Elucidating the Genomic Basis of Rare Paediatric Neurological Diseases in Central Asia and Transcaucasia

Rauan Kaiyrzhanov*[1,2], Nazira Zharkinbekova[1], Ulviyya Guliyeva[3], Manizha Ganieva[4], Zaruhi Tavadyan[5], Tamar Gachechiladze[6], Kamran Salayev[7], Sughra Guliyeva[3], Mariam Isayan[5], Mariam Kekenadze[8], Biayna Sukhudyan[9], Ani Gevorgyan[9], Artsruni Hakobyan[10], Rima Ibadova[11], Nazi Tabatadze[6], Ekaterina Kurua[6], Teona Shatirishvili[12], Nigara Yerkhojayeva[13], Kairgali Koneev[14], Dauren Zhumakhanov[15], Askhat Mukushev[15,16], Altynshash Jaxybayeva[17], Alissa Nauryzbayeva[18], Maksudjon Isrofilov[4], Saadat Badalova[19], Naila Zeyniyeva[19], Ilaha Hajiyeva[20], Leyla Alakbarov[21], Aynur Zeynalova[22], Viorica Chelban[2,23], Jana Vandrovcova[2], Valentina Turchetti[2], David Murphy[24], Stephanie Efthymiou[2], Shahryar Alavi[2], Rahema Mohammad[2], Tinatin Tkemaladze[25,26], Chingiz Shashkin[27], Nana Nino Tatishvili[12], Maia Beridze[8], Samson G. Khachatryan[5], Gia Melikishvili[6], John Hardy[2], Reza Maroofian[2], Henry Houlden[2]

1. Department of Neurology, South Kazakhstan Medical Academy, Al-Farabi Square 1, Shymkent 160001, Kazakhstan
2. Department of Neuromuscular Diseases, UCL Queen Square Institute of Neurology, Queen Square, London WC1N 3BG, UK
3. MediClub Hospital, Islam Safarli st. 33, Baku AZ1009, Azerbaijan
4. Department of Neurology, Avicenna Tajik State Medical University, Rudaki Avenue 139, Dushanbe 734003, Tajikistan
5. Department of Neurology and Neurosurgery, National Institute of Health, Komitas 49/4, Yerevan 0051, Armenia
6. MediClub Georgia Medical Center, 22a Tashkenti St., Tbilisi 0160, Georgia
7. Fetal-Neonatal Neuroimaging & Developmental Science Center, Division of Newborn Medicine, Boston Children's Hospital, 300 Longwood Ave, Boston MA 02115, United States
8. Department of Neurology, Tbilisi State Medical University, 33 Vazha Pshavela Ave, Tbilisi 0186, Georgia
9. Department of Neurology and Epilepsy, Arabkir Medical Complex, 30 Mamikoniants St, Yerevan 0014, Armenia
10. Department of Neurology, Yerevan State Medical University, 2 Koryun St, Yerevan 0025, Armenia
11. Neurology Department, Hb Guven Clinic, Ataturk prospect, Binagadi, Baku AZ1124, Azerbaijan
12. Neuroscience Department, M.Iashvili Central Children's Hospital, 2/6, Lubliana str., Tbilisi 0159, Georgia
13. Faculty of Medicine, Khoja Akhmet Yassawi International Kazakh-Turkish University, Б. Sattarkhanov Street 29, Turkestan 161200, Kazakhstan
14. Department of Neurology and Neurosurgery, Asfendiyarov Kazakh National Medical University, Tole Bi Street 94, Almaty 050000, Kazakhstan
15. Neurolab clinic, Zhetysy-2 microdistrict 70Б, Almaty 050063, Kazakhstan
16. Department of Neurology, Beth Israel Deaconess Medical Center, Harvard Medical School, 330 Brookline Ave, Boston, MA 02215, United States
17. Department of Neurology, Astana Medical University, Beibitshilik St 49/A, Astana 010000, Kazakhstan
18. Department of Neurology of Early Age, National Research Center for Maternal and Child Health, Turan Ave 32, Astana 010000, Kazakhstan
19. Children Neurology Hospital, Taghi Shahbazi, Baku, Yasamal, AZ1065, Azerbaijan
20. Neurology Department, Azerbaijan Medical University, Samad Vurghun, Baku, Nasimi, AZ1022, Azerbaijan
21. Republican Pediatric Center, Hasan bay Zardabi, Baku, Yasamal, AZ1012, Azerbaijan
22. Neuron Medical Center, Nizaminskii r-on, K. Balakishiev 55, 8-i km, Baku, Azerbaijan

23. Neurobiology and Medical Genetics Laboratory, “Nicolae Testemitanu” State University of Medicine and Pharmacy, 165, Stefan cel Mare si Sfant Boulevard, MD 2004, Chisinau, Republic of Moldova
24. Department of Clinical and Movement Neurosciences, UCL Queen Square Institute of Neurology, Queen Square, London WC1N 3BG, UK
25. Department of Molecular and Medical Genetics, Tbilisi State Medical University, 33 Vazha Pshavela Ave, Tbilisi 0186, Georgia
26. Department of Paediatrics, Givi Zhvania Pediatric Academic Clinic, Givi Zhvania Street 11/15, Tbilisi State Medical University, Tbilisi 0186, Georgia
27. Shashkin Clinic, Bukhar-Zhyrau Blvd 45/1, Almaty 050000, Kazakhstan.

*Corresponding author: Rauan Kaiyrzhanov

rauan.kaiyrzhanov.14@ucl.ac.uk

Significant advancements in genomic medicine since the Human Genome Project have provided molecular diagnoses to many families with rare diseases, including rare paediatric neurological diseases (RPND). These advancements have paved the way for personalized medicine, significantly increasing our understanding of human physiology and biochemical pathways. They have also opened new avenues for innovative and more effective treatments, benefiting not only those with rare diseases but also individuals with more common conditions.

However, despite these advancements and the decreasing cost of high-throughput sequencing, many regions worldwide remain underrepresented in human genetic research. Even in developed countries with access to state-of-the-art medical facilities, many families remain without a definitive diagnosis. A significant challenge in diagnosing neurogenetic disorders is the difficulty in interpreting sequence variants and the high prevalence of variants of uncertain significance, largely due to the incomplete catalogue of human variants across populations. This issue is further exacerbated by the scarcity of patients with genetically confirmed rare diseases, driven by limited access to next-generation sequencing and comprehensive genetic testing for the majority of patients globally.

Central Asia and Transcaucasia (CAT) is one such underrepresented region. This area is populated by genetically unique ethnic groups residing in the middle of Eurasia[1,2]. The modern geopolitical boundaries of CAT encompass Kazakhstan, Kyrgyzstan, Uzbekistan, Tajikistan, and Turkmenistan in Central Asia, as well as Armenia, Azerbaijan, and Georgia in Transcaucasia (Fig. 1). It is important to note that the factual geographic distribution of many ethnic Central Asians and their ancestral homelands extends beyond the currently defined boundaries of CAT[3]. The region's geographic location at the crossroads between Europe and East Asia, along with its history of numerous wars, invasions, diverse geography and climate, mass migrations, famines, nomadic lifestyles, and trade through the Silk Road, have all significantly shaped the genetic landscape of these populations. Furthermore, the complex interplay of ancient and historical civilizations, such as the Persians, Scythians, Turks, Arabs, Mongols, and Russians, has contributed to the region's genetic diversity[3]. Additionally, the Soviet Union's massive deportations during the 20th century forcibly relocated various ethnic groups to and within the CAT region, further influencing the genetic composition of its populations. These eight post-Soviet Union countries, with an overall regional population of about 93 million, range from upper-middle to low-middle-income economies. Consanguinity is prevalent in several of these countries, exacerbating the burden of rare recessive diseases. Despite this, very little is known about the genetic causes of RPND in CAT.

To address this gap, University College London Queen Square Institute of Neurology (UCL IoN) partnered with several institutions from CAT in 2018, forming the Central Asian and Transcaucasian Rare Paediatric Neurological Diseases (CAT-RPND) consortium (https://www.cat-genomics.com/). This initiative aims to elucidate the genetic background of RPND in CAT through a large-scale international collaboration. Our focus on RPND was strategic, as nearly half of all rare diseases affect the nervous system and predominantly children, with 90% of rare childhood diseases having significant neurological implications[4].

Over the past four years, we recruited over 2,200 families affected by RPND from 17 centres across CAT (Fig. 1), after obtaining ethical approval and appropriate permissions from local institutional review boards. Our research primarily utilized proband- and trio-exome sequencing at UCL IoN, providing molecular diagnoses for many families, including the discovery of actionable genes that have notably improved patient care and management. Moreover, molecular diagnosis has given families essential information for decision-making.

In addition to identifying causative variants in established disease-causing genes, our project has characterized several novel gene-disease associations in the CAT region. Notable findings include new recessive conditions associated with variants in *ACBD6*[5], *SLC38A3*[6], and *SPATA5L1*[7]. Our work in CAT contributed to the phenotype expansion of the following disease genes: *BRAT1*[8], *NFU1*[9], *ZNF142*[10], *SLC18A2*[11], *PIGH*[12], *ITPA*[13], *CA8*[14], and *EMC10*[15]. Numerous studies involving other novel disease-associated genes identified in CAT are currently in progress.

The consortium is compiling a report on the exome sequencing outcomes for the 2,200 families with RPND from CAT. For families with negative exome sequencing results, further investigations will include genome sequencing, RNA sequencing, and long-read sequencing. This effort has also led to the establishment of a sequence variant database for the CAT region, now part of the Queen Square Genomics Database. This database highlights overlapping variants with neighbouring populations, as well as unique and distinct variants specific to each country in the region. This further underscores the importance of obtaining genetic data from all populations globally.

Beyond scientific discovery, the consortium has facilitated academic exchanges, empowering researchers and clinicians from CAT with advanced skills in clinical phenotyping and genetic analysis of rare neurological diseases. Our network has demonstrated an efficient and scalable

model for resource and skill sharing, promoting open science to establish genomics research in genetically underrepresented regions. The project has also established trial-ready cohorts and natural history study cohorts for several RPNDs in the CAT region.

The consortium aims to raise awareness of RPND in the CAT region both within the region and among international researchers, industries, and pharmaceutical companies. Identifying CAT-specific genetic variants that give rise to RPND is critical for developing newborn and carrier screening and prevention programs. Emphasizing the need for sustainable infrastructure, we advocate for creating national biobanks, databases, and registries for rare diseases within the CAT region.

We believe this initiative will enrich the global genomics landscape and highlight the critical importance of international collaboration in addressing rare diseases and genetic studies in underrepresented regions.

Acknowledgements

We are grateful for the important support from patients and families, our UK and international collaborators, brainbank and biobanks, and grateful for essential funding from The Wellcome Trust, The MRC, The Chung Lab at Boston Children's Hospital/Harvard Medical School, The MSA Trust, The National Institute for Health Research University College London Hospitals Biomedical Research Centre (NIHR-BRC), The Michael J Fox Foundation (MJFF), The Fidelity Trust, Rosetrees Trust, The Dolby Family fund, Alzheimer's Research UK (ARUK), MSA Coalition, The Guarantors of Brain, Cerebral Palsy Alliance, FARA, EAN and the NIH NeuroBioBank, Queen Square BrainBank, Queen Square Genomics, The MRC Brainbank Network. We want to thank Mrs. Aigerim Ussembayeva for her assistance in creating and designing the manuscript figure.

Competing interests

The authors have no competing interests.

Author contributions

R.K. and R.M. wrote the paper. N.Z., U.G., M.G., Z.T., T.G., K.S., S.G., M.I., M.K., B.S., A.G., A.H., R.I., N.T., E.K., T.S., N.Y., K.K., D.Z., A.M., A.J., A.N., M.I., S.B., N.Z., I.H., L.A., A.Z., V.C., J.V., V.T., D.M., S.E., S.A., Ra.M., T.T., C.S., N.N.T., M.B., S.G.K., G.M., J.H., H.H. reviewed the paper and provided feedback.

Figure legend

Fig. 1. The map of Central Asia and Transcaucasia and Diagnostic Outcomes of Exome Sequencing. A. Pins on the map mark the locations of centres participating in the Central Asian and Transcaucasian Rare Paediatric Neurological Disease Genetics Consortium. The centers are as follows: Kazakhstan: South Kazakhstan Medical Academy, Astana Medical University, Shashkin Clinic, Neurolab Clinic. Tajikistan: Avicenna Tajik State Medical University. Armenia: National Institute of Health, Arabkir Medical Complex, Yerevan State Medical University. Azerbaijan: MediClub Baku Center, Hb Guven Clinic Baku, Republican Pediatric Center, Children Neurology Hospital, Azerbaijan Medical University. Georgia: MediClub Georgia Medical Center, Tbilisi State Medical University, Central Children's Hospital Tbilisi, Givi Zhvania Pediatric Academic Clinic. **B.** Diagnostic Outcomes of Exome Sequencing (ES).

References

1. Martínez-Cruz B, Vitalis R, Ségurel L, et al. In the heartland of Eurasia: The multilocus genetic landscape of Central Asian populations. European Journal of Human Genetics 2011; 19(2), 216-223.

2. Comas D, Calafell F, Mateu E, et al. Trading genes along the silk road: mtDNA sequences and the origin of central Asian populations. American journal of human genetics 1998; 63(6), 1824-1838.

3. Kaiyrzhanov, Rauan; (2023) Defining the Genetic Causes of Rare Paediatric Neurological Diseases in Central Asian and Transcaucasian Populations. Doctoral thesis (Ph.D), UCL (University College London).

4. The Lancet Neurology. Rare diseases: maintaining momentum. Lancet Neurol. 2022;21:203

5. Kaiyrzhanov R, Rad A, Lin SJ, Bertoli-Avella A, Kallemeijn WW, Godwin A, et al. Bi-allelic ACBD6 variants lead to a neurodevelopmental syndrome with progressive and complex movement disorders. Brain. 2024 Apr 4;147(4):1436-1456. doi: 10.1093/brain/awad380.

6. Marafi D, Fatih JM, Kaiyrzhanov R, Ferla MP, Gijavanekar C, Al-Maraghi A, et al. Biallelic variants in SLC38A3 encoding a glutamine transporter cause epileptic encephalopathy. Brain. 2022 Apr 29;145(3):909-924. doi: 10.1093/brain/awab369.

7. Richard EM, Bakhtiari S, Marsh APL, Kaiyrzhanov R, Wagner M, Shetty S, et al. Bi-allelic variants in SPATA5L1 lead to intellectual disability, spastic-dystonic cerebral palsy, epilepsy, and hearing loss. Am J Hum Genet. 2021 Oct 7;108(10):2006-2016. doi: 10.1016/j.ajhg.2021.08.003.

8. Engel C, Valence S, Delplancq G, Maroofian R, Accogli A, Agolini E, et al. BRAT1-related disorders: phenotypic spectrum and phenotype-genotype correlations from 97 patients. Eur J Hum Genet. 2023 Sep;31(9):1023-1031. doi: 10.1038/s41431-023-01410-z.

9. Kaiyrzhanov R, Zaki MS, Lau T, Sen S, Azizimalamiri R, Zamani M, et al. Phenotypic continuum of NFU1-related disorders. Ann Clin Transl Neurol. 2022 Dec;9(12):2025-2035. doi: 10.1002/acn3.51679.

10. Christensen MB, Levy AM, Mohammadi NA, Niceta M, Kaiyrzhanov R, Dentici ML, et al. Biallelic variants in ZNF142 lead to a syndromic neurodevelopmental disorder. Clin Genet. 2022 Aug;102(2):98-109. doi: 10.1111/cge.14165.

11. Saida K, Maroofian R, Sengoku T, Mitani T, Pagnamenta AT, Marafi D, et al. Brain monoamine vesicular transport disease caused by homozygous SLC18A2 variants: A study in 42 affected individuals. Genet Med. 2023 Jan;25(1):90-102. doi: 10.1016/j.gim.2022.09.010.

12. Tremblay-Laganière C, Kaiyrzhanov R, Maroofian R, Nguyen TTM, Salayev K, Chilton IT, et al. PIGH deficiency can be associated with severe neurodevelopmental and skeletal manifestations. Clin Genet. 2021 Feb;99(2):313-317. doi: 10.1111/cge.13877.

13. Scala M, Wortmann SB, Kaya N, Stellingwerff MD, Pistorio A, Glamuzina E, et al. Clinico-radiological features, molecular spectrum, and identification of prognostic factors in developmental and epileptic encephalopathy due to inosine triphosphate pyrophosphatase (ITPase) deficiency. Hum Mutat. 2022 Mar;43(3):403-419. doi: 10.1002/humu.24326.

14. Kaiyrzhanov R, Ortigoza-Escobar JD, Stringer BW, Ganieva M, Gowda VK, Srinivasan VM, et al. Clinical and Molecular Spectrum of Autosomal Recessive CA8-Related Cerebellar Ataxia. Mov Disord. 2024 Jun;39(6):983-995. doi: 10.1002/mds.29754.

15. Kaiyrzhanov R, Rocca C, Suri M, Gulieva S, Zaki MS, Henig NZ, et al. Biallelic loss of EMC10 leads to mild to severe intellectual disability. Ann Clin Transl Neurol. 2022 Jul;9(7):1080-1089. doi: 10.1002/acn3.51602.