Can cell-type specific variability be involved in a rare variant of Unverricht-Lundborg? Investigation with iPSC generated models

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RODUCTION

omozygosity for a private synonymous mutation in the **cystatin-B ene** (CSTB, MIM:601145; c.66G>A; p.Q22Q) was detected in a ortuguese patient with a rare, atypical form of a myoclonic epilepsy **Unverricht-Lundborg disease** (ULD, MIM #254800).

his mutation leads to **mis-splicing of CSTB pre-mRNA** in cultured broblasts a **normal and an abnormal transcript were detected**. The bnormal transcript, 451 bp had an inclusion from intron 1 [1], due o the activation of a cryptic 5' splice site. The expected resulting **ltered peptide is a prematurely truncated** (Figure 1A).

n the patients fibroblasts, cystatin B protein has **nuclear location** [2] nd presents a **change from the normal lysosomal distribution** Figure 1B).

's been established that the use of induced Pluripotent Stem Cells **PSC**) can be very useful to **model biological processes**, particularly aluable in the case of cell types that are difficult to obtain [3], such s in neurologic diseases like ULD.

THODS

Generation of iPSCs from fibroblasts using currently established methods (Figure 2);

Differentiation of those iPSCs into Neural Progenitor Cells (NPCs);

Analysis of the transcripts and the protein localization in different cellular types.

ULTS

work is proposed as a future project, using patient derived iPSCs as urce of different cell types. We intend to obtain results regarding type specific abnormal RNA splicing [4] and subsequent racterization of cellular alterations, such as CSTB protein mis-lization.

CUSSION

assessment of cell type specific variation of CSTB expression could tribute to help understanding cell-type specific implications in the nogenesis of ULD as well as to provide specific types of cells to test el therapies.

ences: 1. doi: 10.1016/j.eplepsyres.2011.11.004; 2. doi: 10.1016/j.ymgmr.2015.07.005; : 10.1016/j.scr.2019.101595; 4. doi: 10.1186/gb-2004-5-10-r74

Using patient derived iPSCs as a source of different cell types. We investigate the existence of cell-type specific abnormal RNA splicing and subsequently characterize cellular alterations.

Figure 1: A- aberrant splicing exists in the patient fibroblasts (non disease-target cells). B- Comparison between normal and mutant dermal fibroblasts using anti-CSTB antibody (Abcam), 50X

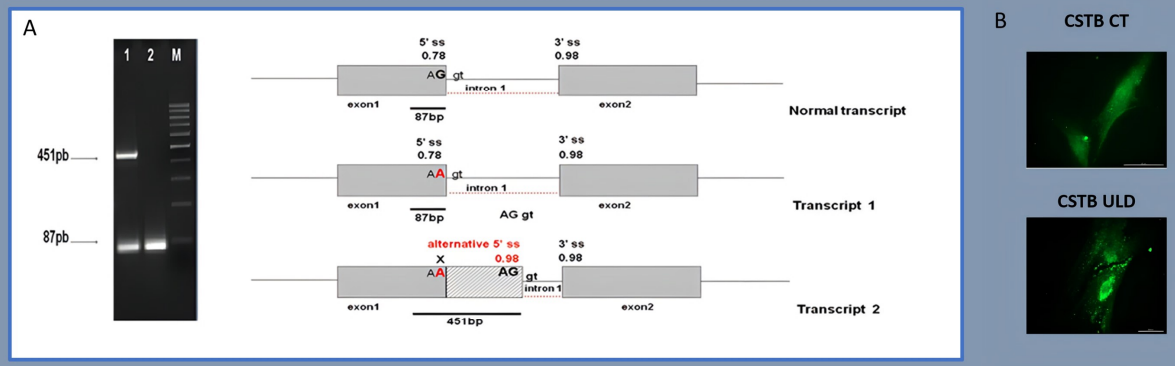
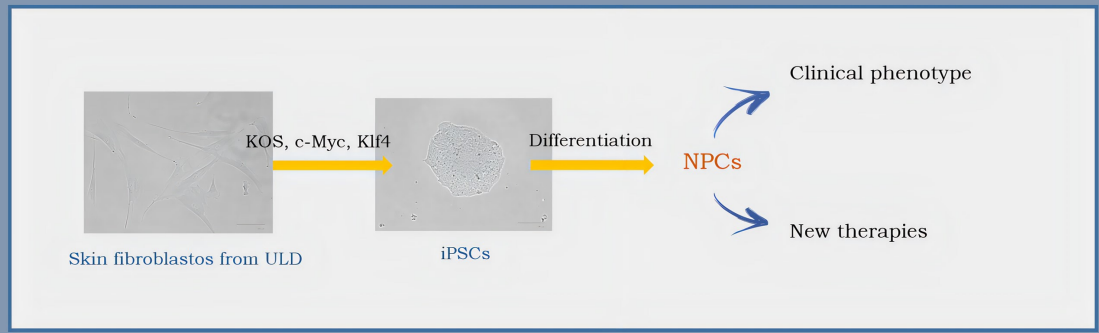


Figure 2: Workflow to verify if NPCs present the same or others aberrant processes that explain the clinical phenotype



These expectations can also be promising in other diseases unveiling differential cell-type specific expression

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Conflict of interests & Ethics

The authors declare no conflicts. Ce lines were obtained from cell bank and/or with appropriate informed consent.

A.J. Duarte and D. Ribeiro are students of Biomedical Sci Doctoral Program at ICBAS- UP.