HHS Public Access

Author manuscript

Am J Med Genet A. Author manuscript; available in PMC 2018 October 30.

Published in final edited form as:

Am J Med Genet A. 2017 October ; 173(10): 2697–2702. doi:10.1002/ajmg.a.38393.

Cystic kidneys in fetal Walker-Warburg Syndrome with *POMT2* mutation: Intrafamilial phenotypic variability in four siblings and review of literature

Marwa M. Nabhan[1,2], **Nour ElKhateeb**[3], **Daniela A. Braun**[4], **Sungho Eun**[4], **Sahar N. Saleem**[5], **Heon Yung Gee**[4,6], **Friedhelm Hildebrandt**[4], and **Neveen A. Soliman**[1,2]

[1]Department of Pediatrics, Centre of Pediatric Nephrology & Transplantation, Kasr Al Ainy School of Medicine, Cairo University, Cairo, Egypt

[2]Egyptian Group for Orphan Renal Diseases (EGORD), Cairo, Egypt

[3]Department of Pediatrics, Centre of Pediatric Neurology & Metabolic diseases, Kasr Al Ainy School of Medicine, Cairo University, Cairo, Egypt

[4]Department of Medicine, Boston Children's Hospital, Harvard Medical School, Boston, Massachusetts, USA

[5]Department of Radiology, Kasr Al Ainy School of Medicine, Cairo University, Cairo, Egypt

[6]Department of Pharmacology, Brain Korea 21 PLUS Project for Medical Sciences, Yonsei University College of Medicine, Seoul, Republic of Korea

Abstract

Walker-Warburg syndrome (WWS) is a severe form of congenital muscular dystrophy (CMD) secondary to α-dystroglycanopathy with muscle, brain and eye abnormalities often leading to death in the first weeks of life. It is transmitted in an autosomal recessive pattern, and has been linked to at least fifteen different genes; including protein O-mannosyltransferase 1 (*POMT1*), protein O-mannosyltransferase 2 (*POMT2*), protein O-mannose beta-1,2-N acetylglucosaminyltransferase (*POMGNT1*) gene, the fukutin (*FKTN*) gene, the fukutin-related protein (*FKRP*) gene, the *LARGE* gene, the isoprenoid synthase domain-containing (*ISPD*) gene and other genes. We report on a family having four consecutive siblings affected by this condition with lethal outcome in three of them, and terminated pregnancy of the fourth based on antenatal fetal MRI complex brain and kidney anomalies that heralded proper and deep clinical phenotyping. The diagnosis of WWS was suggested based on the unique collective phenotype comprising neurological involvement in the form of lissencephaly, subcortical/subependymal heterotopia and cerebellar hypoplasia shared by all four siblings, microphthalmia in one sibling, and large cystic kidneys in the fetus and another sibling. Other unshared neurological abnormalities included hydrocephalus and Dandy-Walker malformation. By whole exome sequencing of the proband fetus, we identified a highly conserved missense mutation in the *POMT2* gene that is known to cause congenital muscular dystrophy-dystroglycanopathy with

Informed consent statement: The reported family provided informed written consent about personal and medical data collection.

Conflict-of-interest statement: All Authors have no conflict of interest related to the manuscript.

brain and eye anomalies, and Walker-Warburg syndrome. In conclusion, the heterogenous clinical presentation in the four affected siblings of this consanguineous family with *POMT2* mutation expands the current clinical spectrum of *POMT2* associated WWS to include large cystic kidneys; and further confirms intra-familial variability in terms of brain, kidney, and eye anomalies.

Introduction

Congenital muscular dystrophies (CMDs) are both clinically and genetically diverse group of muscle disorders, which are characterized by congenital hypotonia, delayed motor milestones and progressive muscle weakness starting early in life, along with dystrophic changes on muscle biopsy. Clinical classification of CMDs has been updated due to the recent advances in the discovery of their molecular basis, with current classification greatly based on their molecular and biochemical characteristics. [1] Most of the different genes involved in the pathogenesis of CMDs are related to the function of the dystrophin-glycoproteins complex (DGC) in the sarcolemma, leading to abnormalities of extracellular matrix proteins or defective glycosylation of alpha dextroglycan. [2] Defects in the DGC appear to play critical roles in several muscular dystrophies due to disruption of basement membrane organization. [3] Alpha-dystroglycan is part of the dystrophin-glycoprotein complex. It is a cell surface receptor for matrix and synaptic proteins such as laminins, agrin, perlecan, neurexin, and pikachurin. [4] It interacts with a transmembrane protein beta dystroglycan, which in turn binds to intracellular dystrophin. [5], while in the extracellular matrix it binds to laminin and other tissue specific extracellular matrix proteins. [6] The binding activity of Alpha-dystroglycan depends on a O-mannosyl glycosylation process, and abnormal glycosylation leads to reduced binding activity and impaired connection between the basement membrane and cytoskeleton. [7,8]

Alpha-dystroglycanopathies (A-DGP) are a group of muscular dystrophies characterized by abnormal glycosylation of α-dystroglycan (A-DG). [9] They include a wide spectrum ranging from the most severe Walker-Warburg syndrome, muscle-eye-brain disease, Fukuyama congenital muscular dystrophy, which show a combination of congenital muscular dystrophy with structural abnormalities in the brain and eyes, to the mildest phenotypes presenting as adult-onset limb-girdle muscular dystrophy with no central nervous system involvement. There is no clear genotype-phenotype correlation, as in the majority of cases the defective gene cannot be predicted from the clinical phenotype. [10,11]

Walker-Warburg syndrome (WWS) is a severe form of α-dystroglycanopathies (a subtype of CMD), and most children die before the age of three years. [12] The four constant clinical features of this syndrome include type II (cobble stone) lissencephaly, cerebellar malformation, retinal abnormalities and CMD. Other frequent anomalies include ventricular dilatation with or without hydrocephalus and anterior chamber eye anomalies. Dandy-Walker malformation associated with posterior encephalocele, microphthalmia, slit-like ventricles, ocular colobomas, congenital cataracts, cleft lip/palate and genital anomalies in males have also been described with this syndrome before. In 1989, Dobyns and colleagues tried to put diagnostic criteria for WWS by reviewing data on 63 patients. They proposed

that the presence of the four constant features mentioned above comprise necessary and sufficient diagnostic criteria for WWS. [13]

Renal involvement in WWS has not been described comprehensively in the literature. An earlier report on three prenatally diagnosed WWS cases describes kidney autopsy findings in the third fetus as renal cysts in addition to stenosis of the pyelo-ureteral junction of the right kidney. [14] Recently, pathology reports identified unilateral kidney agenesis or cystic kidneys as possible associations. [15] Also, multicystic left kidney was described in a fetus with WWS and *ISPD* gene mutation. [16]

The overall incidence of this rare disease is unknown. An incidence rate of 1.2 per 100,000 live births has been reported in north-eastern Italy. [17]

More than 15 causative genes associated with α-dystroglycanopathies have been identified and include POMT1, POMT2, POMGnT1, fukutin, FKRP, LARGE, ISPD, GTDC2 (POMGnT2), DAG1, TMEM5, B3GALNT2, SGK196 (POMK), B3GNT1 (B4GAT1), GMPPB, DOLK, DPM1, DPM2 and DPM3. [9]

The co-expression of protein O-mannosyltransferase 1 (POMT1) and POMT2 catalyzes the initial step of O-mannosylation of alpha-dystroglycan within the endoplasmic reticulum, in which a mannosyl residue is transferred from dolichyl phosphate mannose (Dol-P-Man) to Ser/Thr residues in alpha-DG. *POMT1* or *POMT2* gene mutations lead to formation of non-functional POMT enzyme complexes; as a result glycosylation of α-dystroglycan is impaired. [18] While POMGnT1 acts during the second step in the Golgi apparatus. [19] On the other hand, Fukutin and LARGE are involved in post-phosphoryl modification of O-mannnose on a-DG. [7,20]

Case Report

We report on a family with genetically-confirmed diagnosis of Walker-Warburg syndrome. This family with previous three sibling deaths was referred to the Egyptian Group for Orphan Renal Diseases when the mother was pregnant with the 4th affected fetus, a pregnancy that was shortly thereafter terminated given that the prenatal MRI detected complex anomalies. This was a highly inbred family and parents were first cousins. Four generation family pedigree is illustrated in Figure. 1.

Most of the clinical data we could get on the previously affected siblings had been retrieved from case note reviews, as well as careful interpretation of their neuroimaging studies which represent the very wide phenotypic spectrum of abnormalities seen in WWS with classical intrafamilial variability. These findings are summarized in Table. 1, and the radiologic features are demonstrated in Figures 2 & 3.

Sibling 1

The first affected sibling was a female. Her brain CT showed marked hydrocephalic changes (due to Dandy-Walker malformation), with flat and markedly thinned cerebral cortex (lissencephaly), containing multiple irregular subcortical and subependymal heterotopic foci, associated with cerebellar hypoplasia (more pronounced in the vermis than in the

hemispheres) and a retrocerebellar cyst. Left microphthalmia was also evident. She had large cystic kidneys and died shortly after birth while in renal failure.

Sibling 2

A male sibling whose brain CT images showed quite similar changes to his elder sister in the form of marked hydrocephalic changes (due to Dandy-Walker malformation), with flat and markedly thinned cerebral cortex, containing multiple irregular subcortical and subependymal heterotopic foci, associated with cerebellar hypoplasia (more pronounced in the vermis than in the hemispheres) and a retrocerebellar cyst.

Sibling 3

What stands out this male sibling from his elder siblings is the strikingly abnormal cortical thickening, an irregular severely reduced sulcation and abnormal signal intensity of the white matter. Dilated frontal horns of lateral ventricles, with left frontal colpocephaly and also an occipital encephalocele is seen. Yet, he also shared some changes including multiple irregular subcortical and subependymal heterotopic foci associated with cerebellar hypoplasia (more pronounced in the vermis than in the hemispheres) and a retrocerebellar cyst.

Sibling 4

This male proband had abnormal cortical thickening with an irregular and severely reduced sulcation, abnormal signal intensity of the white matter and dilated frontal horns of lateral ventricles with left occipital colpocephaly (similar to sibling 3), associated with common features to the 4 patients including multiple irregular subcortical and subependymal heterotopic foci associated with cerebellar hypoplasia (more pronounced in the vermis than in the hemispheres) and a retrocerebellar cyst. His MRI revealed also bilateral renal cysts.

Whole-exome sequencing

Whole exome sequencing (WES) and mutation calling were performed as described previously. [21] We performed homozygosity mapping based on variants detected in WES using the Homozygosity Mapper (http://www.homozygositymapper.org/). [22] Homozygosity mapping in the 4th affected sibling (A3831–24) yielded segments of homozygosity by descent with a cumulative genomic length of approximately 345.4 Mb (Supplementary Figure 4). Following variant filtering by homozygosity mapping and WES, 5 rare missense variants in *POMT2*, *GNA15*, *PNPT1*, *CYP2S1*, and *MBD3L2* remained (Supplemental Tables 1 and 2). All of the mutations are not reported as a single nucleotide polymorphism in the dbSNP (http://www.ncbi.nlm.nih.gov/SNP/), the Exome Variant Server (http://evs.gs.washington.edu/EVS/), or Exome Aggregation Consortium (http://exac.broadinstitute.org/) databases. *POMT2* and *PNPT1* have associated diseases in OMIM (Online Mendelian Inheritance in Man, http://omim.org/), whereas *GNA15*, *CYP2S1*, and *MBD3L2* are not associated with any disease. *POMT2* mutations are associated with muscular dystrophy-dystroglycanopathy (MIM 613150, 613156, and 613158), whereas *PNPT1* mutations are associated with deafness (MIM 614934). Based on the clinical

phenotypes of A3831–24, the mutation in *POMT2* seems to be responsible for the disease in this family.

Discussion

The family we are reporting on here shows a heterogeneous affection of four consecutive siblings with Walker-Warburg syndrome including a diverse spectrum of manifestations. We managed to genetically confirm the diagnosis in the 4th affected case where WES identified a highly conserved missense mutation in the *POMT2* gene. Given the severe clinical phenotype and the lethal course of the disease in four siblings, we best categorize them to have WWS rather than the less severe form of Muscle-Eye-Brain disease, which has a longer survival.

The 4 affected siblings showed variable neurological, renal and ophthalmologic involvement. They all shared lissencephaly with subcortical heterotopia and cerebellar hypoplasia, which are two constant features of WWS. Hydrocephalus with Dandy-Walker malformation was present in three and occipital encephalocele in one of them. The 3rd and 4th siblings shared the presence of cortical thickening, abnormal white matter intensity and colpocephaly (denoting agenesis of corpus callosum), which were not present in the elder 2 siblings.

The association between *POMT2* mutations and CNS malformations not included in the constant features of WWS such as Dandy-Walker malformation with resultant hydrocephalus [23], encephaloceles, white matter abnormalities and corpus callosum abnormalities [10,24] has been previously reported in literature, with different mutations in *POMT2* producing different combinations of CNS malformations.

Eye abnormalities are also among the constant features of WWS and the oldest sister in this family had microphthalmia as evident in her brain CT images, nevertheless we cannot exclude any retinal involvement based on data retrieved from case note reviews per se. Unilateral microphthalmia was reported before in a girl with *POMT2 related* WWS, born of consanguineous Moroccan parents, and in many cases with *POMT1* related WWS as well. [25, 26]

This variable constellation of brain and eye anomalies in the four affected siblings highlights the intra-familial variability which is not uncommon in many of the genetic disorders.

The fourth affected sibling had been diagnosed antenatally to have renomegaly with cysts, a shared feature with his sister who was also reported to have large cystic kidneys and renal failure dying shortly after birth. To the best of our knowledge, this is the first report of renomegaly with cysts associated with *POMT2* mutations since the gene was first uncovered in 3 unrelated WWS families by van Reeuwijk and colleagues in 2005. [26] Interestingly, even though cystic renal involvement has been reported in the context of many other well defined syndromes, yet none was identified in cases with *POMT2* related WWS described by either Mercuri et al., or Yanagisawa et al. [27, 28, 29] We hereby add the association of renal cystic disease to expand the spectrum of *POMT2*-associated WWS associated manifestations.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgment:

We sincerely thank the family for sharing medical data and images of their affected siblings.

References

1. Reed UC. 2009 Congenital muscular dystrophy: Part 1: a review of phonotypical and diagnostic aspects. Arq Neuropsiquiatr 67(1):144–168. [PubMed: 19330236]
2. Kaplan JC, Harmoun D. 2014 The 2015 version of the gene table of monogenic neuromuscular disorders (nuclear genome only). Neuromusc Disord 24(12):1123–53. [PubMed: 25625149]
3. Williamson RA, Henry MD, Daniels KJ, Hrstka RF, Lee JC, Sunada Y, Ibraghimov- Beskrovnaya O, Campbell KP. 1997 Dystroglycan is essential for early embryonic development: disruption of Reichert's membrane in Dag1-null mice. Hum Mol Genet 6:831–841. [PubMed: 9175728]
4. Kanagawa M 2014 Dystroglycan glycosylation and its involvement in muscular dystrophy. Trends Glycosci. Glycotech 26:41–57.
5. Barresi R & Campbell KP2006 Dystroglycan: from biosynthesis to pathogenesis of human disease. J. Cell Sci 119:199–207. [PubMed: 16410545]
6. Wallace SE, Conta JH, Winder TL, Willer T, Eskuri JM, Haas R, Patterson K, Campbell KP, Moore SA, Gospe SM. 2014 Novel missense mutation in POMT1 modulates the severe congenital muscular dystrophy phenotype associated with POMT1 nonsense mutations. Neuromuscul Disord 24(4): 312–320. [PubMed: 24491487]
7. Yoshida-Moriguchi T, Yu L, Stalnaker SH, Davis S, Kunz S, Madson M, Oldstone MB, Schachter H, Wells L, Campbell KP. 2010 O-mannosyl phosphorylation of alpha-dystroglycan is required for laminin binding. Science 327:88–92. [PubMed: 20044576]
8. Michele DE, Barresi R, Kanagawa M, Saito F, Cohn RD, Satz JS, Dollar J, Nishino I, Kelley RI, Somer H, Straub V, Mathews KD, Moore SA, Campbell KP. 2002 Post-translational disruption of dystroglycan-ligand interactions in congenital muscular dystrophies. Nature 418:417–22. [PubMed: 12140558]
9. Ohtsuka Y, Kanagawa M, Yu CC, Ito C, Chiyo T, Kobayashi K, Okada T, Takeda S, Toda T. 2015 Fukutin is prerequisite to ameliorate muscular dystrophic phenotype by myofiber-selective LARGE expression. Sci Rep 5: 8316. [PubMed: 25661440]
10. Godfrey C, Clement E, Mein R, Brockington M, Smith J, Talim B, Straub V, Robb S, Quinlivan R, Feng L, Jimenez-Mallebrera C, Mercuri E, Manzur AY, Kinali M, Torelli S, Brown SC, Sewry CA, Bushby K, Topaloglu H, North K, Abbs S, Muntoni F. 2007 Refining genotype phenotype correlations in muscular dystrophies with defective glycosylation of dystroglycan. Brain 130, 2725–35. [PubMed: 17878207]
11. Godfrey C, Foley AR., Clement E & Muntoni F 2011 Dystroglycanopathies: coming into focus. Curr. Opin. Genet. Dev 21: 278–85. [PubMed: 21397493]
12. Vajsar J, Schachter H. 2006 Walker-Warburg syndrome. Orphanet Journal of Rare Diseases 1:29. [PubMed: 16887026]
13. Dobyns WB, Pagon RA, Armstrong D, Curry CJ, Greenberg F, Grix A, Holmes LB, Laxova R, Michels VV, Robinow M, Zimmerman RL, Opitz JM, Renolds JF. 1989 Diagnostic criteria for Walker-Warburg syndrome. Am J Med Genet 32(2):195–210. [PubMed: 2494887]
14. Gasser B, Lindner V, Dreyfus M, Feidt X, Leissner P, Treisser A, Stoll C. 1998 Prenatal diagnosis of Walker-Warburg syndrome in three sibs. Am J Med Genet 5;76(2):107–10. [PubMed: 9511971]
15. Gilbert-Barness E, Spicer DE, Steffensen TS. Renal system. In: Handbook of Pediatric Autopsy Pathology (2nd edition) Springer Science & Business Media 2013: 391–432.
16. Trkova M, Krutilkova V, Smetanova D, Becvarova V, Hlavova E, Jencikova N, Hodacova J, Hnykova L, Hroncova H, Horacek J, Stejskal D. 2015 *ISPD* gene homozygous deletion identified

by SNP array confirms prenatal manifestation of Walker-Warburg syndrome. Eur J Med Genet 58(8):372–5. [PubMed: 26087224]

17. Mostacciuolo ML, Miorin M, Martinello F, Angelini C, Perini P, Trevisan CP. 1996 Genetic epidemiology of congenital muscular dystrophy in a sample from the north-east Italy. Hum Genet 97:277–79. [PubMed: 8786062]
18. Manya H, Chiba A, Yoshida A, Wang X, Chiba, Jigami Y, Margolis RU, Endo T 2004 Demonstration of mammalian protein O-mannosyltransferase activity: coexpression of POMT1 and POMT2 required for enzymatic activity. Proceedings of the National Academy of Sciences of the United States of America 101:500–5. [PubMed: 14699049]
19. Yoshida A, Kobayashi K, Manya H, Taniguchi K, Kano H, Mizuno M, Inazu T, Mitsuhashi H, Takahashi S, Takeuchi M, Herrmann R, Straub V, Talim B, Voit T, Topaloglu H, Toda T, Endo T. 2001 Muscular dystrophy and neuronal migration disorder caused by mutations in a glycosyltransferase, POMGnT1. Dev Cell 1:717–24. [PubMed: 11709191]
20. Kuga A, Kanagawa M, Sudo A, Chan YM, Tajiri M, Manya H, Kikkawa Y, Nomizu M, Kobayashi K, Endo T, Lu QL, Wada Y, Toda T. 2012 Absence of post-phosphoryl modification in dystroglycanopathy mouse models and wild-type tissues expressing non-laminin binding form of α dystroglycan. J. Biol. Chem 287, 9560–67. [PubMed: 22270369]
21. Gee HY, Otto EA, Hurd TW, Ashraf S, Chaki M, Cluckey A, Vega-Warner V, Saisawat P, Diaz KA, Fang H,Kohl S, Allen SJ, Airik R, Zhou W, Ramaswami G, Janssen S, Fu C, Innis JL, Weber S, Vester U, Davis EE,Katsanis N, Fathy HM, Jeck N, 7, Klaus G, Nayir A, Rahim KA, Al Attrach I, Al Hassoun I, Ozturk S, Drozdz D, Helmchen U, O'Toole JF, Attanasio M, Lewis RA, Nürnberg G, Nürnberg P, Washburn J, MacDonald J, Innis JW, Levy S, Hildebrandt F. 2014 Whole-exome resequencing distinguishes cystic kidney diseases from phenocopies in renal ciliopathies. Kidney Int 85(4):880–7. [PubMed: 24257694]
22. Seelow D, Schuelke M, Hildebrandt F & Nurnberg P 2009 HomozygosityMapper—an interactive approach to homozygosity mapping. Nucleic acids research 37:593–99.
23. Abumansour IS, Al Sulmi E, Chodirker BN, Hunt JC. 2015 Prenatal Diagnosis of Walker-Warburg Syndrome Using Single Nucleotide Polymorphism Array: A Clinical Experience from Three Related Palestinian Families with Congenital Hydrocephalus. AJP Rep 5(2):e116–20. Epub 2015 Apr 27 doi: 10.1055/s-0035-1549298. [PubMed: 26495167]
24. Devisme L, Bouchet C, Gonzalès M, Alanio E, Bazin A, Bessières B, Bigi N, Blanchet P, Bonneau D, Bonnières M, Bucourt M, Carles D, Clarisse B, Delahaye S, Fallet-Bianco C, Figarella-Branger D, Gaillard D, Gasser B, Delezoide AL, Guimiot F, Joubert M, Laurent N, Laquerrière A, Liprandi A, Loget P, Marcorelles P, Martinovic J, Menez F, Patrier S, Pelluard F, Perez MJ, Rouleau C, Triau S, Attié-Bitach T, Vuillaumier-Barrot S, Seta N, Encha-Razavi F. 2012 Cobblestone lissencephaly: neuropathological subtypes and correlations with genes of dystroglycanopathies. Brain 135(Pt 2):469–82. [PubMed: 22323514]
25. Dobyns WB, Pagon RA, Armstrong D, Curry CJ, Greenberg F, Grix A, Holmes LB, Laxova R, Michels VV, Robinow M, Zimmerman RL, Opitz JM, Renolds JF. 1989 Diagnostic criteria for Walker-Warburg syndrome. Am J Med Genet 32(2):195–210. [PubMed: 2494887]
26. van Reeuwijk J, Janssen M, van den Elzen C, Beltran-Valero de Bernabé D, Sabatelli P, Merlini L, Boon M, Scheffer H, Brockington M, Muntoni F, Huynen MA, Verrips A, Walsh CA, Barth PG, Brunner HG, van Bokhoven H. 2005 POMT2 mutations cause alpha-dystroglycan hypoglycosylation and Walker-Warburg syndrome. J Med Genet 42: 907–912. [PubMed: 15894594]
27. Soliman NA, Nabhan MM, Bazaraa HM, Badr AM, Shaheen M. 2014 Clinical and ultrasonographical characterization of childhood cystic kidney diseases in Egypt. Renal Failure 36 (5): 694–700. [PubMed: 24655010]
28. Mercuri E, D'Amico A, Tessa A, Berardinelli A, Pane M, Messina S, van Reeuwilk J, Bertini E, Muntoni F, Santorelli FM. 2006 POMT2 mutation in a patient with 'MEB-like' phenotype. Neuromuscul Disord 16:446–448. [PubMed: 16701995]
29. Yanagisawa A, Bouchet C, Van den Bergh PY, Cuisset JM, Viollet L, Leuturcq F, Romero NB, Quijano-Roy S, Fardeau M, Seta N, Guicheney P. 2007 New POMT2 mutations causing congenital muscular dystrophy; identification of a founder mutation. Neurology 69:1254–1260. [PubMed: 17634419]

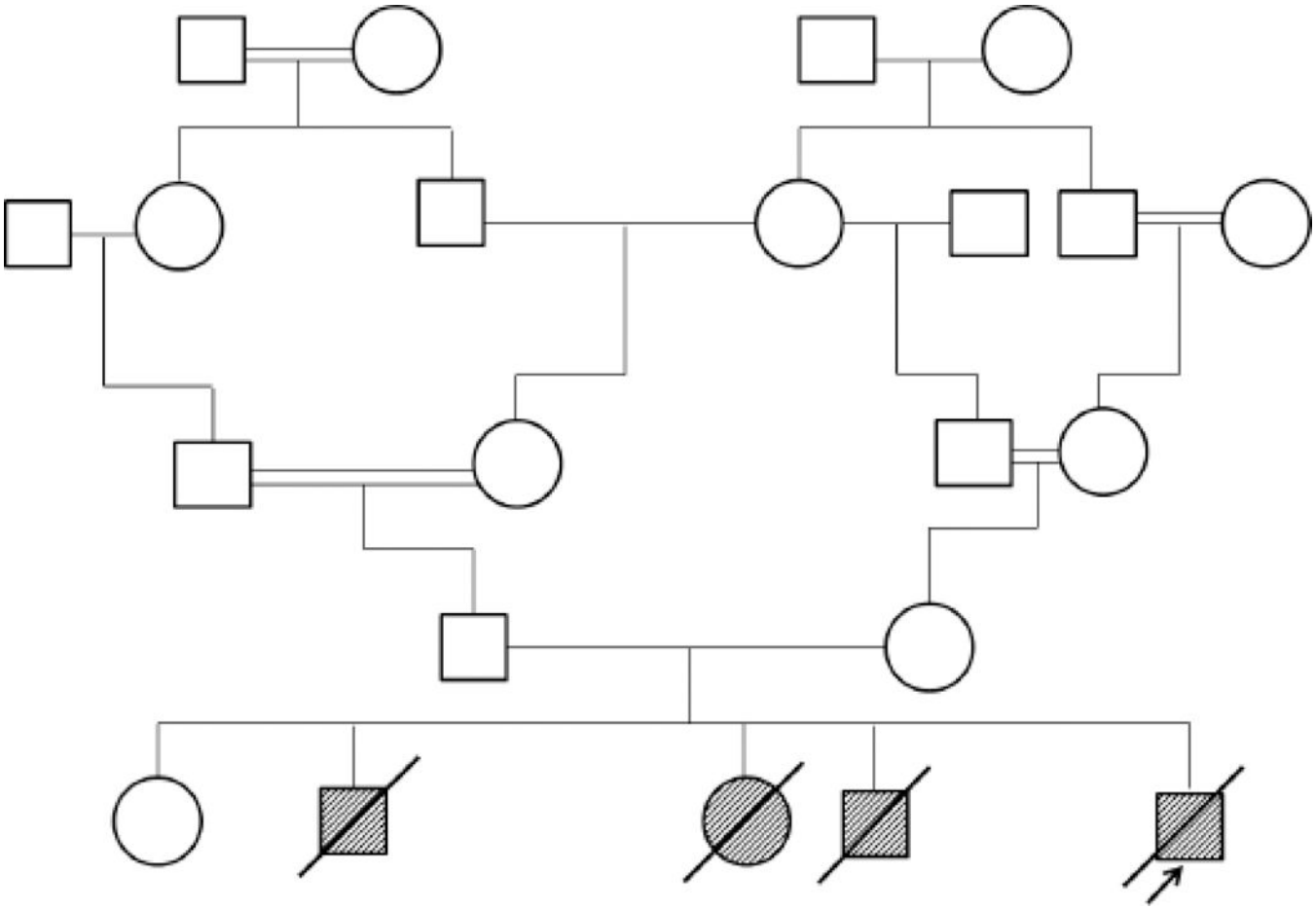

Figure (1):
Family chat of the highly inbred family and the 4 affected siblings with only one living normal girl.

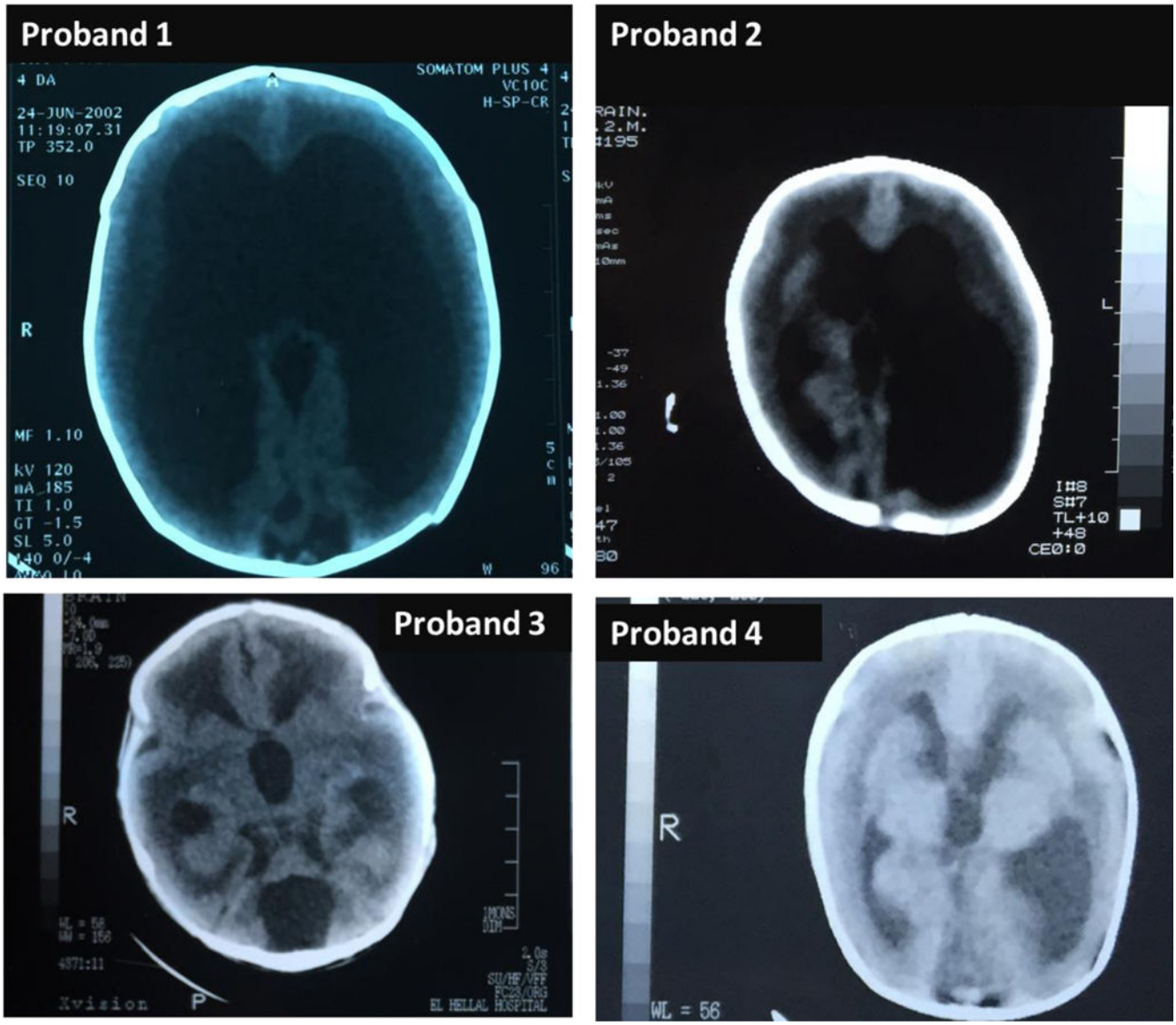

Figure (2):

Brain images of the 3 affected siblings in the first year of life showing: i) hydrocephalus with lissencephaly in proband 1; ii) same findings as proband1 in addition to subcortical and subependymal heterotopia in proband 2; iii) cortical thickening, subcortical and subependymal heterotopia, and a retrocerebellar cyst (Dandy-Walker variant) in proband 3; and abnormal cortical thickening with smooth surface, subcortical and subependymal heterotopia, abnormal white matter intensity, and left occipital colpocephaly in post-mortem images in proband 4.

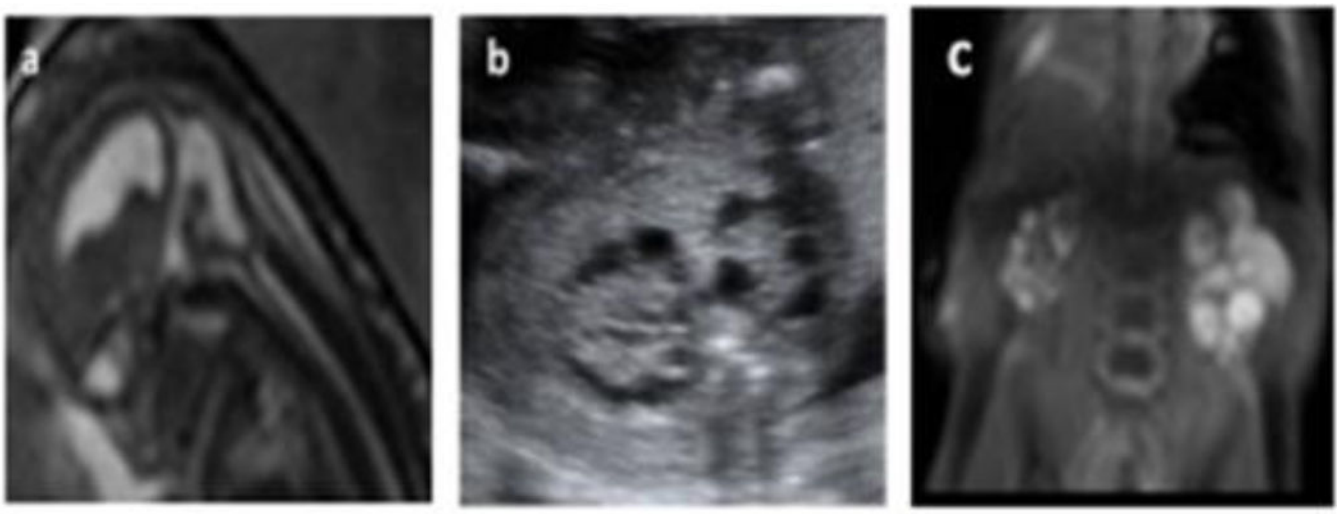

Figure (3):
Antenatal USS of the 4th affected sibling showing brain anomalies in (a); renomegaly and kidney cysts in (b); (c) Post-mortem MRI showing bilateral cystic kidneys

Table (1):

Clinical and radiological characterization of the four affected siblings with Walker Warburg syndrome

	Sibling 1	Sibling 2	Sibling 3	Sibling 4
Hydrocephalus (Dandy-Walker malformation)	+	+	−	+
Cortical thickening	−	−	+	+
Colpocephaly	−	−	+	+
Subcortical and subependymal heterotopia	+	+	+	+
White matter abnormal intensity	−	−	+	+
Cerebellar hypoplasia (with retrocerebellar cyst)	+	+	+	+
Occipital encephalocele	−	−	+	−
Microphthalmia	+	−	−	−
Renomegaly/ cysts	Bilateral	Unknown	Unknown	Bilateral