EBioMedicine 63 (2021) 103180

Contents lists available at ScienceDirect

EBioMedicine

journal homepage: www.elsevier.com/locate/ebiom

Commentary

Dopaminergic neurons in chromosome 22q11.2 deletion syndrome

Haruhisa Inoue[a,b,c]

[a] Center for iPS Cell Research and Application (CiRA), Kyoto University, Japan
[b] iPSC-based Drug Discovery and Development Team, RIKEN BioResource Research Center (BRC), Japan
[c] Medical-risk Avoidance based on iPS Cells Team, RIKEN Center for Advanced Intelligence Project (AIP), Japan

ARTICLE INFO

Article History:
Received 4 December 2020
Accepted 4 December 2020

Chromosome 22q11.2 Deletion Syndrome (22q11DS) is a disease caused by microdeletions in the chromosome 22q11.2 region, the most common interstitial deletion in humans, occurring in approximately one in 2000 to 4000 births. [1–3]. There are approximately 60 known genes in the 3-megabase (Mb) deletion region, which ~87% of 22q11DS patients possess, and 35 known genes in the 1.5Mb region, which 8% of 22q11DS patients have [4]. The clinical manifestations in these patients are diverse. Multiple organs are affected, including the brain, leading to intellectual disability or schizophrenia. The severity of 22q11DS is independent of the size of the deletion, with only the 1.5 Mb deletion affecting the phenotype, indicating that the 35 known genes are critical to the aetiology of this syndrome [4].

It has recently been recognized that adults with 22q11DS are at an increased risk of developing Parkinson disease (PD) [5]. Clinically, the onset of symptoms is asymmetric and is typically accompanied by progressive bradykinesia, rigidity, and tremor [6]. Typically, patients respond well to levodopa therapy [7]. The onset of PD in 22q11DS cases is often earlier, with a mean age of 39.5 ± 8.5 years (range, 18–58 years) [7]. Other symptoms include early dystonia, history of seizures, and neuropsychiatric symptoms [5]. 22q11DS-associated PD has clinical and neuropathological features similar to sporadic PD and some cases of hereditary PD [6].

In a mouse model encompassing the 22q11 genomic deletion region, the Df1/+ model [8], α-synuclein and p62 levels are elevated. Human iPSC technology provides a new experimental platform to examine cellular phenotypes and mechanisms in human disease cell types. So far, patient-derived iPSCs, especially those due to monogenic genetic factors, have been utilized for pathological elucidation and drug discovery research along with animal models. Patient-iPSC-derived disease target cells are useful tools for analysing the cellular and molecular mechanisms at a very early stage, before clinical onset, in genetically complex diseases including 22q11DS.

Arioka and co-workers used the advantages of 22q11DS patient iPSCs to analyse dopaminergic neurons, targets of 22q11DS, since 22q11DS-associated PD is not yet completely understood [9]. Arioka and co-workers differentiated dopaminergic neurons with high efficiency, and found reduced levels of PERK, a key player of endoplasmic reticulum (ER) stress. Besides poor tolerance to ER stress, they also discovered a defect in F-actin dynamics, that are essential for axonal guidance and neural connections. A deficiency in F-actin caused neurite damage, suggesting that impaired F-actin dynamics in 22q11DS dopamine neurons may reflect the clinical phenotype of learning and memory dysfunction [10] in 22q11DS patients. Although genes responsible for 22q11DS-associated PD have been proposed, Arioka and co-workers have suggested DGCR14, located at a microdeletion site in 22q11.2, as a candidate PERK regulator through splicing, although further analysis is necessary. Since PERK and the dopaminergic system are also known to be related to schizophrenia, their work, showing PERK-dependant vulnerabilities of dopaminergic neurons in 22q11DS, would enable us to change our mindset regarding 22q11DS as a disease of dopaminergic neurons for further analysis.

Declaration of Competing Interest

No conflicts of interest to declare.

Contributors

The author confirms sole responsibility for the conception and preparation of this invited Commentary.

References

[1] Carlson C, Sirotkin H, Pandita R, Goldberg R, McKie J, Wadey R, Patanjali SR, Weissman SM, Anyane-Yeboa K, Warburton D, Scambler P, Shprintzen R, Kucherlapati R, Morrow BE. Molecular definition of 22q11 deletions in 151 velo-cardio-facial syndrome patients. Am J Hum Genet 1997;61(3).
[2] Edelmann L, et al. Low-copy repeats mediate the common 3-Mb deletion in patients with velo-cardio-facial syndrome. Am J Hum Genet 1999;64(4):1076–86.
[3] Shaikh TH, et al. Chromosome 22-specific low copy repeats and the 22q11.2 deletion syndrome: genomic organization and deletion endpoint analysis. Hum Mol Genet 2000;9(4):489–501.
[4] Qin X, Chen J, Zhou T. 22q11.2 deletion syndrome and schizophrenia. Acta Biochim Biophys Sin (Shanghai) 2020 https://doi.org/10.1093/abbs/gmaa113.
[5] Boot E, Bassett AS, Marras C. 22q11.2 deletion syndrome-associated parkinson's disease. Mov Disord Clin Pract 2019;6(1):11–6.

E-mail address: haruhisa@cira.kyoto-u.ac.jp

https://doi.org/10.1016/j.ebiom.2020.103180

[6] Alejandra Morato Torres C, Wassouf Z, Zafar F, Sastre D, Outeiro TF, Schüle B. The role of alpha-synuclein and other parkinson's genes in neurodevelopmental and neurodegenerative disorders. Int J Mol Sci 2020;21(16) https://doi.org/10.3390/ijms21165724.
[7] Boot E. Typical features of Parkinson disease and diagnostic challenges with microdeletion 22q11.2. Neurology 2018;90(23):e2059–67.
[8] Lindsay EA, et al. Congenital heart disease in mice deficient for the DiGeorge syndrome region. Nature 1999;401(6751):379–83.
[9] Arioka Y, et al. Chromosome 22q11.2 deletion causes PERK-dependent vulnerability in dopaminergic neurons. EBioMedicine. 2021;63. doi: 10.1016/j.ebiom.2020.103138.
[10] Broussard JI, Yang K, Levine AT, Tsetsenis T, Jenson D, Cao F, Garcia I, Arenkiel BR, Zhou FM, De Biasi M, Dani JA. Dopamine regulates aversive contextual learning and associated in vivo synaptic plasticity in the hippocampus. Cell Rep 2016;14(8). doi: 10.1016/j.celrep.2016.01.070.