BRAIN
LETTER TO THE EDITOR

Reply: Is it time to rename hereditary cases of cerebral palsy?

Hao Hu[1,2,3] and Kaishou Xu[4]

1 Laboratory of Medical Systems Biology, Guangzhou Women and Children's Medical Center, Guangzhou Medical University, Guangdong Provincial Clinical Research Center for Child Health, Guangzhou 510623, China
2 Guangdong Provincial Key Laboratory of Research in Structural Birth Defect Disease, Guangzhou Women and Children's Medical Center, Guangzhou Medical University, Guangdong Provincial Clinical Research Center for Child Health, Guangzhou 510623, China
3 Third Affiliated Hospital of Zhengzhou University, 450052, Zhengzhou, China
4 Department of Rehabilitation, Guangzhou Women and Children's Medical Center, Guangzhou Medical University, Guangdong Provincial Clinical Research Center for Child Health, Guangzhou 510120, China

Correspondence to: Hao Hu
Laboratory of Medical Systems Biology
Guangzhou Women and Children's Medical Center
Guangzhou Medical University
510623, Guangzhou, China
E-mail: huh@cougarlab.org

Correspondence may also be addressed to: Kaishou Xu
Email: xksyi@126.com

We appreciated the concerns of Dr Kavčič[1] for the terminological issues, namely, idiopathic cerebral palsy (CP) and CP-related genes, in our recent paper entitled 'In-depth analysis reveals complex molecular aetiology in a cohort of idiopathic cerebral palsy'.[2] We believed that the definition of idiopathic CP and CP-related genes were specified in this work to describe the research background and the main findings, respectively, and these two terms have been evolving *per se*, following the progress of basic and clinical studies on CP aetiology.

First of all, we adopted a widely-accepted definition of CP, i.e. early-onset non-progressive motor disability with symptom ascertainment at an age of 2 or older.[2] Because the aim of our study was at the genetic/intrinsic attributes of CP, we managed to exclude the individuals with probably extrinsic causalities from the cohort, including perinatal asphyxia, traumatic brain injury, encephalitis, brain tumour, hyperbilirubinaemia, and maternal infection.[2] Also, we filtered out the late-onset CP-mimicries such as hereditary spastic paraplegia and DOPA-responsive dystonia.[2] Most of the cohort members were born at term, and C-section without complications like uterine rupture was not regarded as a risk factor to be ruled out.[2] In fact, idiopathic CP was a generic term that we adopted to delineate the recruitment criteria, not meaning 'free of risk', and it would definitely be subject to adjustment in the subsequent studies. Alternatively, another research group chose 'cryptogenic CP' in a similar situation.[3]

In the past decade, our work and other studies unveiled an important role of genetic alterations in CP aetiology.[2–5] Genetic counselling and gene-based treatment have been considered for CP patients since a growing body of genetic evidence was uncovered.[6–8] To be noticed, not all of the aforementioned studies established a stringent standard to rule out the cases with extrinsic causalities. In our study, we defined a list of CP-related genes, of which the defects may lead to CP; however, we admitted that a major portion of CP cases were not attributable to genetic changes, but to adverse environmental effects, or to an interplay between these two kinds of risk factors. On the other hand, gene-based nomenclature of neurodevelopmental disorders, including CP, intellectual disability (ID) and autism spectrum disorders (ASD), has emerged, since the related genes have been rapidly accruing.[9] OMIM and other similar databases can serve as a framework for categorizing diseases according to either phenotype or genotype. In this sense, the terms like CP, ID, and ASD may dissolve in future, replaced by a large number of gene-based clinical presentations; or the phenotype-based and the genotype-based classification systems may coexist to mutual benefit.

Last but not least, we fully agreed that 'even when a damage in the developing brain (i.e. foetal or neonatal brain) results in motor disability without comorbidity (a classical form of CP), it does not automatically mean that only a motor system of the brain was harmed'. For the convenience of mechanistic research and treatment development, we proposed a dichotomous classification system for CP-related genes in our paper, both of which took a part in cognition and motor coordination in brain, respectively, but they were not mutually exclusive, instead, we could find that the anatomical and functional features of these two sets of genes may overlap to some extent, so there should be no sharp demarcation between them.[2]

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Data availability

Data availability is not applicable to this article as no new data were created or analysed in this study.

Competing interests

The authors report no competing interests.

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