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COMMENTARY

Patient-derived iPS cells for unveiling the molecular pathology of Pelizaeus-Merzbacher disease: a commentary on 'Reduced *PLP1* expression in induced pluripotent stem cells derived from a Pelizaeus–Merzbacher disease patient with a partial *PLP1* duplication'

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In the studies of inherited disorders of the central nerve system (CNS), it is always challenging to determine how alterations in a disease-causing gene or a rearrangement of a genomic segment that contains disease-causing genes can change gene expression and the resulting clinical phenotype. Conventional cell transfection assays employing expression plasmids cannot be used when large genomic intervals that include multiple exons, introns, promoters, distant enhancer/suppressor elements or even multiple genes are involved. Lymphoblasts or fibroblasts established from patients' blood or skin can be examined, but only trace transcripts may be detectable for genes that are predominantly expressed in the CNS.

In this issue of the *Journal of Human Genetics*, Yamamoto and his colleagues have shown that induced pluripotent stem (iPS) cells derived from patients' fibroblasts may serve as resources to directly determine gene expression aberrations.[1] They established iPS cells from three patients with Pelizaeus–Merzbacher disease (PMD), which is an X-linked disorder of the CNS. PMD is caused by mutations of the *PLP1* gene, which is predominantly expressed by oligodendrocytes, but is barely or faintly detectable in the lymphocytes or fibroblasts.[2,3] Of these three patients, one had a rare partial duplication, encompassing a 16-Kb genomic interval that spans exons 1–3 of *PLP1*. In such a case, it is extremely difficult to determine the

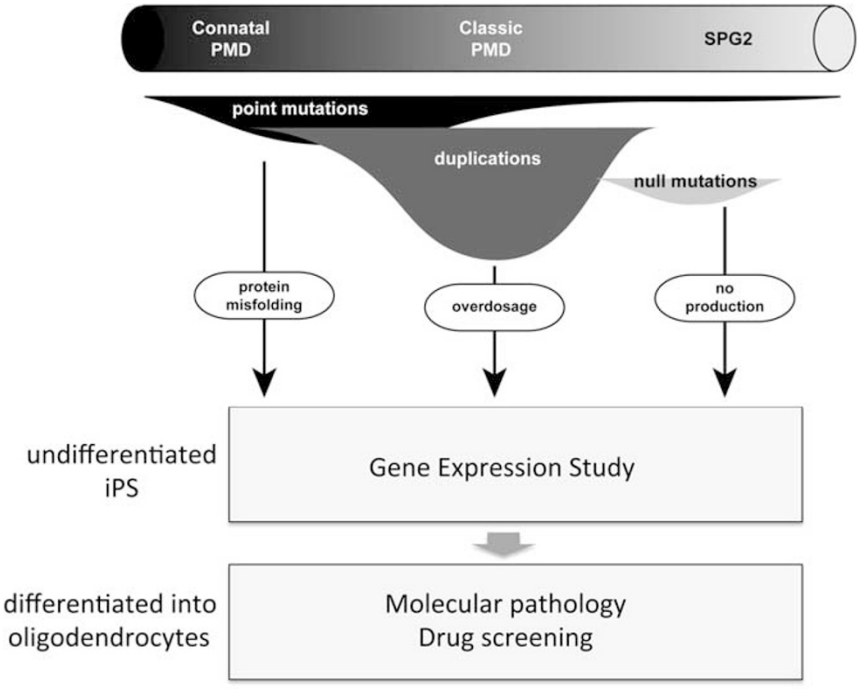

Figure 1 Use of patient-derived iPS cells in the studies of PMD. Point mutations often cause the most severe (connatal) form of PMD but can also cause the classic form or even milder spastic paraplegia type 2 (SPG2). The most common genomic duplications lead to a moderate classic form of PMD. Rare null mutations such as deletion or prematurely terminating mutations may cause spastic paraplegia accompanied by mild neuropathy. Undifferentiated iPS cells can be used in the *PLP1* gene expression study, as demonstrated by Shimojima *et al.*[1] Meanwhile, differentiation into oligodendrocyte lineage is required for studies in molecular mechanisms and drug screening for the treatments.

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molecular outcome of the genomic rearrangement. Yamamoto's group resolved this problem by generating patient-derived iPS cells. They reported that *PLP1* expression in iPS cells was 40 times higher than in fibroblasts. Therefore, it was possible to directly visualize the *PLP1* signals by northern blotting. Thus, undifferentiated iPS cells may serve as a better tool to examine *PLP1* expression in patient-derived cells. They showed that partial duplication of the gene completely diminished *PLP1* expression, and this finding was compatible with the mild clinical presentation of this family.

Meanwhile, limitations in the use of undifferentiated iPS cells in the quantification of cryptic gene expression became apparent. It was expected that the iPS cells derived from a patient carrying a >600-Kb duplication containing the entire *PLP1* gene would show increased transcript levels. However, northern blot performed on three different cell lines showed a tendency only because of the large experimental variation.

iPS cells have greater potential than being a resource for gene expression studies. In PMD, various types of *PLP1* mutations are associated with a spectrum of clinical severities and the molecular mechanisms underlying each type of mutations are distinct (Figure 1).[4] Differentiation of iPS cells into oligodendrocyte lineage cells will enable modeling of the pathological process of different mutations in culture dishes. The potential treatment would differ according to the mutation type. For example, overexpression-induced phenotypes could be mitigated by the downregulation of gene expression, whereas phenotypes arising from point mutations can be rescued via reduced endoplasmic reticulum stress. Differentiation of iPS cells will also facilitate screening or monitoring of the effect of potential therapeutic reagents that could mitigate these cellular phenotypes.

Meanwhile, terminal differentiation of iPS cells into mature oligodendrocytes is both difficult and time consuming (requiring almost 3 months).[5] In addition, these differentiated cells express mature myelin proteins (for example, MBP and PLP1), but myelin-like membrane structures have not been reconstituted *in vitro* thus far. Therefore, technical improvements in differentiation speed and efficiency as well as *in vitro* reconstitution of myelin is required to enable full use of these patient-derived iPS cells.

1 Shimojima, K., Inoue, T., Imai, Y., Arai, Y., Komoike, Y., Sugawara, M. *et al.* Reduced *PLP1* expression in induced pluripotent stem cells derived from a Pelizaeus–Merzbacher disease patient with a partial PLP1 duplication. *J. Hum. Genet.* **57,** 580–586 (2012).
2 Bonnet-Dupeyron, M. N., Combes, P., Santander, P., Cailloux, F., Boespflug-Tanguy, O. & Vaurs-Barrière, C. PLP1 splicing abnormalities identified in Pelizaeus-Merzbacher disease and SPG2 fibroblasts are associated with different types of mutations. *Hum. Mutat* **29,** 1028–1036 (2008).
3 Regis, S., Grossi, S., Corsolini, F., Biancheri, R. & Filocamo, M. PLP1 gene duplication causes overexpression and alteration of the PLP/DM20 splicing balance in fibroblasts from Pelizaeus-Merzbacher disease patients. *Biochim. Biophys. Acta* **1792,** 548–554 (2009).
4 Inoue, K. PLP1-related inherited dysmyelinating disorders: Pelizaeus-Merzbacher disease and spastic paraplegia type 2. *Neurogenetics* **6,** 1–16 (2005).
5 Kang, S.-M., Cho, M. S., Seo, H., Yoon, C. J., Oh, S. K., Choi, Y. M. *et al.* Efficient induction of oligodendrocytes from human embryonic stem cells. *Stem Cells* **25,** 419–424 (2007).