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El-Hattab-Alkuraya Syndrome

Synonym: *WDR45B*-Related Neurodevelopmental Disorder

Mohammed Almannai, MD, FAAP, FACMG,[1] Dana Marafi, MD, MSc,[2] and Ayman W El-Hattab, MD, FAAP, FACMG[3]

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Summary

Clinical characteristics

El-Hattab-Alkuraya syndrome is characterized by microcephaly (often early onset and progressive); severe-to-profound developmental delay; refractory and early-onset seizures; spastic quadriplegia with axial hypotonia; and growth deficiency with poor weight gain and short stature. Characteristic findings on brain imaging include cerebral atrophy that is disproportionately most prominent in the frontal lobes; *ex vacuo* ventricular dilatation with notable posterior horn predominance; brain stem volume loss with flattening of the belly of the pons; and symmetric under-opercularization. Neurologic involvement is progressive, with significant morbidity and mortality.

Diagnosis/testing

The diagnosis of El-Hattab-Alkuraya syndrome is established in a proband by identification of biallelic pathogenic variants in *WDR45B* on molecular genetic testing.

Management

Treatment of manifestations: Standardized treatments for seizures, spasticity, mobility, feeding issues, and ocular manifestations; developmental services and educational interventions for developmental delay and intellectual disability.

Surveillance: Monitor for changes in seizures, tone, movement disorders, nutrition, and safety of oral intake at each visit. Monitor development, educational needs, behavior, vision, and hearing annually or as needed.

Author Affiliations: 1 Genetics and Precision Medicine Department, King Abdullah Specialized Children's Hospital, King Abdulaziz Medical City, Ministry of National Guard Health Affairs, Riyadh, Saudi Arabia; Email: mmannai81@gmail.com. 2 Department of Pediatrics, Faculty of Medicine, Kuwait University, Jabriya, Kuwait; Email: dana.marafie@ku.edu.kw. 3 College of Medicine, University of Sharjah, Sharjah, United Arab Emirates; Email: elhattabaw@yahoo.com.

Genetic counseling

El-Hattab-Alkuraya syndrome is inherited in an autosomal recessive manner. If both parents are known to be heterozygous for a *WDR45B* pathogenic variant, each sib of an affected individual has at conception a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of inheriting neither of the familial pathogenic variants. Once the *WDR45B* pathogenic variants have been identified in an affected family member, carrier testing for at-risk relatives and prenatal/preimplantation genetic testing are possible.

Diagnosis

Suggestive Findings

El-Hattab-Alkuraya syndrome **should be considered** in individuals with the following clinical, imaging, and family history findings.

Clinical findings

- Progressive microcephaly
- Developmental delay
- Early-onset, refractory seizures
- Spastic quadriplegia
- Growth deficiency (poor weight gain, short stature)

Imaging findings on brain MRI

- Cerebral atrophy with disproportionate atrophy of the frontal lobes
- *Ex vacuo* ventricular dilatation with posterior horn predominance
- Brain stem volume loss with flattening of the belly of the pons
- Symmetric under-opercularization

Family history is consistent with autosomal recessive inheritance (e.g., affected sibs and/or parental consanguinity). Absence of a known family history does not preclude the diagnosis.

Establishing the Diagnosis

The diagnosis of El-Hattab-Alkuraya syndrome **is established** in a proband with suggestive findings and biallelic pathogenic (or likely pathogenic) variants in *WDR45B* identified by molecular genetic testing (see Table 1).

Note: (1) Per ACMG/AMP variant interpretation guidelines, the terms "pathogenic variants" and "likely pathogenic variants" are synonymous in a clinical setting, meaning that both are considered diagnostic and both can be used for clinical decision making [Richards et al 2015]. Reference to "pathogenic variants" in this section is understood to include any likely pathogenic variants. (2) Identification of biallelic *WDR45B* variants of uncertain significance (or of one known *WDR45B* pathogenic variant and one *WDR45B* variant of uncertain significance) does not establish or rule out a diagnosis.

Molecular genetic testing in a child with developmental delay may begin with exome sequencing, a multigene panel, or chromosomal microarray analysis. Note: Single-gene testing (sequence analysis of *WDR45B*) is rarely useful and typically NOT recommended.

- **Comprehensive genomic testing** does not require the clinician to determine which gene(s) are likely involved. **Exome sequencing** is most commonly used, and yields results similar to an intellectual disability (ID) multigene panel, with the additional advantage that exome sequencing includes genes recently identified as causing ID whereas some multigene panels may not. **Genome sequencing** is also possible.

For an introduction to comprehensive genomic testing click here. More detailed information for clinicians ordering genomic testing can be found here.

- **A multigene panel** that includes *WDR45B* and other genes of interest (see Differential Diagnosis) may be considered to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

  For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.

Table 1. Molecular Genetic Testing Used in El-Hattab-Alkuraya Syndrome

Gene [1]	Method	Proportion of Pathogenic Variants [2] Detectable by Method
WDR45B	Sequence analysis [3]	100% [4]
	Gene-targeted deletion/duplication analysis [5]	None reported [4]

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on variants detected in this gene.
3. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
4. Data derived from the subscription-based professional view of Human Gene Mutation Database [Stenson et al 2020]
5. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.

Clinical Characteristics

Clinical Description

El-Hattab-Alkuraya syndrome is characterized by congenital and progressive microcephaly, developmental delay, seizures, spastic quadriplegia, associated brain imaging findings, and progressive neurologic involvement with significant morbidity and mortality. To date, 22 individuals with biallelic pathogenic variants in *WDR45B* have been identified [Najmabadi et al 2011, Anazi et al 2017, Suleiman et al 2018, Almannai et al 2022]. The following description of the phenotypic features associated with this condition is based on these reports.

Table 2. El-Hattab-Alkuraya Syndrome: Frequency of Select Features

Feature	Proportion of Persons w/Feature [1, 2]	Comment
Microcephaly	19/22	
Developmental delay	22/22	Severe to profound
Seizures	16/18	Refractory, early onset
Spastic quadriplegia	15/17	
Poor weight gain	7/11	

Table 2. continued from previous page.

Feature	Proportion of Persons w/Feature [1, 2]	Comment
Short stature	10/12	

1. Average age at the time of evaluation was 6.5 years (range 7 months – 14 years)
2. Denominator reflects the number of persons assessed for the feature.

Microcephaly. The majority of affected individuals had progressive microcephaly. Most individuals had congenital microcephaly (in those with a known birth head circumference). Microcephaly was identified prenatally in some individuals [Najmabadi et al 2011, Anazi et al 2017, Suleiman et al 2018, Almannai et al 2022].

Developmental delay. All individuals had severe-to-profound development delay. Individuals with loss-of-function *WDR45B* variants were profoundly delayed and unable to ambulate or communicate. Two sibs homozygous for a *WDR45B* missense variant were severely delayed but showed slow acquisition of some skills, and regression was not evident by ages four and 14 years. The two sibs were able to follow simple commands and speak a few monosyllables. Ambulation was achieved by age 30 months in the older sib, but had not been achieved by age four years in the younger sib.

Seizures. Refractory, early-onset seizures were reported in most individuals. The most common seizure type was generalized tonic-clonic. Other reported seizure types included myoclonic and focal. Seizures were refractory and required at least two anti-seizure medications (ASMs) in most individuals. Responses to ASMs were variable, with no particular ASM being more effective.

Spastic quadriplegia. Most individuals had spastic quadriplegia that was associated with axial hypotonia.

Growth deficiency. Poor weight gain was reported in most individuals. Feeding and swallowing problems were commonly observed. Method of feeding was reported for three individuals, who all required gastric tube feeding. Most affected individuals with loss-of-function variants are expected to require tube feeding given the extent of neurologic involvement. Short stature was reported in ten of 12 affected individuals for whom measurements were available.

Ocular manifestations. Most individuals have poor visual tracking; one individual was diagnosed with cortical blindness. Optic atrophy was reported in two individuals, and two other individuals were reported to have strabismus.

Nonspecific dysmorphic features were reported in most individuals. The most common reported features were thick, highly arched eyebrows, large ears, bitemporal narrowing, and long philtrum.

Common **neuroradiographic findings** include:

- Cerebral atrophy with disproportionate atrophy of the frontal lobe
- Giant cisterna magna
- Corpus callosum thinning
- Brain stem volume loss with flattening of the belly of the pons
- *Ex vacuo* ventricular dilatation with posterior horn predominance pattern of the ventriculomegaly
- Symmetric under-opercularization
- Dysplastic hippocampi
- Cerebellar atrophy
- Cervical spine atrophy

Other. One individual had behavioral issues including aggression and self-harming behavior.

Prognosis. Five individuals are deceased at the time of this report. The age of death ranged from two to 15 years; mean age of death was 7.9 years. When reported, the most common cause for death was aspiration pneumonia.

Genotype-Phenotype Correlations

The number of affected individuals is insufficient to establish genotype-phenotype correlations. However, two sibs homozygous for missense variant c.674G>A had milder clinical features; only one sib had seizures, and neither sib had characteristic brain MRI findings or spastic quadriplegia [Almannai et al 2022].

Nomenclature

El-Hattab-Alkuraya syndrome may also be referred to as *WDR45B*-related neurodevelopmental disorder based on the dyadic naming approach proposed by Biesecker et al [2021] to delineate mendelian genetic disorders.

Prevalence

The exact prevalence is unknown, but El-Hattab-Alkuraya syndrome appears to be rare, with only 22 individuals reported to date. Most affected individuals are of Arab ancestry.

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with germline pathogenic variants in *WDR45B*.

Differential Diagnosis

Because the phenotypic features associated with El-Hattab-Alkuraya syndrome are not sufficient to diagnose this condition, all disorders with intellectual disability without other distinctive findings should be considered in the differential diagnosis. See OMIM Autosomal Dominant, Autosomal Recessive, Nonsyndromic X-Linked, and Syndromic X-Linked Intellectual Developmental Disorder Phenotypic Series.

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with El-Hattab-Alkuraya syndrome, the evaluations summarized in Table 3 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Table 3. Recommended Evaluations Following Initial Diagnosis in Individuals with El-Hattab-Alkuraya Syndrome

System/Concern	Evaluation	Comment
Neurologic	Neurologic eval	• To incl brain MRI to evaluate extent of disorder • EEG
Development	Developmental assessment	• To incl motor, adaptive, cognitive, & speech/language eval • Assess needs for speech, OT, PT. • Eval for early intervention / special education
Gastrointestinal	• Nutritional eval • Swallowing assessment for feeding difficulties	
Ophthalmologic	Formal ophthalmologic eval	

Table 3. continued from previous page.

System/Concern	Evaluation	Comment
ENT	Hearing assessment	Although hearing issues have not been reported, hearing assessment is recommended due to developmental issues.
Genetic counseling	By genetics professionals [1]	To inform affected persons & their families re nature, MOI, & implications of El-Hattab-Alkuraya syndrome to facilitate medical & personal decision making
Family support & resources	Assess need for: • Community or online resources such as Parent to Parent; • Social work involvement for parental support; • Home nursing referral.	

MOI = mode of inheritance; OT = occupational therapy; PT = physical therapy
1. Medical geneticist, certified genetic counselor, certified advanced genetic nurse

Treatment of Manifestations

Supportive care to improve quality of life, maximize function, and reduce complications is recommended. This can include multidisciplinary care by specialists in neurology, nutrition, ophthalmology, clinical genetics/metabolism, developmental pediatrics, speech-language therapy, occupational therapy, physical therapy, and audiology.

Table 4. Treatment of Manifestations in Individuals with El-Hattab-Alkuraya Syndrome

Manifestation/Concern	Treatment	Considerations/Other
Epilepsy	Standardized treatment w/ASM by experienced neurologist	Seizures are refractory & often require at least 2 ASMs for seizure control.
Developmental delay / Intellectual disability	See Developmental Delay / Intellectual Disability Management Issues.	
Spasticity / Mobility issues	Consultation w/physical medicine & rehab to help w/mobility or assistive devices (e.g., wheelchair)	
Poor weight gain	• Feeding therapy • Nasogastric tube or gastrostomy tube are frequently needed due to feeding difficulties & poor weight gain.	
Ocular manifestations	Treatment per ophthalmologist	

ASM = anti-seizure medication

Developmental Delay / Intellectual Disability Management Issues

The following information represents typical management recommendations for individuals with developmental delay / intellectual disability in the United States; standard recommendations may vary from country to country.

Ages 0-3 years. Referral to an early intervention program is recommended for access to occupational, physical, speech, and feeding therapy as well as infant mental health services, special educators, and sensory impairment specialists. In the US, early intervention is a federally funded program available in all states that provides in-home services to target individual therapy needs.

Ages 3-5 years. In the US, developmental preschool through the local public school district is recommended. Before placement, an evaluation is made to determine needed services and therapies and an individualized

education plan (IEP) is developed for those who qualify based on established motor, language, social, or cognitive delay. The early intervention program typically assists with this transition. Developmental preschool is center based; for children too medically unstable to attend, home-based services are provided.

All ages. Consultation with a developmental pediatrician is recommended to ensure the involvement of appropriate community, state, and educational agencies (US) and to support parents in maximizing quality of life. Some issues to consider:

- IEP services:
  - An IEP provides specially designed instruction and related services to children who qualify.
  - IEP services will be reviewed annually to determine whether any changes are needed.
  - Special education law requires that children participating in an IEP be in the least restrictive environment feasible at school and included in general education as much as possible, when and where appropriate.
  - Vision and hearing consultants should be a part of the child's IEP team to support access to academic material.
  - PT, OT, and speech services will be provided in the IEP to the extent that the need affects the child's access to academic material. Beyond that, private supportive therapies based on the affected individual's needs may be considered. Specific recommendations regarding type of therapy can be made by a developmental pediatrician.
  - As a child enters the teen years, a transition plan should be discussed and incorporated in the IEP. For those receiving IEP services, the public school district is required to provide services until age 21.
- A 504 plan (Section 504: a US federal statute that prohibits discrimination based on disability) can be considered for those who require accommodations or modifications such as front-of-class seating, assistive technology devices, classroom scribes, extra time between classes, modified assignments, and enlarged text.
- Developmental Disabilities Administration (DDA) enrollment is recommended. DDA is a US public agency that provides services and support to qualified individuals. Eligibility differs by state but is typically determined by diagnosis and/or associated cognitive/adaptive disabilities.
- Families with limited income and resources may also qualify for supplemental security income (SSI) for their child with a disability.

Motor Dysfunction

Gross motor dysfunction

- Physical therapy is recommended to maximize mobility and to reduce the risk for later-onset orthopedic complications (e.g., contractures, scoliosis, hip dislocation).
- Consider use of durable medical equipment and positioning devices as needed (e.g., wheelchairs, walkers, bath chairs, orthotics, adaptive strollers).
- For muscle tone abnormalities including hypertonia or dystonia, consider involving appropriate specialists to aid in management of baclofen, tizanidine, Botox®, anti-parkinsonian medications, or orthopedic procedures.

Fine motor dysfunction. Occupational therapy is recommended for difficulty with fine motor skills that affect adaptive function such as feeding, grooming, dressing, and writing.

Oral motor dysfunction should be assessed at each visit and clinical feeding evaluations and/or radiographic swallowing studies should be obtained for choking/gagging during feeds, poor weight gain, frequent respiratory illnesses, or feeding refusal that is not otherwise explained. Assuming that the child is safe to eat by mouth, feeding therapy (typically from an occupational or speech therapist) is recommended to help improve

coordination or sensory-related feeding issues. Feeds can be thickened or chilled for safety. When feeding dysfunction is severe, an NG-tube or G-tube may be necessary.

Communication issues. Consider evaluation for alternative means of communication (e.g., augmentative and alternative communication [AAC]) for individuals who have expressive language difficulties. An AAC evaluation can be completed by a speech-language pathologist who has expertise in the area. The evaluation will consider cognitive abilities and sensory impairments to determine the most appropriate form of communication. AAC devices can range from low-tech, such as picture exchange communication, to high-tech, such as voice-generating devices. Contrary to popular belief, AAC devices do not hinder verbal development of speech, but rather support optimal speech and language development.

Social/Behavioral Concerns

Children may qualify for and benefit from interventions used in treatment of autism spectrum disorder, including applied behavior analysis (ABA). ABA therapy is targeted to the individual child's behavioral, social, and adaptive strengths and weaknesses and typically performed one on one with a board-certified behavior analyst.

Consultation with a developmental pediatrician may be helpful in guiding parents through appropriate behavior management strategies or providing prescription medications, such as medication used to treat attention-deficit/hyperactivity disorder, when necessary.

Concerns about serious aggressive or destructive behavior can be addressed by a pediatric psychiatrist.

Surveillance

To monitor existing manifestations, the individual's response to supportive care, and the emergence of new manifestations, the evaluations in Table 5 are recommended.

Table 5. Recommended Surveillance for Individuals with El-Hattab-Alkuraya Syndrome

System/Concern	Evaluation	Frequency
Neurologic	• Monitor those w/seizures as clinically indicated. • Assess for new manifestations incl seizures, changes in tone, & mvmt disorders.	At each visit
Development	Monitor developmental progress & educational needs.	Annually &/or as needed
Gastrointestinal/ Nutrition	Eval of nutritional status & safety of oral intake	At each visit
Psychiatric/ Behavioral	Behavioral assessment for anxiety, attention, & aggressive or self-injurious behavior	Annually &/or as needed
Eyes	Ophthalmology exam	Annually
Hearing	Audiology eval	

Evaluation of Relatives at Risk

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

Therapies Under Investigation

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for access to information on clinical studies for a wide range of diseases and conditions. Note: There may not be clinical trials for this disorder.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

El-Hattab-Alkuraya syndrome is inherited in an autosomal recessive manner.

Risk to Family Members

Parents of a proband

- The parents of an affected child are presumed to be heterozygous for a *WDR45B* pathogenic variant.
- Molecular genetic testing is recommended for the parents of a proband to confirm that both parents are heterozygous for a *WDR45B* pathogenic variant and to allow reliable recurrence risk assessment.
- If a pathogenic variant is detected in only one parent and parental identity testing has confirmed biological maternity and paternity, it is possible that one of the pathogenic variants identified in the proband occurred as a *de novo* event in the proband or as a postzygotic *de novo* event in a mosaic parent [Jónsson et al 2017]. If the proband appears to have homozygous pathogenic variants (i.e., the same two pathogenic variants), additional possibilities to consider include:
  - A single- or multiexon deletion in the proband that was not detected by sequence analysis and that resulted in the artifactual appearance of homozygosity;
  - Uniparental isodisomy for the parental chromosome with the pathogenic variant that resulted in homozygosity for the pathogenic variant in the proband.
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

Sibs of a proband

- If both parents are known to be heterozygous for a *WDR45B* pathogenic variant, each sib of an affected individual has at conception a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of inheriting neither of the familial pathogenic variants.
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

Offspring of a proband. To date, individuals with El-Hattab-Alkuraya syndrome are not known to reproduce.

Other family members. Each sib of the proband's parents is at a 50% risk of being a carrier of a *WDR45B* pathogenic variant.

Carrier Detection

Carrier testing for at-risk relatives requires prior identification of the *WDR45B* pathogenic variants in the family.

Related Genetic Counseling Issues

Family planning

- The optimal time for determination of genetic risk and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are carriers or are at risk of being carriers.

Prenatal Testing and Preimplantation Genetic Testing

Once the *WDR45B* pathogenic variants have been identified in an affected family member, prenatal and preimplantation genetic testing are possible.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing. While most centers would consider use of prenatal testing to be a personal decision, discussion of these issues may be helpful.

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.

- **American Association on Intellectual and Developmental Disabilities (AAIDD)**
  Phone: 202-387-1968
  Fax: 202-387-2193
  www.aaidd.org
- **American Epilepsy Society**
  www.aesnet.org
- **Canadian Epilepsy Alliance**
  Canada
  Phone: 1-866-EPILEPSY (1-866-374-5377)
  www.canadianepilepsyalliance.org
- **CDC - Developmental Disabilities**
  Phone: 800-CDC-INFO
  Email: cdcinfo@cdc.gov
  Intellectual Disability
- **Epilepsy Canada**
  Canada
  Phone: 877-734-0873
  Email: epilepsy@epilepsy.ca
  www.epilepsy.ca
- **Epilepsy Foundation**
  Phone: 301-459-3700
  Fax: 301-577-2684
  www.epilepsy.com
- **MedlinePlus**
  Intellectual Disability

Molecular Genetics

Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.

Table A. El-Hattab-Alkuraya Syndrome: Genes and Databases

Gene	Chromosome Locus	Protein	HGMD	ClinVar
WDR45B	17q25.3	WD repeat domain phosphoinositide-interacting protein 3	WDR45B	WDR45B

Data are compiled from the following standard references: gene from HGNC; chromosome locus from OMIM; protein from UniProt. For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click here.

Table B. OMIM Entries for El-Hattab-Alkuraya Syndrome (View All in OMIM)

609226	WD REPEAT-CONTAINING PROTEIN 45B; WDR45B
617977	NEURODEVELOPMENTAL DISORDER WITH SPASTIC QUADRIPLEGIA AND BRAIN ABNORMALITIES WITH OR WITHOUT SEIZURES; NEDSBAS

Molecular Pathogenesis

WDR45B encodes for WD (tryptophan-aspartic acid) repeat-containing protein 45B, a member of the WIPI protein family. This protein family plays an important role in autophagy [Bakula et al 2017].

Mechanism of disease causation. Loss of function

Table 6. Notable *WDR45B* Pathogenic Variants

Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Comment
NM_019613.4 NP_062559.2	c.674G>A	p.Arg225Gln	See Genotype-Phenotype Correlations.

Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.
GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.

Chapter Notes

Revision History

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References

Literature Cited

Almannai M, Marafi D, Abdel-Salam GMH, Zaki MS, Duan R, Calame D, Herman I, Levesque F, Elbendary HM, Hegazy I, Chung WK, Kavus H, Saeidi K, Maroofian R, AlHashim A, Al-Otaibi A, Al Madhi A, Abou Al-Seood HM, Alasmari A, Houlden H, Gleeson JG, Hunter JV, Posey JE, Lupski JR, El-Hattab AW. El-Hattab-Alkuraya syndrome caused by biallelic WDR45B pathogenic variants: further delineation of the phenotype and genotype. Clin Genet. 2022;101:530–40. PubMed PMID: 35322404.

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. Clinical genomics expands the

morbid genome of intellectual disability and offers a high diagnostic yield. Mol Psychiatry. 2017;22:615–24. PubMed PMID: 27431290.

Bakula D, Müller AJ, Zuleger T, Takacs Z, Franz-Wachtel M, Thost AK, Brigger D, Tschan MP, Frickey T, Robenek H, Macek B, Proikas-Cezanne T. WIPI3 and WIPI4 β-propellers are scaffolds for LKB1-AMPK-TSC signalling circuits in the control of autophagy. Nat Commun. 2017;8:15637. PubMed PMID: 28561066.

Biesecker LG, Adam MP, Alkuraya FS, Amemiya AR, Bamshad MJ, Beck AE, Bennett JT, Bird LM, Carey JC, Chung B, Clark RD, Cox TC, Curry C, Dinulos MBP, Dobyns WB, Giampietro PF, Girisha KM, Glass IA, Graham JM Jr, Gripp KW, Haldeman-Englert CR, Hall BD, Innes AM, Kalish JM, Keppler-Noreuil KM, Kosaki K, Kozel BA, Mirzaa GM, Mulvihill JJ, Nowaczyk MJM, Pagon RA, Retterer K, Rope AF, Sanchez-Lara PA, Seaver LH, Shieh JT, Slavotinek AM, Sobering AK, Stevens CA, Stevenson DA, Tan TY, Tan WH, Tsai AC, Weaver DD, Williams MS, Zackai E, Zarate YA. A dyadic approach to the delineation of diagnostic entities in clinical genomics. Am J Hum Genet. 2021;108:8–15. PubMed PMID: 33417889.

Jónsson H, Sulem P, Kehr B, Kristmundsdottir S, Zink F, Hjartarson E, Hardarson MT, Hjorleifsson KE, Eggertsson HP, Gudjonsson SA, Ward LD, Arnadottir GA, Helgason EA, Helgason H, Gylfason A, Jonasdottir A, Jonasdottir A, Rafnar T, Frigge M, Stacey SN, Th Magnusson O, Thorsteinsdottir U, Masson G, Kong A, Halldorsson BV, Helgason A, Gudbjartsson DF, Stefansson K. Parental influence on human germline de novo mutations in 1,548 trios from Iceland. Nature. 2017;549:519–22. PubMed PMID: 28959963.

Najmabadi H, Hu H, Garshasbi M, Zemojtel T, Abedini SS, Chen W, Hosseini M, Behjati F, Haas S, Jamali P, Zecha A, Mohseni M, Püttmann L, Vahid LN, Jensen C, Moheb LA, Bienek M, Larti F, Mueller I, Weissmann R, Darvish H, Wrogemann K, Hadavi V, Lipkowitz B, Esmaeeli-Nieh S, Wieczorek D, Kariminejad R, Firouzabadi SG, Cohen M, Fattahi Z, Rost I, Mojahedi F, Hertzberg C, Dehghan A, Rajab A, Banavandi MJ, Hoffer J, Falah M, Musante L, Kalscheuer V, Ullmann R, Kuss AW, Tzschach A, Kahrizi K, Ropers HH. Deep sequencing reveals 50 novel genes for recessive cognitive disorders. Nature. 2011;478:57–63. PubMed PMID: 21937992.

Richards S, Aziz N, Bale S, Bick D, Das S, Gastier-Foster J, Grody WW, Hegde M, Lyon E, Spector E, Voelkerding K, Rehm HL, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015;17:405–24. PubMed PMID: 25741868.

Stenson PD, Mort M, Ball EV, Chapman M, Evans K, Azevedo L, Hayden M, Heywood S, Millar DS, Phillips AD, Cooper DN. The Human Gene Mutation Database (HGMD®): optimizing its use in a clinical diagnostic or research setting. Hum Genet. 2020;139:1197–207. PubMed PMID: 32596782.

Suleiman J, Allingham-Hawkins D, Hashem M, Shamseldin HE, Alkuraya FS, El-Hattab AW. WDR45B-related intellectual disability, spastic quadriplegia, epilepsy, and cerebral hypoplasia: a consistent neurodevelopmental syndrome. Clin Genet. 2018;93:360–4. PubMed PMID: 28503735.

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