neurogenetics (2019) 20:109–115
https://doi.org/10.1007/s10048-019-00573-6

SHORT COMMUNICATION

Truncating biallelic variant in *DNAJA1*, encoding the co-chaperone Hsp40, is associated with intellectual disability and seizures

Saud Alsahli[1,2] · Ahmed Alfares[3,4] · Francisco J. Guzmán-Vega[5] · Stefan T. Arold[5] · Duaa Ba-Armah[2,6] · Fuad Al Mutairi[2,7]

Received: 20 November 2018 / Accepted: 14 March 2019 / Published online: 10 April 2019

Abstract

Intellectual disability poses a huge burden on the health care system, and it is one of the most common referral reasons to the genetic and child neurology clinic. Intellectual disability (ID) is genetically heterogeneous, and it is associated with several other neurological conditions. Exome sequencing is a robust genetic tool and has revolutionized the process of molecular diagnosis and novel gene discovery. Besides its diagnostic clinical value, novel gene discovery is prime in reverse genetics, when human mutations help to understand the function of a gene and may aid in better understanding of the human brain and nervous system. Using WES, we identified a biallelic truncating variant in *DNAJA1* gene (c.511C>T p.(Gln171*) in a multiplex Saudi consanguineous family. The main phenotype shared between the siblings was intellectual disability and seizure disorder.

Keywords Intellectual disability · Seizure disorder · *DNAJA1* · Exome sequencing · Chaperonopathy · Chaperone · Co-chaperone · Hsp40

Introduction

Intellectual disability (ID) is a neurodevelopmental disorder that is defined as an impairment in intellectual and adaptive functioning [1]. ID is a relatively common medical condition affecting at least 1% of the general population, and it can result from myriad of causes [2]. ID can be generally classified based on other associated systemic findings as syndromic and nonsyndromic. ID is genetically heterogeneous, and the level of genetic involvement in ID has not thus far been elucidated; however, genetics is the most likely culprit in the majority of cases even when the child lacks syndromic or other systemic features [2]. Comparative genomic hybridization (CGH) is considered now the first-tier diagnostic test to order; nevertheless with the introduction of next-generation sequencing (NGS), many now are advocating exome sequencing (WES) as the first-tier test [3]. WES has shown to be cost-effective and led to a shorter diagnostic interval [4]. The diagnostic yield of NGS in CGH negative syndromic and nonsyndromic ID has been reported as 68 and 50%, respectively [2]. Several studies have demonstrated a

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s10048-019-00573-6) contains supplementary material, which is available to authorized users.

✉ Fuad Al Mutairi
almutairifu@ngha.med.sa

[1] Department of Pediatric Neurology, Texas Children's Hospital, Baylor College of Medicine, Houston, TX, USA

[2] King Abdullah International Medical Research Center (KAIMRC), College of Medicine, King Saud bin Abdulaziz University for Health Sciences, Riyadh, Saudi Arabia

[3] Department of Pathology and Laboratory Medicine, King Abdulaziz Medical City, Ministry of National Guard-Health Affairs (MNGHA), Riyadh, Saudi Arabia

[4] Department of Pediatrics, Qassim University, Almulyda, Buraydah, Saudi Arabia

[5] Division of Biological and Environmental Sciences and Engineering (BESE), King Abdullah University of Science and Technology (KAUST), Computational Bioscience Research Center (CBRC), Thuwal 23955-6900, Saudi Arabia

[6] Department of Pediatrics, King Abdulaziz Medical City, Division of Pediatric Neurology, Ministry of National Guard-Health Affairs (MNGHA), Riyadh, Saudi Arabia

[7] Division of Genetics, Department of Pediatrics, King Abdulaziz Medical City, Ministry of National Guard-Health Affairs (MNGHA), Riyadh, Saudi Arabia

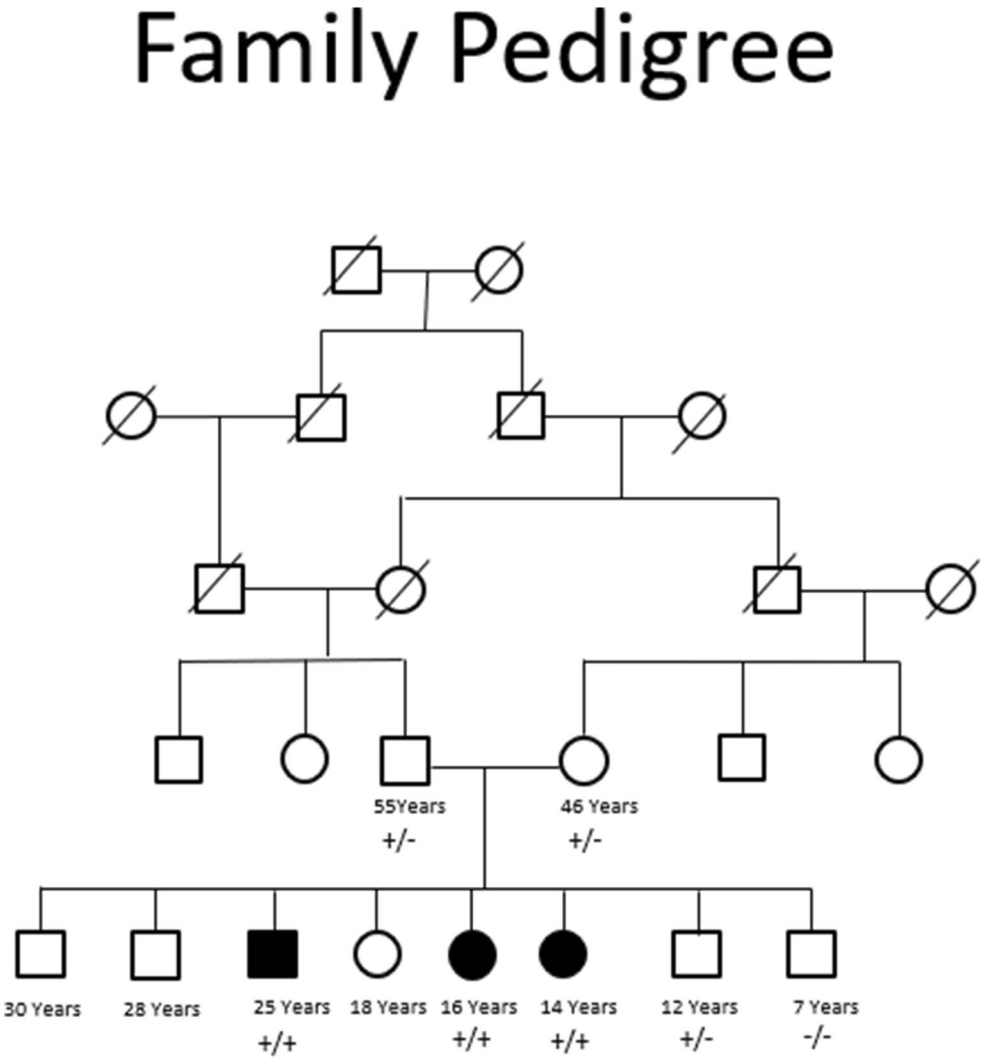

Fig. 1 Family pedigree of the current cohort

high diagnostic yield in sequencing inbred populations that reached up to 50% [2, 5–7]. More importantly, NGS has accelerated the process of novel gene discovery or candidate gene proposal, and it led to an unprecedented expansion in the number of genes linked to ID with an estimated more than 2500 genes thus far [8]. Gene hunting in inbred populations is easier due to autozygosity mapping in multiplex families, which narrows the field of search and ending a journey of diagnostic odyssey. Reaching for an accurate diagnosis is particularly important for inbred populations where autosomal recessive founder mutations make a relatively large fraction of the molecular pool, and perhaps a preventable cause of ID and other neurodevelopmental disorders [9, 10].

DNAJA1 gene encodes a member of the DNAJ family of proteins, also known as heat shock protein 40 (Hsp40 or Hsc40), which acts as co-chaperone for Hsp70 and Hsp90. DNAJ proteins are responsible for several essential cellular processes including folding polypeptide chains, modulate protein assembly, disassembly, translocation through membranes into cellular compartments, assist in conformational maturation and maintenance, and finally targeting of proteins for degradation through proteolytic processes of client proteins [11]. Herein, we show that a biallelic truncating variant in *DNAJA1* gene may cause ID and seizures in humans.

Human subjects and method

Human subjects

Three siblings from a Saudi consanguineous family presented to our practice. Their parents are a first-degree consanguineous couple with five healthy children (Fig. 1). All the affected siblings underwent a clinical evaluation by neurologists and clinical geneticists. Our institution's standardized clinical exome consent was obtained from their parents, and the study received ethical approval from King Abdullah International Medical Research Center (KAIMRC). Additional informed consent was obtained from all individual participants for whom identifying information is included in this article.

Table 1 Current cohort phenotype

	Patient 1	Patient 2	Patient 3
Age	14 years	16 years	25 years
Onset of the symptoms	3 months as seizure	12 months as DD	Early childhood as DD
Seizures	+	+	+
Seizures age of onset	3 months	11 years	12 years
Intellectual disability	+	+	+
Behavioral disorders	–	+	–
Dysmorphic features	+	+	+
• Round face	+	+	+
• Protruding ears	+	+	+
• Short neck	+	+	+
• Concave nail beds	++	+ +	+ +
BMI	29.2	44.7	38.1
Brain MRI	Thickened corpus callosum	NA	Normal
EEG	Normal	NA	Normal
Other findings	Renal stone Gallbladder stone	Cleft palate	Deviated nasal septum and otitis media

DD developmental delay, *BMI* body mass index, *MRI* magnetic resonance imaging, *EEG* electroencephalography, *NA* not available

Molecular analysis

Autozygome analysis

Blood samples were collected from all affected individuals, the parents, and two healthy siblings in EDTA tubes, and DNA was extracted from whole blood. We started with whole-genome array-based comparative genomic hybridization (aCGH) and genome-wide single nucleotide polymorphism (SNP) for the affected siblings and their parents as previously described [12]. We did not detect any significant copy number changes; however, it showed large regions of homozygosity between the affected siblings and their parents (Table S1).

Exome sequencing

We then proceeded with WES in all affected patients and their parents as previously described [13]. The generated library is sequenced on an Illumina platform to obtain an average coverage depth of ~ 100×. Typically, ~ 97% of the targeted bases are covered > 10×. An end-to-end in-house bioinformatic pipeline including base calling, alignment of reads to GRCh37/hg19 genome assembly, primary filtering out of low-quality reads and probable artifacts, and subsequent annotation of variants was applied. Evaluation is focused on coding exons along with flanking ± 20 intronic bases. All inheritance patterns were considered. In addition, provided family history and clinical information were used to evaluate eventually identified variants.

Results

The three affected siblings share a strikingly similar phenotype, and they look phenotypically different from their unaffected siblings. All of them are overweight, intellectually disabled with a generalized tonic clonic seizure disorder, have moon facies, protruding ears, and short neck. Epilepsy gene panel was negative (Table 1) (Fig. 3) (see Table S2 for a detailed clinical synopsis).

Initial filtering for intellectual disability and seizure disorder variants revealed no mutations. All the affected siblings were homozygous for a truncating variant in *DNAJA1* gene (NM_001539.3) c.511C>T p.(Gln171*)). We confirmed the variant by Sanger sequencing in all patients, and the variant segregated well in unaffected family members (Fig. 2). This variant was absent as well as other truncating variants in a large-scale exome sequencing databases such as Exome Aggregation Consortium (ExAC), dbSNP/1000 genome, or Exome Sequencing Project (ESP) and in the Genome Aggregation Database (gnomAD) databases. Also, this variant along with other truncating variants were absent from 2000 ethnically matched controls in local database and our institute's database Majeen (1200 exomes).

Structural and functional analysis

DNAJA1 is composed of a N-terminal J-domain followed by a G/F-rich region and two zinc finger motifs, which connect to

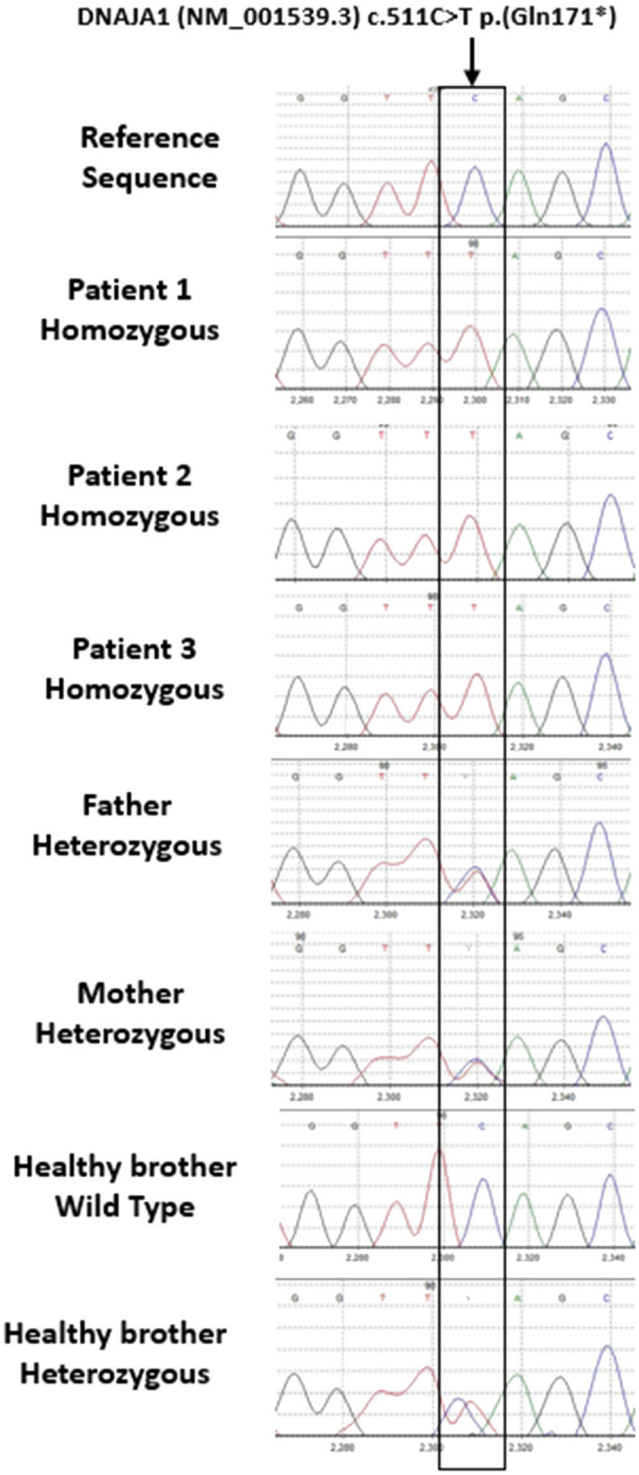

Fig. 2 Electropherograms of the cohort, their parents, and two healthy family members

the peptide binding fragment located at the C-terminus. The 3D structure of this protein was modeled using I-TASSER, which selected as the best template of the crystal structure of the type I Hsp40 Ydj1 from yeast with a sequence identity of 45% (Fig. 3) (I-TASSER template *Z*-score 5.58, model *C*-score − 2.78) [14]. The premature stop codon at Gln171 omits 227 of the 397 protein residues. This truncation results in the loss of two of the CXXCXGXG zinc-binding motifs, most of the peptide-binding fragment, and the putative C-terminal dimerization domain (Fig. 4). Only the J-domain and the G/F-rich regions are preserved, and hence, the Gln171* mutant would only preserve functions associated with these regions.

Discussion

DNAJ family is the largest HSP family in humans and is characterized by its highly conserved J-domain [15]. Hsp40 co-chaperones (also called DNAJ proteins), which are broadly expressed throughout the nervous system and within neuronal subcompartments, work in synchrony with Hsp70 and Hsp90 to help in ATP hydrolysis for protein folding [16, 17]. Several chaperones and co-chaperones were linked to many human diseases, and *DNAJA1* has been associated with epileptogenesis in rats [18, 19]. Hsp70 is a housekeeping protein (proteostasis) that assists in the folding and function of the human proteome, and it is considered one of the most important chaperones as they play important role in synaptic plasticity through its interactions with Hsp40 [20, 21]. The nervous system in particular seems to be susceptible to chaperonopathy due to the sustained nature of neurotransmission. Thus, the synaptic proteome is perilously liable to misfolding and aggregation [22]. This occurs because of the relatively great distance between synapses and the neuronal cell body, where the majority of proteins are synthesized and folded [23]. Nevertheless, there are small subsets of proteins that are locally translated at postsynaptic spines and the presynaptic termini [24, 25]. Synaptic function requires a large complement of specialized proteins, such as neurotransmitter receptors, synaptic vesicle, exocytosis, and endocytosis and all of which are essential for neurotransmission [22]. Through dedicated synapse-specific proteostasis machinery localized to pre- and post-synaptic compartments, of which Hsp60, Hsp70, and Hsp90 are an integral component, neurons maintain their specialized structure and function [22, 26]. The synaptic chaperone complement also includes other Hsp40/DNAJ client proteins such as DNAJC5 (CSPa), DNAJC6 (auxilin), and receptor-mediated endocytosis 8 (RME-8) which all participate in either synaptic exocytic and endocytic machinery and neuroprotection through regulating distinct steps of the synaptic vesicle cycle [22, 27]. Recent studies link ID and seizures to some genetic defects that encode proteins involved in the aforementioned steps that may ultimately affect their roles in synaptic proteostasis and plasticity [28, 29].

The proposal for *DNAJA1* as the most likely culprit in this family comes from several lines of evidence. It falls within the area of homozygosity that is shared between the affected siblings, and it segregated well in the unaffected family members. The three affected siblings share a strikingly similar phenotype, and

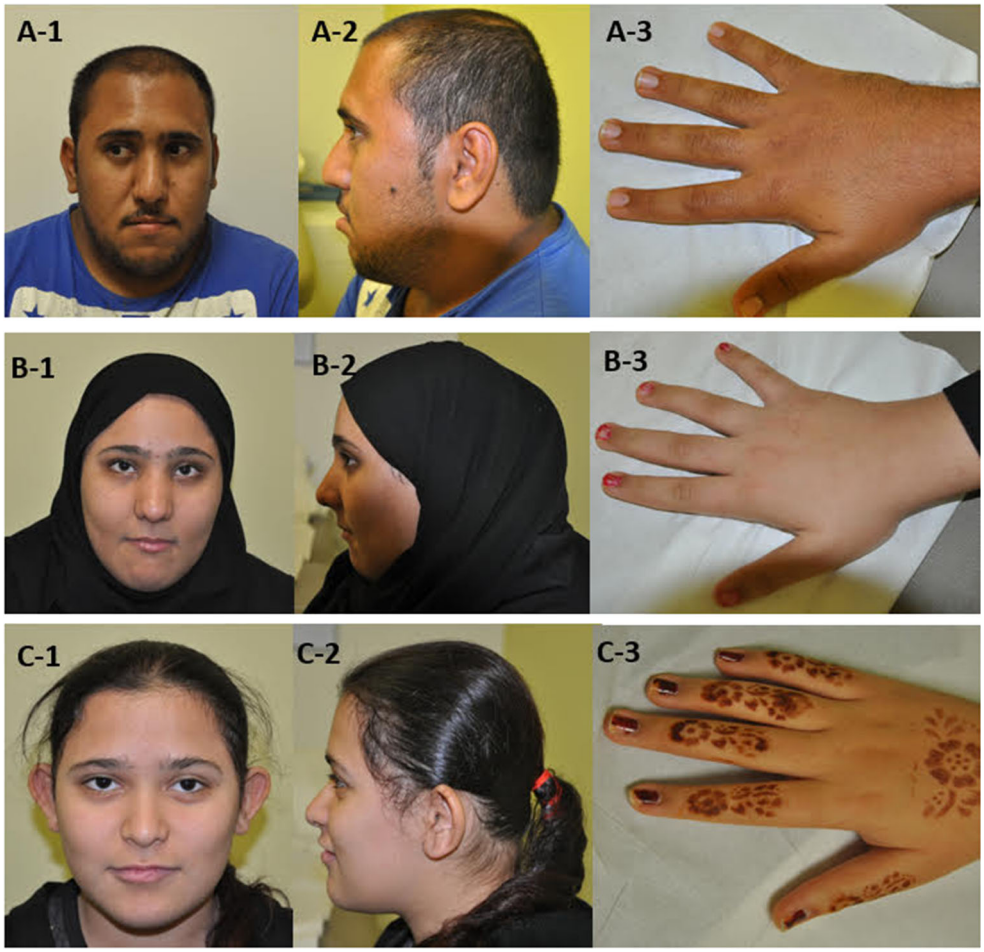

Fig. 3 Clinical pictures of the three siblings showing moon facies, protruding ears, short neck, and concave nail beds

their phenotype differs completely from their unaffected siblings. *DNAJA1* has been associated with epileptogenesis in rats before [18, 19]. We did not identify any variant in known ID and epilepsy genes, and the truncating nature of this variant, which only preserves the J-domain and the G/F-rich regions, further supports this variant candidacy. The J-domain is able to interact with Hsp70 and stimulate ATP hydrolysis, possibly with the intervention of the G/F domain as observed in *Escherichia coli* DnaJ [30]. Hence, the mutated DNAJA1 might conserve the ability to promote ATPase activity in Hsp70. However, it would no longer be able to interact with the hydrophobic side chains of non-native polypeptides through the peptide-binding fragment and prevent their aggregation. Consequently, the Gln171* mutant loses its capability of delivering misfolded polypeptides to Hsp70 to continue the folding process. Finally yet importantly, DNAJA1 acts as a co-chaperone for the potassium channel KCNH2 [31]. Mutations in *KCNH2* gene have been reported to cause epilepsy as well as long QT syndrome [32, 33]. Intriguingly, knockdown of DNAJA1 has been shown to hinder the maturation of KCNH2 [31].

In summary, we identified *DNAJA1* as a strong candidate gene for intellectual disability and seizure disorder in a Saudi

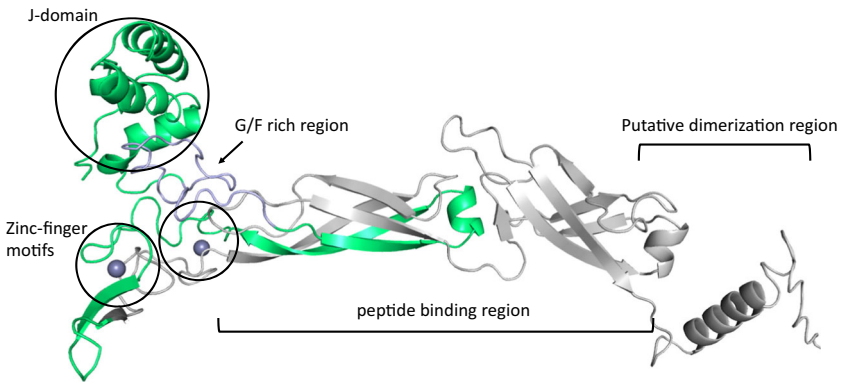

Fig. 4 Computational analysis of the 3D structure of DNAJA1. The structure has been inferred based on PDB id 1nlt. The region lost in the Gln171* mutant is colored in grey and includes both zinc finger motifs (zinc is shown as grey sphere), most of the peptide-binding fragment, and the putative C-terminal dimerization domain. The G/F rich region is colored in blue

family. However, given the lack of functional studies or a second hit in another family, further research in this area is needed as the current literature is relatively deficient in defining the role of chaperones in human disease overall and in the CNS particularly.

Acknowledgments We would thank the studied family for their enthusiastic participation.

Contributorship statement SA and FA created the presented idea and wrote the manuscript. SA, DB, and FA contributed to the patient care and diagnosis. SA, AA, DB, and FA prepared the tables. SA, AA, STA, FJG, and FA prepared the figures. SA, AA, STA, FJG, DB, and FA edited the manuscript.

Funding information The research by STA and FJGV reported in this publication was supported by funding from King Abdullah University of Science and Technology (KAUST) through the baseline fund and the Office of Sponsored Research (OSR), under award number FCC/1/1976-25-01.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

References

1. American Psychiatric Association., American Psychiatric Association. DSM-5 Task Force (2013) Diagnostic and statistical manual of mental disorders: DSM-5, 5th edn. American Psychiatric Association, Washington, D.C
2. Anazi S, Maddirevula S, Faqeih E, Alsedairy H, Alzahrani F, Shamseldin HE, Patel N, Hashem M, Ibrahim N, Abdulwahab F, Ewida N, Alsaif HS, Al Sharif H, Alamoudi W, Kentab A, Bashiri FA, Alnaser M, AlWadei AH, Alfadhel M, Eyaid W, Hashem A, Al Asmari A, Saleh MM, AlSaman A, Alhasan KA, Alsughayir M, Al Shammari M, Mahmoud A, Al-Hassnan ZN, Al-Husain M, Osama Khalil R, Abd El Meguid N, Masri A, Ali R, Ben-Omran T, El Fishway P, Hashish A, Ercan Sencicek A, State M, Alazami AM, Salih MA, Altassan N, Arold ST, Abouelhoda M, Wakil SM, Monies D, Shaheen R, Alkuraya FS (2017) Clinical genomics expands the morbid genome of intellectual disability and offers a high diagnostic yield. Mol Psychiatry 22(4):615–624. https://doi.org/10.1038/mp.2016.113
3. Miller DT, Adam MP, Aradhya S, Biesecker LG, Brothman AR, Carter NP, Church DM, Crolla JA, Eichler EE, Epstein CJ, Faucett WA, Feuk L, Friedman JM, Hamosh A, Jackson L, Kaminsky EB, Kok K, Krantz ID, Kuhn RM, Lee C, Ostell JM, Rosenberg C, Scherer SW, Spinner NB, Stavropoulos DJ, Tepperberg JH, Thorland EC, Vermeesch JR, Waggoner DJ, Watson MS, Martin CL, Ledbetter DH (2010) Consensus statement: chromosomal microarray is a first-tier clinical diagnostic test for individuals with developmental disabilities or congenital anomalies. Am J Hum Genet 86(5):749–764. https://doi.org/10.1016/j.ajhg.2010.04.006
4. Stark Z, Schofield D, Martyn M, Rynehart L, Shrestha R, Alam K, Lunke S, Tan TY, Gaff CL, White SM (2019) Does genomic sequencing early in the diagnostic trajectory make a difference? A follow-up study of clinical outcomes and cost-effectiveness. Genet Med 21(1):173–180. https://doi.org/10.1038/s41436-018-0006-8
5. Alfares A, Alfadhel M, Wani T, Alsahli S, Alluhaydan I, Al Mutairi F, Alothaim A, Albalwi M, Al Subaie L, Alturki S, Al-Twaijri W, Alrifai M, Al-Rumayya A, Alameer S, Faqeeh E, Alasmari A, Alsamman A, Tashkandia S, Alghamdi A, Alhashem A, Tabarki B, AlShahwan S, Hundallah K, Wali S, Al-Hebbi H, Babiker A, Mohamed S, Eyaid W, Zada AAP (2017) A multicenter clinical exome study in unselected cohorts from a consanguineous population of Saudi Arabia demonstrated a high diagnostic yield. Mol Genet Metab 121(2):91–95. https://doi.org/10.1016/j.ymgme.2017.04.002
6. Anazi S, Maddirevula S, Salpietro V, Asi YT, Alsahli S, Alhashem A, Shamseldin HE, AlZahrani F, Patel N, Ibrahim N, Abdulwahab FM, Hashem M, Alhashmi N, Al Murshedi F, Al Kindy A, Alshaer A, Rumayyan A, Al Tala S, Kurdi W, Alsaman A, Alasmari A, Banu S, Sultan T, Saleh MM, Alkuraya H, Salih MA, Aldhalaan H, Ben-Omran T, Al Musafri F, Ali R, Suleiman J, Tabarki B, El-Hattab AW, Bupp C, Alfadhel M, Al Tassan N, Monies D, Arold ST, Abouelhoda M, Lashley T, Houlden H, Faqeih E, Alkuraya FS (2017) Expanding the genetic heterogeneity of intellectual disability. Hum Genet 136(11–12):1419–1429. https://doi.org/10.1007/s00439-017-1843-2
7. Harripaul R, Vasli N, Mikhailov A, Rafiq MA, Mittal K, Windpassinger C, Sheikh TI, Noor A, Mahmood H, Downey S, Johnson M, Vleuten K, Bell L, Ilyas M, Khan FS, Khan V, Moradi M, Ayaz M, Naeem F, Heidari A, Ahmed I, Ghadami S, Agha Z, Zeinali S, Qamar R, Mozhdehipanah H, John P, Mir A, Ansar M, French L, Ayub M, Vincent JB (2018) Mapping autosomal recessive intellectual disability: combined microarray and exome sequencing identifies 26 novel candidate genes in 192 consanguineous families. Mol Psychiatry 23(4):973–984. https://doi.org/10.1038/mp.2017.60
8. Musante L, Ropers HH (2014) Genetics of recessive cognitive disorders. Trends Genet 30(1):32–39. https://doi.org/10.1016/j.tig.2013.09.008
9. Ozand PT, Devol EB, Gascon GG (1992) Neurometabolic diseases at a national referral center: five years experience at the King Faisal Specialist Hospital and Research Centre. J Child Neurol 7(Suppl):S4–S11. https://doi.org/10.1177/08830738920070010211
10. Alkuraya FS (2014) Genetics and genomic medicine in Saudi Arabia. Mol Genet Genomic Med 2(5):369–378. https://doi.org/10.1002/mgg3.97
11. Fontaine SN, Zheng D, Sabbagh JJ, Martin MD, Chaput D, Darling A, Trotter JH, Stothert AR, Nordhues BA, Lussier A, Baker J, Shelton L, Kahn M, Blair LJ, Stevens SM Jr, Dickey CA (2016) DnaJ/Hsc70 chaperone complexes control the extracellular release of neurodegenerative-associated proteins. EMBO J 35(14):1537–1549. https://doi.org/10.15252/embj.201593489
12. Wiszniewska J, Bi W, Shaw C, Stankiewicz P, Kang SH, Pursley AN, Lalani S, Hixson P, Gambin T, Tsai CH, Bock HG, Descartes M, Probst FJ, Scaglia F, Beaudet AL, Lupski JR, Eng C, Cheung SW, Bacino C, Patel A (2014) Combined array CGH plus SNP genome analyses in a single assay for optimized clinical testing. Eur J Hum Genet 22(1):79–87. https://doi.org/10.1038/ejhg.2013.77
13. Alsahli S, Arold ST, Alfares A, Alhaddad B, Al Balwi M, Kamsteeg EJ, Al-Twaijri W, Alfadhel M (2018) KIF16B is a candidate gene for a novel autosomal-recessive intellectual disability syndrome. Am J Med Genet A 176(7):1602–1609. https://doi.org/10.1002/ajmg.a.38723
14. Yang J, Zhang Y (2015) I-TASSER server: new development for protein structure and function predictions. Nucleic Acids Res 43(W1):W174–W181. https://doi.org/10.1093/nar/gkv342
15. Kampinga HH, Hageman J, Vos MJ, Kubota H, Tanguay RM, Bruford EA, Cheetham ME, Chen B, Hightower LE (2009)

Guidelines for the nomenclature of the human heat shock proteins. Cell Stress Chaperones 14(1):105–111. https://doi.org/10.1007/s12192-008-0068-7

16. Harris JM, Nguyen PP, Patel MJ, Sporn ZA, Hines JK (2014) Functional diversification of hsp40: distinct j-protein functional requirements for two prions allow for chaperone-dependent prion selection. PLoS Genet 10(7):e1004510. https://doi.org/10.1371/journal.pgen.1004510
17. Finka A, Mattoo RU, Goloubinoff P (2016) Experimental milestones in the discovery of molecular chaperones as polypeptide unfolding enzymes. Annu Rev Biochem 85:715–742. https://doi.org/10.1146/annurev-biochem-060815-014124
18. Keck M, Androsova G, Gualtieri F, Walker A, von Ruden EL, Russmann V, Deeg CA, Hauck SM, Krause R, Potschka H (2017) A systems level analysis of epileptogenesis-associated proteome alterations. Neurobiol Dis 105:164–178. https://doi.org/10.1016/j.nbd.2017.05.017
19. Gorter JA, van Vliet EA, Aronica E, Breit T, Rauwerda H, Lopes da Silva FH, Wadman WJ (2006) Potential new antiepileptogenic targets indicated by microarray analysis in a rat model for temporal lobe epilepsy. J Neurosci 26(43):11083–11110. https://doi.org/10.1523/JNEUROSCI.2766-06.2006
20. Hartl FU, Bracher A, Hayer-Hartl M (2011) Molecular chaperones in protein folding and proteostasis. Nature 475(7356):324–332. https://doi.org/10.1038/nature10317
21. Suzuki T, Usuda N, Murata S, Nakazawa A, Ohtsuka K, Takagi H (1999) Presence of molecular chaperones, heat shock cognate (Hsc) 70 and heat shock proteins (Hsp) 40, in the postsynaptic structures of rat brain. Brain Res 816(1):99–110
22. Gorenberg EL, Chandra SS (2017) The role of co-chaperones in synaptic proteostasis and neurodegenerative disease. Front Neurosci 11:248. https://doi.org/10.3389/fnins.2017.00248
23. Weiler IJ, Spangler CC, Klintsova AY, Grossman AW, Kim SH, Bertaina-Anglade V, Khaliq H, de Vries FE, Lambers FA, Hatia F, Base CK, Greenough WT (2004) Fragile X mental retardation protein is necessary for neurotransmitter-activated protein translation at synapses. Proc Natl Acad Sci U S A 101(50):17504–17509. https://doi.org/10.1073/pnas.0407533101
24. Shigeoka T, Jung H, Jung J, Turner-Bridger B, Ohk J, Lin JQ, Amieux PS, Holt CE (2016) Dynamic axonal translation in developing and mature visual circuits. Cell 166(1):181–192. https://doi.org/10.1016/j.cell.2016.05.029
25. Younts TJ, Monday HR, Dudok B, Klein ME, Jordan BA, Katona I, Castillo PE (2016) Presynaptic protein synthesis is required for long-term plasticity of GABA release. Neuron 92(2):479–492. https://doi.org/10.1016/j.neuron.2016.09.040
26. Burre J, Beckhaus T, Corvey C, Karas M, Zimmermann H, Volknandt W (2006) Synaptic vesicle proteins under conditions of rest and activation: analysis by 2-D difference gel electrophoresis. Electrophoresis 27(17):3488–3496. https://doi.org/10.1002/elps.200500864
27. Elsayed LE, Drouet V, Usenko T, Mohammed IN, Hamed AA, Elseed MA, Salih MA, Koko ME, Mohamed AY, Siddig RA, Elbashir MI, Ibrahim ME, Durr A, Stevanin G, Lesage S, Ahmed AE, Brice A (2016) A novel nonsense mutation in DNAJC6 expands the phenotype of autosomal-recessive juvenile-onset Parkinson's disease. Ann Neurol 79(2):335–337. https://doi.org/10.1002/ana.24591
28. Guarnieri FC, Pozzi D, Raimondi A, Fesce R, Valente MM, Delvecchio VS, Van Esch H, Matteoli M, Benfenati F, D'Adamo P, Valtorta F (2017) A novel SYN1 missense mutation in non-syndromic X-linked intellectual disability affects synaptic vesicle life cycle, clustering and mobility. Hum Mol Genet 26(23):4699–4714. https://doi.org/10.1093/hmg/ddx352
29. Chia PH, Zhong FL, Niwa S, Bonnard C, Utami KH, Zeng R, Lee H, Eskin A, Nelson SF, Xie WH, Al-Tawalbeh S, El-Khateeb M, Shboul M, Pouladi MA, Al-Raqad M, Reversade B (2018) A homozygous loss-of-function CAMK2A mutation causes growth delay, frequent seizures and severe intellectual disability. Elife 7. https://doi.org/10.7554/eLife.32451
30. Szabo A, Korszun R, Hartl FU, Flanagan J (1996) A zinc finger-like domain of the molecular chaperone DnaJ is involved in binding to denatured protein substrates. EMBO J 15(2):408–417
31. Walker VE, Wong MJ, Atanasiu R, Hantouche C, Young JC, Shrier A (2010) Hsp40 chaperones promote degradation of the HERG potassium channel. J Biol Chem 285(5):3319–3329. https://doi.org/10.1074/jbc.M109.024000
32. Partemi S, Cestele S, Pezzella M, Campuzano O, Paravidino R, Pascali VL, Zara F, Tassinari CA, Striano S, Oliva A, Brugada R, Mantegazza M, Striano P (2013) Loss-of-function KCNH2 mutation in a family with long QT syndrome, epilepsy, and sudden death. Epilepsia 54(8):e112–e116. https://doi.org/10.1111/epi.12259
33. Zamorano-Leon JJ, Yanez R, Jaime G, Rodriguez-Sierra P, Calatrava-Ledrado L, Alvarez-Granada RR, Mateos-Caceres PJ, Macaya C, Lopez-Farre AJ (2012) KCNH2 gene mutation: a potential link between epilepsy and long QT-2 syndrome. J Neurogenet 26(3–4):382–386. https://doi.org/10.3109/01677063.2012.674993