

Received: 14 July 2020

Revised: 21 August 2020






Accepted: 2 September 2020

DOI: 10.1111/cge.13845

Check for updates

SHORT REPORTCLINICAL
GENETICS | WILEY

Comprehensive genotype-phenotype correlation in AP-4 deficiency syndrome; Adding data from a large cohort of Iranian patients

Maryam Beheshtian¹ | Tara Akhtarkhavari¹ | Sepideh Mehvari¹ |
 Marzieh Mohseni¹  | Zohreh Fattahi¹ | Seyedeh Sedigheh Abedini¹ |
 Sanaz Arzhang¹ | Mahsa Fadaee¹ | Payman Jamali² | Reza Najafipour³ |
 Vera M. Kalscheuer⁴  | Hao Hu⁵ | Hans-Hilger Ropers^{4,6}  |
 Hossein Najmabadi^{1,7}  | Kimia Kahrizi¹ 

¹Genetics Research Center, University of Social Welfare and Rehabilitation Sciences, Tehran, Iran

²Genetic Counseling Center, Shahroud Welfare Organization, Semnan, Iran

³Cellular and Molecular Research Centre, Genetic Department, Qazvin University of Medical Sciences, Qazvin, Iran

⁴Research Group Development and Disease, Max Planck Institute for Molecular Genetics, Berlin, Germany

⁵Guangzhou Women and Children's Medical Center, Guangzhou, China

⁶Institute for Human Genetics, University Medicine, Mainz, Germany

⁷Kariminejad - Najmabadi Pathology and Genetics Center, Molecular division, Tehran, Islamic Republic of Iran, Tehran, Iran

Correspondence

Hossein Najmabadi and Kimia Kahrizi, Genetics Research Center, University of Social Welfare and Rehabilitation Sciences, Koodakyar Alley, Daneshjoo Blvd., Evin Street, Tehran, Iran.

Email: hnajm12@yahoo.com (H. N.) and kahrizi@yahoo.com (K. K.)

Funding information

Iran National Science Foundation (INSF), Grant/Award Numbers: 950022, 96.11200; National Institute for Medical Research Development (NIMAD), Grant/Award Number: 957060; University of Social Welfare and Rehabilitation Sciences (USWR), Grant/Award Number: 94/801/T/29490

Abstract

Mutations in adaptor protein complex-4 (AP-4) genes have first been identified in 2009, causing a phenotype termed as AP-4 deficiency syndrome. Since then several patients with overlapping phenotypes, comprised of intellectual disability (ID) and spastic tetraplegia have been reported. To delineate the genotype-phenotype correlation of the AP-4 deficiency syndrome, we add the data from 30 affected individuals from 12 out of 640 Iranian families with ID in whom we detected disease-causing variants in AP-4 complex subunits, using next-generation sequencing. Furthermore, by comparing genotype-phenotype findings of those affected individuals with previously reported patients, we further refine the genotype-phenotype correlation in this syndrome. The most frequent reported clinical findings in the 101 cases consist of ID and/or global developmental delay (97%), speech disorders (92.1%), inability to walk (90.1%), spasticity (77.2%), and microcephaly (75.2%). Spastic tetraplegia has been reported in 72.3% of the investigated patients. The major brain imaging findings are abnormal corpus callosum morphology (63.4%) followed by ventriculomegaly (44.5%). Our result might suggest the AP-4 deficiency syndrome as a major differential diagnostic for unknown hereditary neurodegenerative disorders.

KEYWORDS

AP-4 deficiency syndrome, consanguinity, genotype-phenotype correlation, intellectual disability, Iranian families

Hossein Najmabadi and Kimia Kahrizi contributed equally to this study.