Review of: "A reference induced pluripotent stem cell line for large-scale collaborative studies"

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The manuscript entitled: “A reference induced pluripotent stem cell line for large-scale collaborative studies”, is a multi-lab approach to establishing a well-characterized induced pluripotent stem cell (iPSC) reference line to underpin collaborative studies. The authors curated nine male iPSC lines readily available from the public repositories. They established clonal sub-lines from each parental iPSC line. In addition, they used CRISPR/Cas9 editing to correct a mutation present in one copy of AIRD2. They then characterized one sub-clone from each parental iPSC line for the pluripotent state, genomic integrity, efficiency of CRISPR genome editing, and differentiation efficiency into multiple lineages. As a result, the authors identified the genome-edited iPSC sub-line (named KOLF2.1J) as an all-around well-performing cell line. Authors envisage the usage of KOLF2.1J as a reference line to derive hundreds of gene-edited and functionalized sub-clones for modelling Alzheimer’s Disease and Related Dementias (ADRD). The authors are willing to distribute generated sub-lines across the research community with associated datasets.

I find that the characterization experiments are well designed. This type of multimodal genetic and phenotypic comparison is very laborious. It was great to see the multi-lab approach applied here. I do not doubt that the KOLF2.1J is well-characterized and fit for developing isogenic edited lines relevant to ADRD. The KOLF2.1J is freely available and accompanied by a plentiful of raw data. It is undoubtedly a great resource to the field. However, I also have concerns that I have listed below.

Generation of isogenic edited iPSC is an excellent approach, especially concerning monogenic diseases. The ADRD is a complex disorder, and authors have envisaged the generation of hundreds of CRISPR/Cas9-edited lines relevant to a single deeply characterized genetic background. It has its challenges, which might outweigh the benefits of using isogenic lines. Authors should compare their strategy to, for example, a multiplexing strategy, such as in PMID: 33664506.

As the authors have stated in the text, the limitation to the study is that they have characterized less than a dozen publicly available lines. It is unclear if the multifactorial pipeline described here allow for the high-throughput screening for the lead iPS line?

The authors have acknowledged that the KOLF2.1J is the reference for the ADRD field. However, there is no sufficient data on differentiation to other cell lineages to be considered an idealized line for all purposes. Perhaps authors could

consider incorporating quantitative analyses to predict the differentiation propensity of iPSC, similar to the landmark study described in PMID: 21295703?

It would be interesting to see how the WGS data compares to recently published studies PMID: 35176222 and https://doi.org/10.1101/2022.03.04.482992.