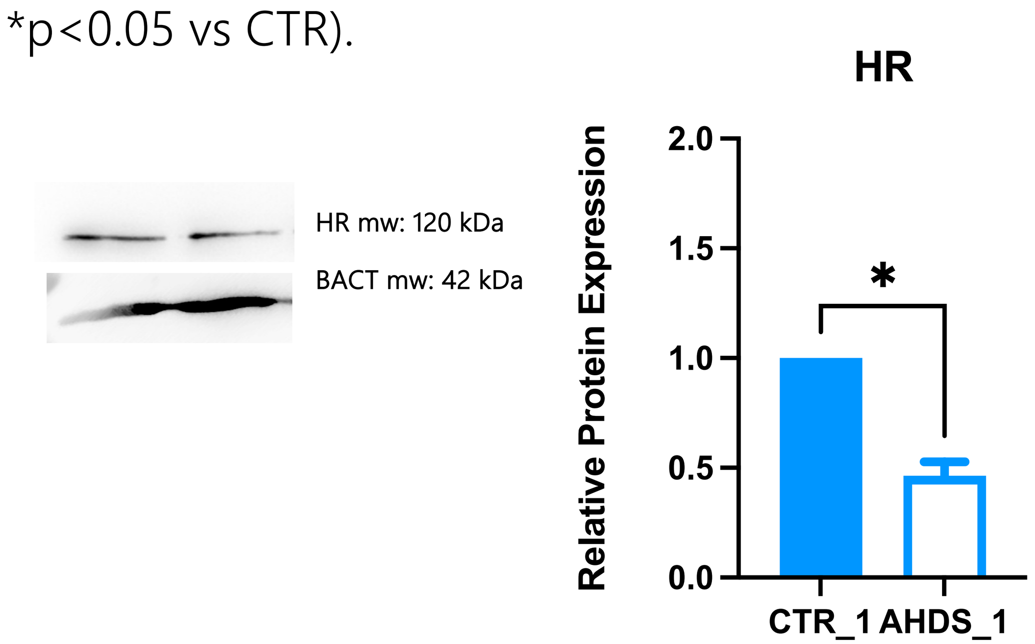


Figure 6. RT-qPCR Analysis of MBP (Myelin basic protein) RNA expression (n=3, *p<0.05 vs CTR).

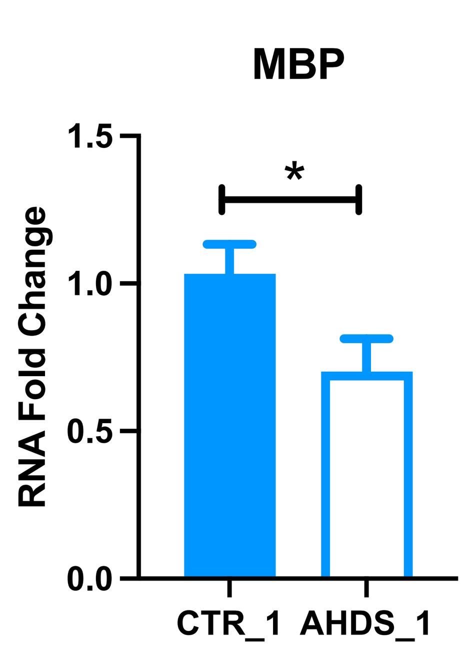
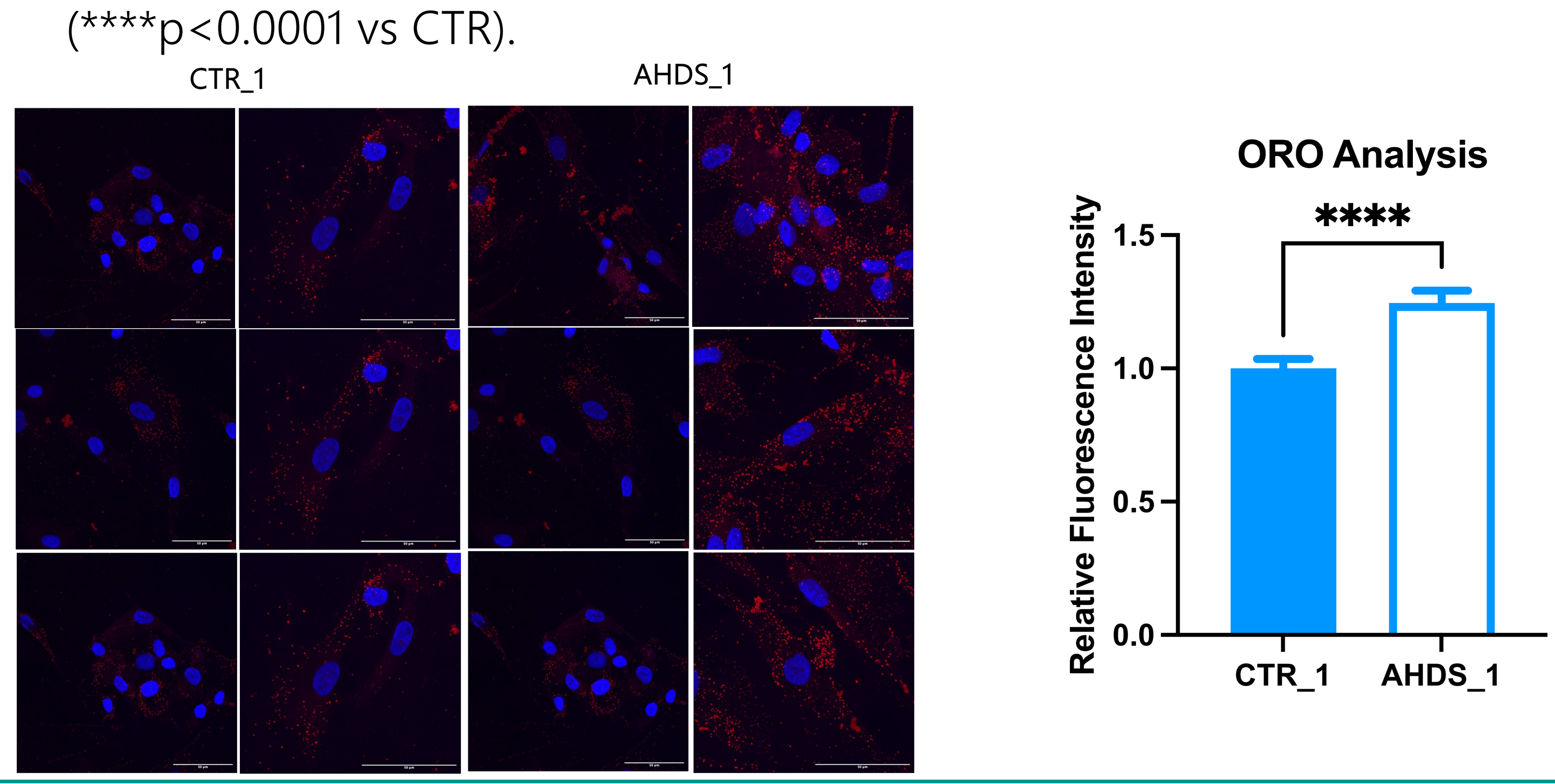


Figure 7. The Oil Red O staining revealed an increasing presence of lipid droplets (****p<0.0001 vs CTR).



Conclusions

Our preliminary data emphasize an impairment in AHDS primary fibroblasts used as potential *in vitro* experimental model to increase our understanding in the pathogenic mechanisms related to the disease.

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