Int J Mol Epidemiol Genet 2023;14(3):34-41
www.ijmeg.org /ISSN:1948-1756/IJMEG0150203

Review Article

Facial and ocular manifestations of male patients affected by the *HUWE1*-related intellectual developmental disorder

Sharanya P Deshmukh[1], Natario L Couser[2,3,4]

[1]Virginia Commonwealth University School of Medicine, Richmond, VA, USA; [2]Department of Human and Molecular Genetics, Virginia Commonwealth University School of Medicine, Richmond, VA, USA; [3]Department of Ophthalmology, Virginia Commonwealth University School of Medicine, Richmond, VA, USA; [4]Department of Pediatrics, Virginia Commonwealth University School of Medicine, Children's Hospital of Richmond at VCU, Richmond, VA, USA

Received March 17, 2023; Accepted October 11, 2023; Epub October 15, 2023; Published October 30, 2023

Abstract: Turner-type X-linked syndromic intellectual developmental disorder (MRXST) is a rare neurodevelopmental disorder. MRXST is caused by pathogenic variants in the *HUWE1* gene on chromosome Xp11.22. The *HUWE1* gene encodes a ubiquitin ligase, which has downstream effects on the n-MYC protein and DLL3 Notch ligand, ultimately affecting neuronal differentiation. In addition to intellectual disability and developmental delay, other clinical features such as absent or delayed speech, skeletal abnormalities, abnormalities in hands or feet, seizures, and hypotonia have been described in case reports. Facial dysmorphic features and eye manifestations have been reported in patients with MRXST, but have not been identified as distinctive to this condition. We report two cases of individuals affected by *HUWE1*-Related Intellectual Developmental Disorder and present a review of literature of male patients affected by this disorder. Based on the literature review and findings in our two patients, it is our observation that patients with MRXST present with distinctive features, which include broad nasal tip, root, or prominent nose (39%), blepharophimosis (27%), epicanthic folds (25%), ear abnormalities (25%), thin upper lip (23%), and deep set eyes (23%). Furthermore, we note that oculofacial abnormalities are seen more frequently in patients with missense variants than patients with duplications in the *HUWE1* gene. The findings noted in this paper may help clinicians suspect a diagnosis of MRXST when presented with these distinctive ocular and facial features.

Keywords: *HUWE1*, intellectual development disorder, phenotype, Xp11.22, turner type

Introduction

Turner-type X-linked syndromic intellectual developmental disorder (MRXST; MIM#309590) is caused by pathogenic variants in the *HUWE1* gene on chromosome Xp11.22. A nonsyndromic form of X-linked intellectual development disorder is caused by microduplications of chromosome Xp11.22 that include the *HUWE1* and *HSD17B10* genes. Other names for this *HUWE1*-Related Intellectual Developmental Disorder include Juberg-Marsidi Syndrome and Brooks-Wisniewski-Brown syndrome.

The HUWE1 gene plays a role in suppressing neuronal proliferation and initiating differentiation [1]. *HUWE1* encodes a HECT domain ubiquitin-protein ligase [1]. The ubiquitin ligase suppresses the activity of the n-MYC protein, which regulates the expression of the DLL3 Notch ligand [1]. In mouse models, *HUWE1* null brains showed an accumulation of N-Myc protein, which correlated with phenotypic features [1]. *HUWE1* expression is regulated by oxygen concentration during embryonic development [2]. In a study conducted on discarded IVF human embryos, it was observed that high levels of oxidative stress inhibited *HUWE1* expression. This indicated that *HUWE1* plays an important role in early embryonic development [2].

The inheritance pattern of MRXST is X-linked recessive in some families. However, there have been cases in which the inheritance is

X-linked dominant due to skewed X inactivation in females [3]. The condition primarily affects males and presents at an early age. Females may also be affected but have been noted to have a milder phenotypic expression [4]. The first reported case, published in 1994, included a multi-generation family with severe intellectual disability in males and a milder intellectual impairment in affected females [4].

Clinical features are variable among affected individuals. Intellectual disability, limited speech, short stature, and dysmorphic features are frequently present [4]. Due to a high frequency of ocular anomalies, ophthalmologic anomalies must be screened for in these affected patients [3]. The diagnosis of MRXST focuses heavily on genetic testing. Broad based sequencing methods such as whole-genome and whole-exome sequencing may be used. Alternatively, a more targeted sequencing approach such as utilizing an Autism/Intellectual Disability gene panel that contains the associated gene, may be conducted to identify disease-causing variants in the *HUWE1* gene.

Current treatment options focus on management of symptoms. Efficacy has been variable depending on the severity of the underlying symptoms. Treatment has primarily been reported to be supportive. Growth hormone supplementation [5] and medications for seizure prevention have been prescribed [6].

Long-term prognosis for MRXST has not been well documented as there are a limited number of longitudinal studies on this condition. A follow-up study was conducted in 2016 [5] on two cases which were originally reported in 1994 [7] and 1980 [8]. The clinical update revealed that these patients continued to have long-term intellectual disability, limb abnormalities, low growth parameters, and remained nonverbal with hearing loss [5].

Facial dysmorphic features and eye manifestations have been commonly associated with this disorder, but have not been well characterized. We present two brothers with variants in the *HUWE1* gene and clinical features consistent with the *HUWE1*-Related Intellectual Developmental Disorder. We compare their clinical presentations to other male patients previously reported in literature, with a focus on distinctive facial and ophthalmic manifestations.

Case report

Our patients are two brothers, age 9- and 10-year-old males at the time of visit. The patients were born to non-consanguineous parents. There was no reported family history of birth defects, developmental delay, intellectual disability, early infant deaths, or multiple miscarriages.

The older sibling was 10 years old at the time of evaluation. He presented with global developmental delay including intellectual disability, fine motor delay, low muscle tone, speech and language delay. He had a history of nocturnal enuresis which was managed with overnight diapers and hypothyroidism treated with supplemental levothyroxine. Head circumference measured 53 cm, which was around the 50th percentile for his age. He was in the 19th percentile based on stature-for-age and the 98th percentile based on CDC weight-for-age data.

The younger sibling was 9 years old at the time of evaluation. He had previously been diagnosed with global developmental delay including speech and language delays. He did not meet the diagnostic criteria for autism. Head circumference measured 50.3 cm, which was less than the 5th percentile for his age. Patient was in the 4th percentile based on stature-for-age data and the 8th percentile based on CDC weight-for-age data.

Both siblings had dysmorphic features that included an asymmetric face, long philtrum, thick eyebrows, thin upper lip, elongated thumbs, and elongated toes. The older sibling had mildly deep-set eyes, mild left ptosis, and a minimal refractive error for which glasses were not prescribed (**Figure 1A-C**). The younger sibling also had mild right ptosis and astigmatism in both eyes, for which he was prescribed glasses (**Figure 2A-C**). His fundoscopic examination was notable for having a mild tilt of the optic disc in both eyes.

Chromosomal microarray testing revealed that both siblings had a copy number gain at 7q21.2, a 135 kB duplication that involved a portion of the *AKAP9* gene, classified as a variant of uncertain significance. Autism Expanded Panel testing in both siblings revealed that each sibling had a hemizygous, pathogenic, maternally

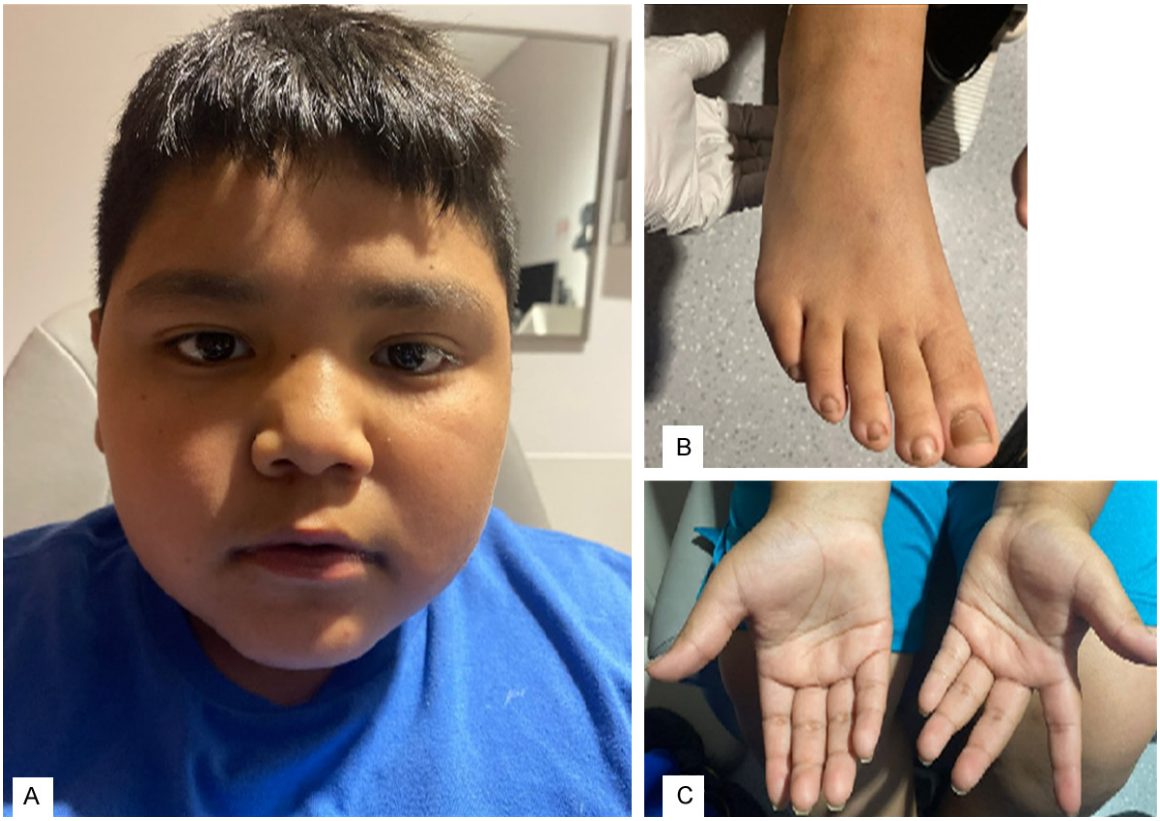

Figure 1. 10-year-old boy with dysmorphic ocular, facial and extremity characteristics. A. Facial features were notable for deep set eyes, mild left ptosis, asymmetric facies, long philtrum, thick eyebrows, and thin upper lips. B. Elongated toes on the dorsal aspect of the right foot shown. C. Bilaterally elongated thumbs were present as shown on a view of the palmar aspect of the hands.

inherited variant c.12559 C>T, p. Arg4187Cys in the *HUWE1* gene.

Methods

Inclusion criteria

We conducted a systematic review of the literature to summarize the ocular and facial dysmorphic features in male patients with *HUWE1* gene variants. A PubMed search of "HUWE1" led to 285 results. 270 articles were excluded either due to a lack of clinical facial and eye descriptions, lack of genetic evidence confirming the *HUWE1* mutation, or publication in a language other than English. Due to variable effects of X inactivation in biological females, only biological male patients with confirmed *HUWE1* disease-causing variants were included. No articles were excluded based on the year of publication. The remaining 15 articles results yielded adequate eye and facial descriptions of a total of 80 patients with the *HUWE1*-Related Intellectual Developmental Disorder. A total of 82 patients were included in the analysis, which included our 2 cases.

Systematic review of literature

A systematic review was conducted to evaluate the frequency of intellectual disability, developmental delay, and facial and ocular characteristics in the confirmed cases. The 80 patients were characterized as having either missense mutations (29 patients) or duplications (51 patients) in the *HUWE1* gene. Clinical characteristics of each patient are presented in the Supplementary Tables 1, 2, 3, 4, 5, 6 [3-19].

Results

We report data on 82 patients with the *HUWE1*-Related Intellectual Developmental Disorder, which included our two cases. **Table 1** lists the percentages of ocular, facial, and intellectual/developmental findings in patients with *HUWE1*

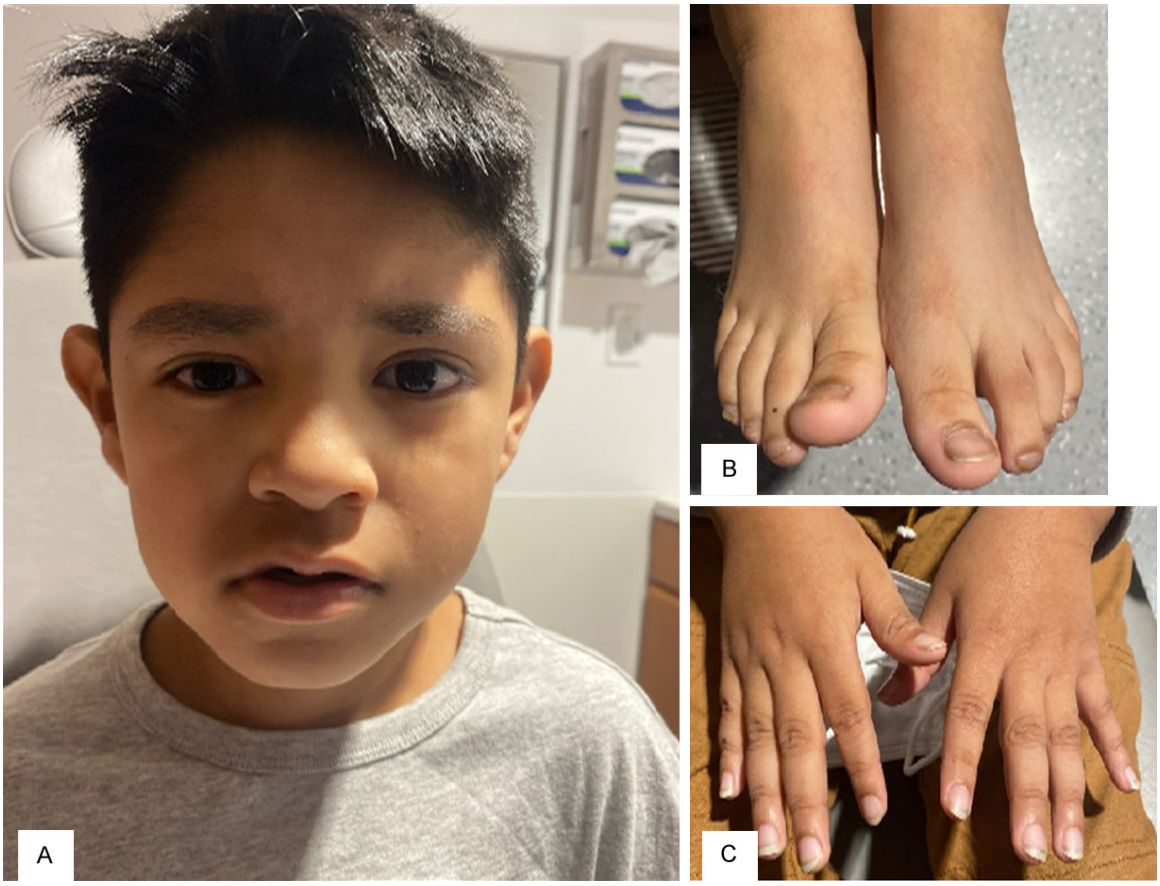

Figure 2. 9-year-old boy with dysmorphic ocular, facial and extremity characteristics. A. Facial features were notable for mild right ptosis, asymmetric facies, long philtrum, thick eyebrows, and thin upper lips. B. Bilaterally elongated toes on the dorsal aspect of feet shown. C. Bilaterally elongated thumbs were present as shown on a view of the dorsal aspect of the hands.

mutations. Ocular and facial manifestations were noted in a higher percentage of patients with missense mutations as compared to patients with duplications in *HUWE1*.

Ocular manifestations

In patients with *HUWE1* missense mutations, the following ocular characteristics were commonly reported: deep set eyes (52%), blepharophimosis (48%), epicanthic folds (41%), strabismus (41%), refraction error (17%), nystagmus (14%), downslanting palpebral fissures (14%), retinopathy (3%). The same characteristics were evaluated in cases with duplications, yielding the following results: downslanting palpebral fissures (15%), epicanthic folds (11%), blepharophimosis (9%), strabismus (5%). The following ocular characteristics were not observed in the duplication group: deep set eyes, retinopathy, nystagmus, and abnormal refraction errors. **Figure 3** summarizes the ocular characteristics of both groups.

Facial manifestations

The following facial characteristics were commonly observed in cases with *HUWE1* missense mutations: broad nasal root or tip/prominent or bulbous nose (52%), thin upper lip (52%), microcephaly (41%), short philtrum (38%), high forehead (28%), full lower lip (24%), hypotelorism (21%), hypertelorism (17%), ear abnormality (low set, cupped, malformed) (17%), long face (14%), small nose (10%). In comparison, these characteristics were observed at the following frequencies in *HUWE1* duplications: ear abnormality (low set, cupped, malformed) (31%), broad nasal root or tip/prominent or bulbous nose (29%), high forehead (15%), long face (11%), short philtrum (7%), hypertelorism (4%), small nose (4%), full

Table 1. Common ocular, facial, intellectual, and developmental findings in patients with HUWE1 mutations

Ocular	Percentage
Blepharophimosis	27%
Epicanthic folds	25%
Deep set eyes	23%
Strabismus	21%
Downslanting palpebral fissure	14%
Refraction error	9%
Nystagmus	7%
Retinopathy	2%
Facial	Percentage
Broad root, nasal tip/prominent or bulbous nose	39%
Ear abnormality (low set, cupped, malformed)	25%
Short philtrum	23%
Thin upper lip	23%
High forehead	21%
Microcephaly	19%
Full lower lip	14%
Long face	13%
Hypotelorism	11%
Hypertelorism	11%
Small nose	7%
Intellectual and Developmental	Percentage
Intellectual Disability	86%
Developmental Delay	70%

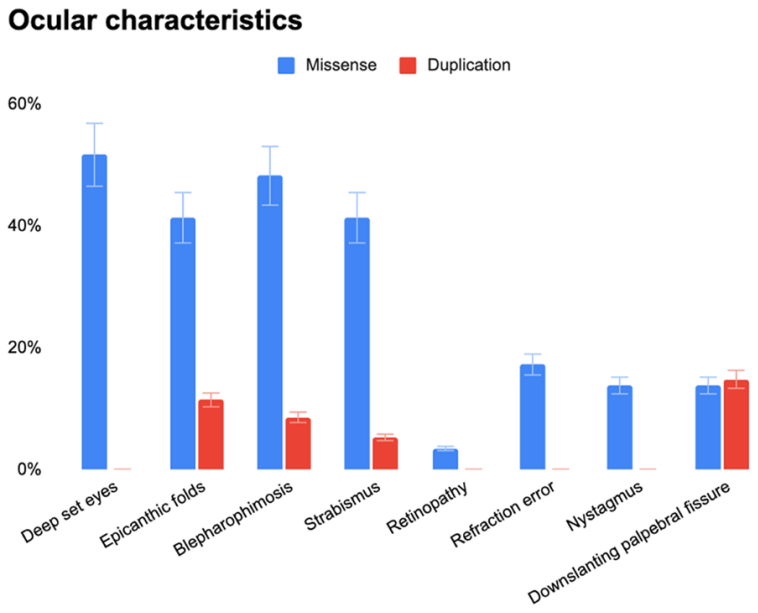

Figure 3. Comparison of ocular manifestations in cases of *HUWE1* missense and duplication.

lower lip (4%), microcephaly (4%). The following facial characteristics were not observed in the duplication group: hypotelorism and thin upper lip. **Figure 4** summarizes the facial characteristics of both groups.

Intellectual disability and developmental delay

Intellectual disability was noted in 90% and developmental delay in 76% of all patients in the missense group. Similar frequencies were observed in the duplication group, with a frequency of 84% intellectual disability and 59% developmental delay. **Figure 5** presents the intellectual and developmental percentages of both groups.

Discussion

We report two cases of individuals affected by *HUWE1*-Related Intellectual Developmental Disorder and present a review of literature of male patients affected by this disorder.

The two patients we report in this paper exhibit clinical phenotypic features including deep set eyes, thin upper lip, refraction error (astigmatism), in addition to intellectual disability and developmental delay. These findings are similar to those reported in the literature [4-6].

Facial dysmorphic features and eye manifestations have been described, but have not been identified as distinctive to this condition. Based on the literature review and clinical findings in our two patients, it is our observation that patients with MRXST present with distinctive features which include broad nasal tip, root, or prominent nose (39%), blepharophimosis (27%), epicanthic folds (25%), ear abnormalities (25%), thin upper lip (23%), and deep set eyes (23%). We also note

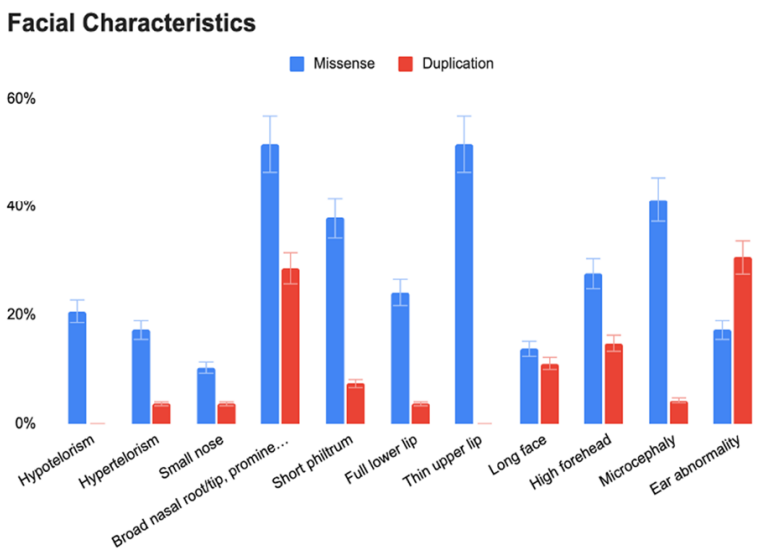

Figure 4. Comparison of facial manifestations in cases of *HUWE1* missense and duplication.

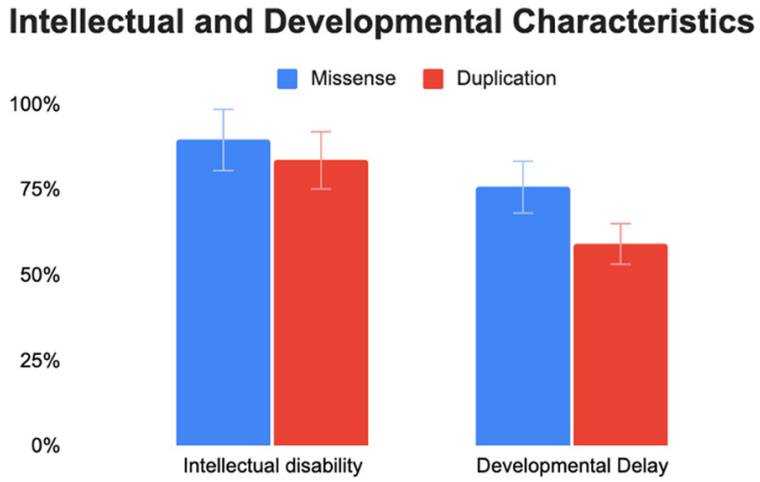

Figure 5. Comparison of intellectual and developmental manifestations in cases of *HUWE1* missense and duplication.

that oculofacial abnormalities are seen more frequently in patients with missense variants than patients with duplications in the *HUWE1* gene. The reason for the higher incidence of ocular and facial phenotypic features in patients with missense mutation has not been identified.

Due to the variability in presentation, incorporating genetic testing can be beneficial to obtain molecular confirmation. Treatment of this condition is supportive and should be individualized and focused on the management of symptoms present.

The biochemical pathways involved in the pathophysiology of MRXST are not yet well understood. Studying the role of *HUWE1* in embryonic neural development may provide additional insight into the development of this condition. Future research could focus on evaluating the dose-dependent effects of *HUWE1* on patient's phenotypic expression.

One of the limitations of this study is that it is an observational study. We also had a limited sample size. There is scope for future studies as more cases are reported in the literature.

Based on our study of previously published case reports, we observe that patients with MRXST have distinctive facial and ocular abnormalities along with intellectual disability. Our two patients presented similarly with intellectual disability, speech and motor delay, and oculofacial features. One should suspect MRXST when these distinctive features are observed in the proper clinical setting. The findings noted in this paper may help clinicians suspect a diagnosis of MRXST when presented with these distinctive ocular and facial features.

Disclosure of conflict of interest

Dr. Natario L Couser: Retrophin, Inc./Travere Therapeutics, Inc. (Clinical Trial), National Cancer Institute/Children's Oncology Group (Clinical Trial), Elsevier (Book editor), Patient-Centered Outcomes Research Institute (PCORI; Advisory Panel on Rare Disease), National Institutes of Health/National Eye Institute (Grant Review Panelist). Sharanya P Deshmukh: no disclosures.

Address correspondence to: Dr. Natario L Couser, Department of Pediatrics, Virginia Commonwealth

University School of Medicine, Children's Hospital of Richmond at VCU, 1000 E. Broad Street, Children's Pavilion, 6th FL, Suite K, Richmond, VA 23298, USA. Tel: 804-828-9315; ORCID: 0000-0001-8713-2097; Fax: 804-628-9544; E-mail: natario.couser@vcuhealth.org

References

[1] Zhao X, D'Arca D, Lim WK, Brahmachary M, Carro MS, Ludwig T, Cardo CC, Guillemot F, Aldape K, Califano A, Iavarone A and Lasorella A. The N-Myc-DLL3 cascade is suppressed by the ubiquitin ligase HUWE1 to inhibit proliferation and promote neurogenesis in the developing brain. Dev Cell 2009; 17: 210-221.

[2] Chen LJ, Xu WM, Yang M, Wang K, Chen Y, Huang XJ and Ma QH. HUWE1 plays important role in mouse preimplantation embryo development and the dysregulation is associated with poor embryo development in humans. Sci Rep 2016; 6: 37928.

[3] Moortgat S, Berland S, Aukrust I, Maystadt I, Baker L, Benoit V, Caro-Llopis A, Cooper NS, Debray FG, Faivre L, Gardeitchik T, Haukanes BI, Houge G, Kivuva E, Martinez F, Mehta SG, Nassogne MC, Powell-Hamilton N, Pfundt R, Rosello M, Prescott T, Vasudevan P, van Loon B, Verellen-Dumoulin C, Verloes A, Lippe CV, Wakeling E, Wilkie AOM, Wilson L, Yuen A, Study D, Low KJ and Newbury-Ecob RA. HUWE1 variants cause dominant X-linked intellectual disability: a clinical study of 21 patients. Eur J Hum Genet 2018; 26: 64-74.

[4] Turner G, Gedeon A and Mulley J. X-linked mental retardation with heterozygous expression and macrocephaly: pericentromeric gene localization. Am J Med Genet 1994; 51: 575-580.

[5] Friez MJ, Brooks SS, Stevenson RE, Field M, Basehore MJ, Adès LC, Sebold C, McGee S, Saxon S, Skinner C, Craig ME, Murray L, Simensen RJ, Yap YY, Shaw MA, Gardner A, Corbett M, Kumar R, Bosshard M, van Loon B, Tarpey PS, Abidi F, Gecz J and Schwartz CE. HUWE1 mutations in Juberg-Marsidi and Brooks syndromes: the results of an X-chromosome exome sequencing study. BMJ Open 2016; 6: e009537.

[6] Santos-Rebouças CB, de Almeida LG, Belet S, Dos Santos SR, Ribeiro MG, da Silva AF, Medina-Acosta E, Dos Santos JM, Gonçalves AP, Bahia PR, Pimentel MM and Froyen G. Novel microduplications at Xp11.22 including HUWE1: clinical and molecular insights into these genomic rearrangements associated with intellectual disability. J Hum Genet 2015; 60: 207-211.

[7] Brooks SS, Wisniewski K and Brown WT. New X-linked mental retardation (XLMR) syndrome with distinct facial appearance and growth retardation. Am J Med Genet 1994; 51: 586-590.

[8] Juberg RC and Marsidi I. A new form of X-linked mental retardation with growth retardation, deafness, and microgenitalism. Am J Hum Genet 1980; 32: 714-722.

[9] Ibarluzea N, Hoz AB, Villate O, Llano I, Ocio I, Martí I, Guitart M, Gabau E, Andrade F, Gener B and Tejada MI. Targeted next-generation sequencing in patients with suggestive X-linked intellectual disability. Genes (Basel) 2020; 11: 51.

[10] Yahia A, Ayed IB, Hamed AA, Mohammed IN, Elseed MA, Bakhiet AM, Guillot-Noel L, Abozar F, Adil R, Emad S, Abubaker R, Musallam MA, Eltazi IZM, Omer Z, Maaroof OM, Soussi A, Bouzid A, Kmiha S, Kamoun H, Salih MA, Ahmed AE, Elsayed L, Masmoudi S and Stevanin G. Genetic diagnosis in Sudanese and Tunisian families with syndromic intellectual disability through exome sequencing. Ann Hum Genet 2022; 86: 181-194.

[11] Paderova J, Drabova J, Holubova A, Vlckova M, Havlovicova M, Gregorova A, Pourova R, Romankova V, Moslerova V, Geryk J, Norambuena P, Krulisova V, Krepelova A, Macek M Sr and Macek M Jr. Under the mask of Kabuki syndrome: elucidation of genetic-and phenotypic heterogeneity in patients with Kabuki-like phenotype. Eur J Med Genet 2018; 61: 315-321.

[12] Paděrová J, Holubová A, Simandlová M, Puchmajerová A, Vlčková M, Malíková M, Pourová R, Vejvalková S, Havlovicová M, Šenkeříková M, Ptáková N, Drábová J, Geryk J, Maver A, Křepelová A and Macek M Jr. Molecular genetic analysis in 14 Czech Kabuki syndrome patients is confirming the utility of phenotypic scoring. Clin Genet 2016; 90: 230-237.

[13] Zhu X, Petrovski S, Xie P, Ruzzo EK, Lu YF, McSweeney KM, Ben-Zeev B, Nissenkorn A, Anikster Y, Oz-Levi D, Dhindsa RS, Hitomi Y, Schoch K, Spillmann RC, Heimer G, Marek-Yagel D, Tzadok M, Han Y, Worley G, Goldstein J, Jiang YH, Lancet D, Pras E, Shashi V, McHale D, Need AC and Goldstein DB. Whole-exome sequencing in undiagnosed genetic diseases: interpreting 119 trios. Genet Med 2015; 17: 774-781.

[14] Froyen G, Corbett M, Vandewalle J, Jarvela I, Lawrence O, Meldrum C, Bauters M, Govaerts K, Vandeleur L, Van Esch H, Chelly J, Sanlaville D, van Bokhoven H, Ropers HH, Laumonnier F, Ranieri E, Schwartz CE, Abidi F, Tarpey PS, Futreal PA, Whibley A, Raymond FL, Stratton MR, Fryns JP, Scott R, Peippo M, Sipponen M, Partington M, Mowat D, Field M, Hackett A,

Marynen P, Turner G and Gécz J. Submicroscopic duplications of the hydroxysteroid dehydrogenase HSD17B10 and the E3 ubiquitin ligase HUWE1 are associated with mental retardation. Am J Hum Genet 2008; 82: 432-443.

[15] Wang Q, Chen P, Liu J, Lou J, Liu Y and Yuan H. Xp11.22 duplications in four unrelated Chinese families: delineating the genotype-phenotype relationship for HSD17B10 and FGD1. BMC Med Genomics 2020; 13: 66.

[16] Demily C, Lesca G, Poisson A, Till M, Barcia G, Chatron N, Sanlaville D and Munnich A. Additive effect of variably penetrant 22q11.2 duplication and pathogenic mutations in autism spectrum disorder: to which extent does the tree hide the forest? J Autism Dev Disord 2018; 48: 2886-2889.

[17] Froyen G, Belet S, Martinez F, Santos-Rebouças CB, Declercq M, Verbeeck J, Donckers L, Berland S, Mayo S, Rosello M, Pimentel MM, Fintelman-Rodrigues N, Hovland R, Rodrigues dos Santos S, Raymond FL, Bose T, Corbett MA, Sheffield L, van Ravenswaaij-Arts CM, Dijkhuizen T, Coutton C, Satre V, Siu V and Marynen P. Copy-number gains of HUWE1 due to replication- and recombination-based rearrangements. Am J Hum Genet 2012; 91: 252-264.

[18] Grams SE, Argiropoulos B, Lines M, Chakraborty P, Mcgowan-Jordan J, Geraghty MT, Tsang M, Eswara M, Tezcan K, Adams KL, Linck L, Himes P, Kostiner D, Zand DJ, Stalker H, Driscoll DJ, Huang T, Rosenfeld JA, Li X and Chen E. Genotype-phenotype characterization in 13 individuals with chromosome Xp11.22 duplications. Am J Med Genet A 2016; 170A: 967-977.

[19] Orivoli S, Pavlidis E, Cantalupo G, Pezzella M, Zara F, Garavelli L, Pisani F and Piccolo B. Xp11.22 microduplications including HUWE1: case report and literature review. Neuropediatrics 2016; 47: 51-56.

Supplementary Table 1. Ocular manifestations in patients with missense *HUWE1* variants

Source	Patient identifier	*HUWE 1* variant	Sex	Deep set eyes	Epicanthic folds	Blepahro-phimosis	Strabismus	Retinopathy	Refraction error	Nystagmus	Upslating palpebral fissure	Downslanting palpebral fissure	Other
[3]	p6	c.1978G>A	M	0	1	1	1	0	0	0	0	0	0
[3]	p8	c.3982A>G	M	1	1	1	1	1	0	0	0	1	0
[3]	p12	c.9581T>C	M	1	1	1	1	0	1	0	0	0	0
[3]	p13	c.12067C>T	M	1	1	1	0	0	0	0	0	0	0
[3]	p14	c.12067C>T	M	1	1	1	0	0	0	0	0	0	0
[3]	p20	c.12885G>C	M	1	1	1	1	0	1	0	0	0	0
[3]	p21	c.12885G>C	M	1	1	1	1	0	1	0	0	0	0
[5]	Juberg Marsidi 1	p.G4310R	M	1	1	1	1	0	0	0	0	0	pale retina
[5]	Juberg Marsidi 2	p.G4310R	M	0	1	1	1	0	0	0	0	0	pale retina
[5]	Juberg Marsidi 3	p.G4310R	M	0	0	1	1	0	0	0	0	0	pale retina
[5]	Juberg Marsidi 4	p.G4310R	M	0	0	1	0	0	0	0	0	0	pale retina
[5]	Brooks et al	c.12928G>C	M	1	1	1	1	0	0	1	0	0	Optic Atrophy, esotropia
[5]	Brooks et al	c.12928G>C	M	1	1	1	1	0	0	1	0	0	0
[5]	Brooks et al	c.12928G>C	M	1	1	1	0	0	0	1	0	0	0
[5]	Family 3	c.12188G>A	M	1	0	0	0	0	0	0	0	0	0
[5]	Family 3	c.12188G>A	M	1	0	0	0	0	1	0	0	0	0
[5]	Froyen A323	12037C > T	M	0	0	0	0	0	0	0	0	0	0
[5]	Froyen A323	12037C > T	M	0	0	0	0	0	0	0	0	0	0
[5]	Froyen A323	12037C > T	M	0	0	0	0	0	0	0	0	0	0
[5]	Froyen A323	12037C > T	M	0	0	0	0	0	0	0	0	0	0
[5]	Isrie	chrX:53581342-53581342 G>A	M	1	0	0	0	0	0	0	0	1	0
[5]	Isrie	chrX:53581342-53581342 G>A	M	0	0	0	0	0	0	0	0	1	0
[9]	Fam ID 1128	c.1125G>T	M	0	0	0	0	0	0	0	0	0	0
[10]	Fam 5	c.12639G>A	M	1	0	0	1	0	0	1	0	0	0
[11]	KLS1	c.328C > T	M	0	0	0	0	0	0	0	0	1	0
[11]	KS10	c.328C>T	M	0	0	0	0	0	0	0	0	0	0
[13]	Trio 99	c.328C>T	M	0	0	0	1	0	0	0	0	0	0
Our Patient	10M	c.12559C>T	M	1	0	0	0	0	0	0	0	0	mild left ptosis, mild tilt optic disc both eyes
Our Patient 2	9M	c.12559C>T	M	0	0	0	0	0	1	0	0	0	mild right ptosis

Supplementary Table 2. Facial manifestations in patients with missense *HUWE1* variants

Source	Patient identifier	*HUWE 1* variant	Sex	Hypo-telorism	Hyper-telorism	Small nose	Broad nasal root, tip/ prominent or bulbous nose	Short philtrum	Full lower lip	Thin upper lip	Long face	High fore-head	Micro-cephaly	Ear abnormality (low set, cupped, malformed)	Other
[3]	p6	c.1978G>A	M	0	1	0	1	0	0	1	0	1	0	0	0
[3]	p8	c.3982A>G	M	1	0	0	1	1	1	0	1	0	0	0	0
[3]	p12	c.9581T>C	M	0	1	1	1	0	0	1	0	1	0	0	anterior flammus naevus
[3]	p13	c.12067C>T	M	0	0	0	1	1	1	0	0	0	0	0	cleft palate, retrognathia, thick columella, narrow mouth
[3]	p14	c.12067C>T	M	0	0	0	1	1	1	0	1	0	0	0	cleft palate
[3]	p20	c.12885G>C	M	0	0	0	1	1	0	1	1	0	0	0	0
[3]	p21	c.12885G>C	M	0	1	0	1	0	0	1	1	1	0	0	0
[5]	Juberg Marsidi 1	p.G4310R	M	1	0	0	1	1	0	1	0	1	1	1	bifrontal narrowing, contractures, deafness
[5]	Juberg Marsidi 2	p.G4310R	M	1	0	0	0	1	0	1	0	1	1	0	deafness
[5]	Juberg Marsidi 3	p.G4310R	M	1	0	0	0	1	0	0	0	1	1	0	deafness
[5]	Juberg Marsidi 4	p.G4310R	M	1	0	0	0	1	0	0	0	1	1	0	deafness
[5]	Brooks et al	c.12928G>C	M	0	0	0	1	1	0	1	0	0	1	0	bifrontal narrowing, contractures, clumsiness, triangular face, low posterior hairline, deafness (1/3)
[5]	Brooks et al	c.12928G>C	M	0	0	0	1	1	0	1	0	0	1	0	0
[5]	Brooks et al	c.12928G>C	M	0	0	0	1	1	0	1	0	0	1	0	0
[5]	Family 3	c.12188G>A	M	0	0	0	1	0	1	0	0	0	1	1	wide mouth, prognathism, thick eyebrows
[5]	Family 3	c.12188G>A	M	0	0	0	1	0	1	0	0	0	1	0	0
[5]	Froyen A323	12037C > T	M	0	0	0	0	0	0	1	0	0	0	0	hypotonia
[5]	Froyen A323	12037C > T	M	0	0	0	0	0	0	0	0	0	0	0	Hypotonia
[5]	Froyen A323	12037C > T	M	0	0	0	0	0	0	0	0	0	0	0	0
[5]	Froyen A323	12037C > T	M	0	0	0	0	0	0	0	0	0	0	0	0
[5]	Isrie	chrX:53581342-53581342 G>A	M	0	1	0	0	0	0	0	0	0	0	0	0
[5]	Isrie	chrX:53581342-53581342 G>A	M	0	1	0	0	0	0	0	0	0	0	0	0
[9]	Fam ID 1128	c.1125G>T	M	0	0	0	0	0	0	0	0	0	0	0	0
[10]	Fam 5	c.12639G>A	M	0	0	1	1	0	1	1	0	1	1	1	sparse eyebrows, broad philtrum
[11]	KLS1	c.328C > T	M	1	0	1	0	0	0	1	0	0	1	1	sparse scalp hair, highly arched eyebrows, broad columnella, micrognathia, depressed nasal bridge, open mouth, long philtrum
[11]	KS10	c.328C>T	M	0	0	0	1	0	1	1	0	0	1	1	arched eyebrows, long palpebral fissure, flat philtrum, small mandible, hypotonia

[13]	Trio 99	c.328C>T	M	0	0	0	0	0	0	0	0	0	0	0	seizures, hearing loss
Our Patient	10M	c.12559C>T	M	0	0	0	0	0	0	1	0	0	0	0	Asymmetric face, long philtrum, thick eyebrows
Our Patient 2	9M	c.12559C>T	M	0	0	0	0	0	0	1	0	0	0	0	Asymmetric face, long philtrum, thick eyebrows

Supplementary Table 3. Intellectual and developmental manifestations in patients with missense *HUWE1* variants

Source	Patient identifier	*HUWE 1* variant	Sex	Intellectual disablity	Developmental delay
[3]	p6	c.1978G>A	M	1	1
[3]	p8	c.3982A>G	M	1	1
[3]	p12	c.9581T>C	M	1	1
[3]	p13	c.12067C>T	M	0	1
[3]	p14	c.12067C>T	M	1	1
[3]	p20	c.12885G>C	M	1	1
[3]	p21	c.12885G>C	M	1	1
[5]	Juberg Marsidi 1	p.G4310R	M	1	1
[5]	Juberg Marsidi 2	p.G4310R	M	1	1
[5]	Juberg Marsidi 3	p.G4310R	M	1	1
[5]	Juberg Marsidi 4	p.G4310R	M	1	1
[5]	Brooks et al	c.12928G>C	M	1	1
[5]	Brooks et al	c.12928G>C	M	1	1
[5]	Brooks et al	c.12928G>C	M	0	1
[5]	Family 3	c.12188G>A	M	1	1
[5]	Family 3	c.12188G>A	M	1	1
[5]	Froyen A323	12037C > T	M	1	0
[5]	Froyen A323	12037C > T	M	1	0
[5]	Froyen A323	12037C > T	M	1	0
[5]	Froyen A323	12037C > T	M	1	0
[5]	Isrie	chrX:53581342-53581342 G>A	M	1	0
[5]	Isrie	chrX:53581342-53581342 G>A	M	1	0
[9]	Fam ID 1128	c.1125G>T	M	1	0
[10]	Fam 5	c.12639G>A	M	1	1
[11]	KLS1	c.328C > T	M	1	1
[11]	KS10	c.328C>T	M	1	1
[13]	Trio 99	c.328C>T	M	0	1
Our Patient	10M	c.12559C>T	M	1	1
Our Patient 2	9M	c.12559C>T	M	1	1

Supplementary Table 4. Ocular manifestations in patients with *HUWE1* duplications

Source	Patient identifier	*HUWE* 1 duplication	Sex	Deep set eyes	Epicanthic folds	Blepahro-phimosis	Stra-bismus	Reti-nopathy	Refraction error	Nystag-mus	Upslating palpebral fissure	Downslanting palpebral fissure	Other
[14]			M	0/8	3/8	3/8	1/11	0	0	0	0	0	0
[6]	611	758 kb	M	0	0	0	0	0	0	0	0	0	0
[6]	3272	905 kb	M	0	0	0	0	0	0	0	0	0	0
[15]		292 kb	M	0	0	0	0	0	0	0	0	0	0
[15]		564 kb	M	0	0	0	0	0	0	0	0	0	0
[15]		1.9 mb	M	0	0	0	0	0	0	0	0	0	0
[15]		2.6 mb	M	0	0	0	0	0	0	0	0	0	0
[16]		1.25 mb	M	0	0	0	0	0	0	0	0	0	0
[17]	F538, II4	1.02 mb	M	0	0	0	0	0	0	0	0	0	unequal pupils
[17]	F538, III5	1.02 mb	M	0	0	0	0	0	0	0	0	0	0
[17]	EX469	472 kb	M	0	0	0	0	0	0	0	0	0	0
[17]	EX469	472 kb	M	0	0	0	0	0	0	0	0	0	0
[17]	FTD	1.04 mb	M	0	0	0	0	0	0	0	0	0	0
[17]	AU88848	931 kb	M	0	0	0	0	0	0	0	0	0	0
[17]	AU88848	931 kb	M	0	0	0	0	0	0	0	0	0	0
[17]	SB1	430 kb	M	0	0	0	0	0	0	0	0	1	prominent supraorbital ridge
[17]	SB1	430 kb	M	0	0	0	0	0	0	0	0	1	prominent supraorbital ridge
[17]	SB1	430 kb	M	0	0	0	0	0	0	0	0	1	prominent supraorbital ridge
[17]	ON1	730 kb	M	0	0	0	0	0	0	0	0	0	microphthalmos
[17]	HF	73 kb	M	0	0	0	0	0	0	0	0	0	0
[17]	VS1	73 kb	M	0	0	0	0	0	0	0	0	0	0
[18]	1	553 kb	M	0	0	0	0	0	0	0	0	0	bilateral pterygia of the eyes
[18]	7	771 kb	M	0	0	0	0	0	0	0	0	0	0
[18]	10	61 kb	M	0	0	0	1	0	0	0	0	1	0
[18]	11	513 kb	M	0	0	0	0	0	0	0	0	0	small palpebral fissure
[18]	12	513 kb	M	0	0	0	0	0	0	0	0	0	0
[18]	13	4614 kb	M	0	0	0	0	0	0	0	0	0	0
[19]	0	363 kb	M	0	1	0	0	0	0	0	0	0	brief, <5 min self resolving episode of ocular revulsion at age 7

Supplementary Table 5. Facial manifestations in patients with *HUWE1* duplications

Source	Patient identifier	*HUWE 1* duplication	Sex	Hypo-telorism	Hyper-telorism	Small nose	Broad nasal root, tip/ prominent or bulbous nose	Short philtrum	Full lower lip	Thin upper lip	Long face	High fore-head	Micro-cephaly	Ear abnormality (low set, cupped, malformed)	Other
[14]		0	0	0	0	0	44993	0	0	0/9	0	0	44945	44993	0
[6]	611	758 kb	M	0	1	0	1	0	0	0	1	0	1	1	brachycephaly, enophtalmia, prominent supraorbital ridges, high arched palate, squared teeth,
[6]	3272	905 kb	M	0	0	0	1	1	0	0	0	0	0	1	flat and 'triangular' facies, malar hypoplasia, prognathism, prominent nasal root, broad nose, enophthalmia, short philtrum, short oral frenula, hypertrophied alveolar ridges, squared small teeth, separated superior central incisors. Normal set ears with malformed auricles,
[15]		292 kb	M	0	0	0	0	0	0	0	0	0	0	0	0
[15]		564 kb	M	0	0	0	0	0	0	0	0	0	0	0	0
[15]		1.9 mb	M	0	0	0	0	0	0	0	0	0	0	0	0
[15]		2.6 mb	M	0	0	0	0	0	0	0	0	0	0	0	0
[16]		1.25 mb	M	0	0	0	0	0	0	0	0	0	0	0	0
[17]	F538, II4	1.02 mb	M	0	0	0	0	0	0	0	0	1	0	1	0
[17]	F538, III5	1.02 mb	M	0	0	0	0	0	0	0	0	0	0	0	Macrocephaly, stutter
[17]	EX469	472 kb	M	0	0	0	0	0	0	0	0	0	0	0	cafe au lait, poor speech
[17]	EX469	472 kb	M	0	0	0	0	0	0	0	0	0	0	0	cafe au lait, poor speech
[17]	FTD	1.04 mb	M	0	0	0	1	0	0	0	0	0	0	1	some teeth absent
[17]	AU88848	931 kb	M	0	0	0	0	0	0	0	0	0	0	0	0
[17]	AU88848	931 kb	M	0	0	0	0	0	0	0	0	0	0	0	0
[17]	SB1	430 kb	M	0	0	0	0	0	0	0	0	0	0	0	0
[17]	SB1	430 kb	M	0	0	0	0	0	0	0	0	0	0	0	0
[17]	SB1	430 kb	M	0	0	0	0	0	0	0	0	0	0	0	0
[17]	ON1	730 kb	M	0	0	0	1	0	0	0	0	0	0	1	high arched palate, square small teeth, micrognathism
[17]	HF	73 kb	M	0	0	0	0	0	0	0	0	0	0	0	epilepsy
[17]	VS1	73 kb	M	0	0	0	0	0	0	0	0	0	0	0	0
[18]	1	553 kb	M	0	0	0	0	1	0	0	1	1	0	1	high and narrow palate, large mouth which is often open and droolin
[18]	7	771 kb	M	0	0	0	0	0	0	0	0	1	0	0	small face
[18]	10	61 kb	M	0	0	0	1	0	0	0	0	0	0	0	hypotonia
[18]	11	513 kb	M	0	0	0	1	0	0	0	0	0	0	0	mild sinophyris, prominent metopic suture, high palate, flat philtrum, midline gap w prominent, serated front teeth
[18]	12	513 kb	M	0	0	0	1	0	0	0	0	1	0	0	high palate, triangular face, midline gap w prominent, serated front teeth

[18]	13	4614 kb	M	0	0	0	0	0	0	0	1	0	0	1	bitemporal narrowing, hypotonia
[19]	0	363 kb	M	0	0	1	0	0	1	0	0	0	0	1	rounded head, bitemporal narrowing, epicanthal folds, flat nasal bridge, full lips, upper lip eversion, and mildly low-set ears with thickened helix and large lobes ([**Figure 1**]).

Supplementary Table 6. Intellectual and developmental manifestations in patients with *HUWE1* duplications

Source	Patient identifier	*HUWE 1* duplication	Sex	Intellectual disablity	Developmental delay
[14]		0	0	45277	?
[6]	611	758 kb	M	1	1
[6]	3272	905 kb	M	1	1
[15]		292 kb	M	1	1
[15]		564 kb	M	1	1
[15]		1.9 mb	M	1	1
[15]		2.6 mb	M	1	1
[16]		1.25 mb	M	0	speech delay
[17]	F538, II4	1.02 mb	M	1	0
[17]	F538, III5	1.02 mb	M	1	0
[17]	EX469	472 kb	M	1	0
[17]	EX469	472 kb	M	1	0
[17]	FTD	1.04 mb	M	1	1
[17]	AU88848	931 kb	M	1	0
[17]	AU88848	931 kb	M	1	0
[17]	SB1	430 kb	M	1	1
[17]	SB1	430 kb	M	1	0
[17]	SB1	430 kb	M	1	0
[17]	ON1	730 kb	M	1	1
[17]	HF	73 kb	M	1	speech
[17]	VS1	73 kb	M	1	seizures, hearing loss
[18]	1	553 kb	M	1	1
[18]	7	771 kb	M	1	1
[18]	10	61 kb	M	0	1
[18]	11	513 kb	M	0	1
[18]	12	513 kb	M	0	1
[18]	13	4614 kb	M	0	1
[19]	0	363 kb	M	1	1