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Brown-Vialetto-Van Laere Syndrome In East-Africa: A Treatable Disorder Of Riboflavin Metabolism

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Abstract

Background: Brown-Vialetto-Van Laere syndrome is an autosomal recessive riboflavin transporter deficiency syndrome. It has been described in various populations but has yet to be recorded in East Africa. **Case Report:** In a patient who was admitted with aspiration pneumonia, *SLC52A3* gene screening was performed based on a combination of bulbar weakness, ptosis, tongue atrophy, and hyperreflexia, which is compatible with Brown-Vialetto-Van Laere syndrome. A heterozygous pathogenic *SLC52A3* variant was identified but no second potential pathogenic variant was detected. There was notable clinical improvement with riboflavin supplementation. **Discussion:** Our findings provide evidence of a wider geographical distribution of this rare condition. They also illustrate the clinical recognizability of this rare and treatable movement disorder in resource-limited areas.

Keywords: Brown-Vialetto-Van Laere syndrome, Africa, *SLC52A3*, RFT2, Riboflavin, Motor Neuron Disease.

Background

Brown-Vialetto-Van Laere syndrome (BVVL; OMIM # 211530), also known as ponto-bulbar palsy with deafness or bulbar hereditary motor neuropathy type 1, is a rare autosomal recessive degenerative disorder that is caused by riboflavin transporter deficiency [1]. It is characterized by progressive sensorineural deafness, which is followed by bulbar weakness involving the facial, glossopharyngeal, and hypoglossal nerves, and, less commonly, the spinal motor nerves and upper motor neurons. Symptoms can present as early as six months up to adulthood, with a female-to-male ratio of 3:1 [2]. The rare symptoms include peripheral neuropathy, seizures, intellectual disability, and autonomic dysfunction.

Although the first clinical description was conducted by Charles Brown in 1894 [3], the genetic and pathophysiological basis has only been discovered relatively recently [4]. Riboflavin, a water-soluble B vitamin, is an essential nutrient with an important function as a co-factor in amino acid, carbohydrate, and lipid metabolism. Additionally, it is required for the biosynthesis of two other important co-factors, namely flavin adenine dinucleotide and flavin mononucleotide, which play vital roles in energy metabolism, signal transduction, DNA repair, and cell death [5].

Riboflavin transporter type 2 (RFT2) is highly expressed in the gut, whereas riboflavin transporter type 3 (RFT3) is predominantly expressed in the brain. Very little expression was observed in the skin (proteinatlas.org reference). Homozygous or compound heterozygous pathogenic variants in the riboflavin transporter genes *SLC52A2* (coding for RFT3) and *SLC52A3* (coding for RFT2) can cause BVVL or Fazio-Londe syndrome [6]. Fazio-Londe syndrome does not present with sensorineural hearing loss [2] and solely arises from mutations within *SLC52A3*.

Oral riboflavin supplementation at a dose of 10 mg/kg/day has been a successful treatment for BVVL [2]; however, some patients require up to 60 mg/kg/day [6]. In this context, we present the case of a 13-year-old girl with features of BVVL who showed good improvement with riboflavin supplementation.

Case Report

A 13-year-old female patient presented with respiratory insufficiency and aspiration pneumonia. She was the eldest of four children that were born to nonconsanguineous parents. There was no medical or family history of neurological disorders, and, to date, none of the other children displayed symptoms or signs of BVVL syndrome.

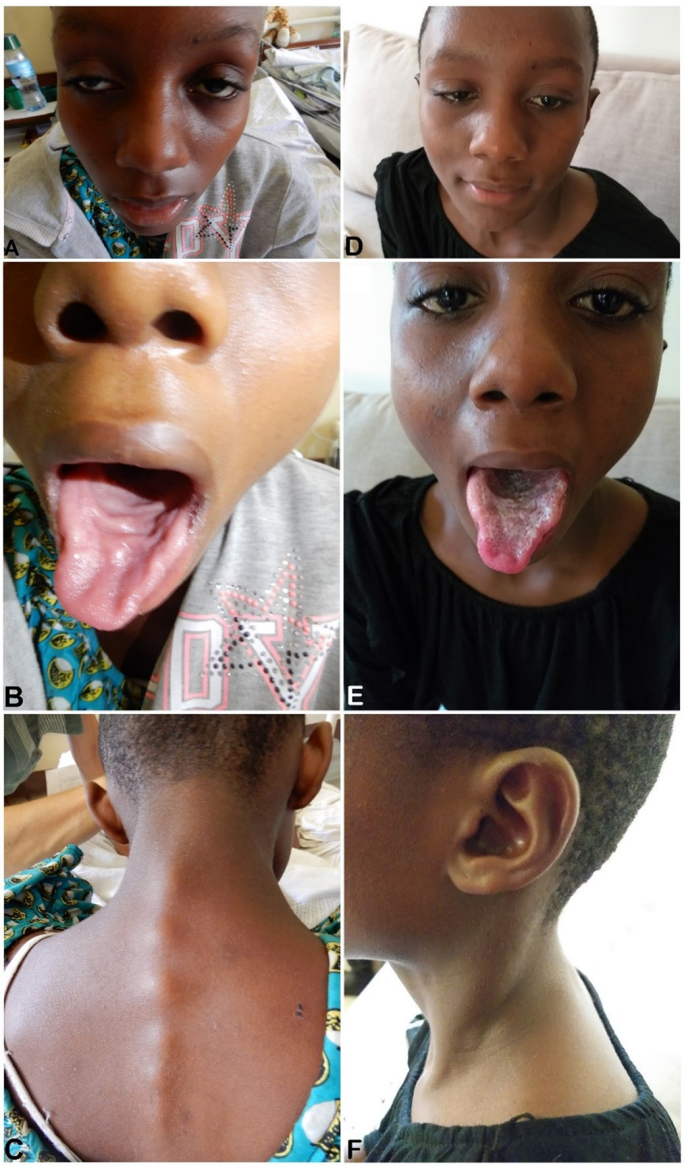
Approximately one year previously, she experienced increasing difficulty in swallowing and chewing, and on admission, she could not swallow her saliva. She also complained of difficulty breathing and general body weakness within the same time frame. Notably, there were no motor or sensory complaints in the upper or lower limbs bilaterally, and sphincter disturbances were not observed. Her parents also noticed that she could not hear well.

On general examination, the patient was drowsy and dyspneic. On neurological examination, she had symmetrical facial weakness with the ability to close her eyes, asymmetrical bilateral ptosis (Figure 1A) with normal eye movement, and no fatigue. Mild hearing loss was also observed. Additionally, there was mild head drop with neck extensor weakness and a Medical Research Council (MRC) muscle power scale of 4/5. Her tongue was severely wasted and crenelated, with fasciculations (Figure 1B). Intraoral examination revealed wide and likely atrophied pharyngeal arches with a spastic and slow gag reflex. Atrophy of the trapezius muscle and neck extensors with easily visible spinous processes was observed (Figure 1C). Her voice was hypophonic with the escape of false air, and she had pseudo-bulbar affect and poor articulation. There were no obvious signs of atrophy, fasciculations, or minimal loss of power (MRC grade 4/5) in her arms and legs. The muscle mass of the first dorsal interosseous and extensor digitorum brevis muscles was normal. The reflexes were brisk in both arms and legs, although they were less responsive in the arms, with ankle clonus and bilateral Babinski signs.

The haematological, renal, liver, and human immunodeficiency virus serology laboratory test results were all within the normal range. The chest X-ray findings showed bilateral basal infiltrates. The audiometry revealed bilateral moderate sensorineural hearing loss (Figure 2). The electromyography showed denervation activity (fasciculations and fibrillations) and broadened old neurogenic motor units in the craniocervical (tongue included), thoracic, and lumbosacral segments.

Based on the history and clinical presentation, the clinical diagnosis was BVVL. Her presentation with a combination of early-onset muscle weakness and ptosis, tongue atrophy, and pyramidal signs did not correspond to myopathy, a motor neuron disease, or a disorder of neuromuscular transmission. A venous blood sample was taken, and a skin biopsy was performed to determine if pathogenic variants in the *SLC52A3* or *SLC52A2* genes were the causes of the BVVL phenotype that was reported in this patient. Venous blood sampling was also performed on the patient's father, who accompanied her to the hospital.

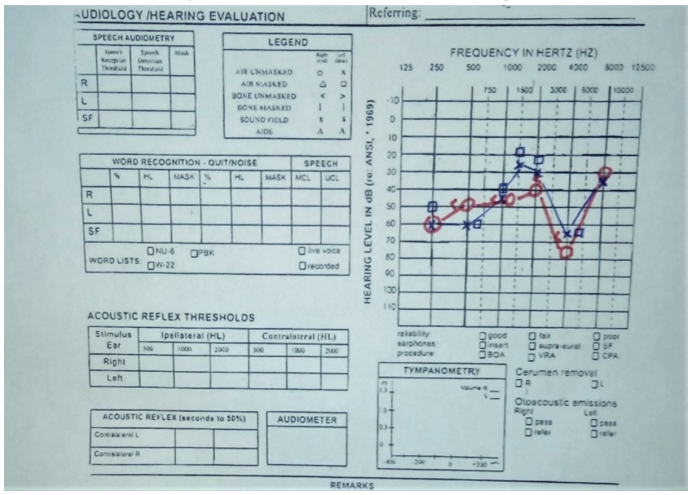
Figure 1. Neurological examination upon admission showed A) asymmetrical bilateral ptosis; B) a severely atrophied and crenelated tongue with fasciculations; and C) easily visible spinous processes. Neurological examination upon follow-up showed D) less ptosis; E) persistence of tongue atrophy and crenelation with fasciculations; F) no progression of the muscle atrophy.



Sanger sequencing was performed on both the *SLC52A3* and *SLC52A2* genes. The Sanger sequence analysis of the SLC52A3 (reference sequence NM_033409.3) and *SLC52A2* (reference sequence NM_024531.4) genes identified the following heterozygous variants in the *SLC52A3* gene: c.-354G>T (p.(?); class 3 variant based on the American College of Medical Genetics and Genomics [ACMG] guidelines, indicating a variant of unknown significance in this population; Chr20(GRCh38): g.768599C>A), which is located in the 5' UTR, with unknown significance, and pathogenic c.615delC (p.(Leu206Cysfs*25); class 5 variant and pathogenic based on the ACMG guidelines;

Chr20(GRCh38): g.763956del) [7]. No additional potentially pathogenic variants were found in either gene. Her father exhibited heterozygosity for the same two variants, confirming that both variants were located on the same allele. No material from the mother was available for the DNA analysis.

Figure 2. Audiometry of the right ear indicated a hearing range of 30 to 80 dB, suggesting mild to moderately severe sensorineural hearing loss, while that for the left ear was 25 to 65 dB, suggesting mild to moderately severe sensorineural hearing loss.



Since two *in cis* variants did not confirm the genetic diagnosis of autosomal recessive BVVL, the *SLC52A3* complementary DNA (cDNA) that was derived from the RNA that was isolated from the patient's fibroblasts was analysed. Unfortunately, this was unsuccessful, most likely because the *SLC52A3* gene is not expressed (well) in fibroblasts and because of the omission of the analysis of *SLC52A3* cDNA in the control subjects' fibroblasts.

The patient was started on supraphysiological supplementation of riboflavin tablets at 300 mg a day. After three months, modest improvement was reported. However, this improvement became more pronounced when the initial dosage was doubled from 300 to 600 mg a day (13 mg/kg). One year later upon reassessment, substantial clinical improvement was observed, including weight gain (45 kg), clearer articulation, and less salivation (Figure 1D). Marked reductions in fatigue, along with improvements in appetite and nutritional condition, were evident. Upon formal neurological examination, there was a gradual improvement in her general condition and muscle power during her most recent visit at the two-and-a-half-year mark since the initiation of her treatment (Figures 1 and 3).

Discussion

This case report describes a clinically recognizable and rare but treatable neurometabolic condition. Riboflavin transport-associated disease has been described in various regions of the world (Figure 4). Over 200 patients with RFT2- or RFT3-associated conditions have been identified worldwide (Figure 5). Most BVVL cases are from Europe, followed by Asia, and the Americas, with only a few documented cases in Africa [8]. Notably, consanguinity plays an important role in the patient population. Cases have been reported from infancy to the mid-forties but the common age of presentation is in the second decade of life [4], which was similar to the age of our patient's onset at 13 years old. Underreporting from the African continent is confounded by the lower density of healthcare facilities, which likely contributes to under-recognition of the condition. For instance, in Tanzania, there is only one neurologist per 8–10 million inhabitants [9].

Figure 3. Further improvement in the patient's overall condition was evident, with reduced ptosis and no muscle atrophy.

The clinical presentation and improvement upon riboflavin supplementation clearly indicated BVVL. However, the identification of only one heterozygous pathogenic *SLC52A3* allele, which was paternally inherited, did not fully confirm BVVL in the patient. Nevertheless, because BVVL is an autosomal recessive disorder, it is highly probable that the other (maternal) allele contains a genetic aberration that could not be identified using our methodology. The *SLC52A3* gene analysis involves Sanger sequencing of all the exons and flanking intronic regions that are amplified by a polymerase chain reaction from the genomic DNA. In principle, this method identifies all the missense and nonsense variants, small deletions, small duplications, and small insertions in the analysed fragments. However, the presence of large deletions, duplications, or pathogenic variants that are located outside the analysed fragments, for example, deep intronic variants, cannot be excluded. Unfortunately, *SLC52A3* did not appear to be expressed in skin fibroblasts, and further re-

search on the cDNA expression of this gene showed that it was absent in most cell lines and the skin. Therefore, this provides insight into its non-expressed in skin fibroblasts [10]. Furthermore, MLPA analysis, which can detect large genomic deletions in or encompassing *SLC52A3*, is not available for this gene.

The 5' UTR c.-354G>T (p.?) variant has not been previously described but was reported in the Genome Aggregation Database with an allele frequency of 1.71% in Africans (more specific ethnic origins were not specified). Its potential impact on gene or protein expression and clinical significance remains unknown. The c.615del (p.Leu206Cysfs*25) variant has also not been previously described. The variant leads to a frameshift and premature stop codon and is interpreted as pathogenic (class 5 DNA variant). In a recent and relatively large sample of clinically confirmed BVVL patients, molecular confirmation was not possible in 30% of the cases [5]. When reviewing all the available clinical literature on BVVL, 231 patients (Figure 4) were clinically identified (including the current patient), with genetic confirmation in 144 patients (Figure 5; Supplementary Data Table 1).

Figure 4. FNumber of Brown-Vialetto-Van Laere (BVVL) syndrome cases that have been reported worldwide with the present case included (for the references see Supplementary Data Table 1).

Figure 5. FDistribution of Brown-Vialetto-Van Laere syndrome in patients with SLC52A2 and SLC52A3 mutations with the present case included (for the references see Supplementary Data Table 1).

A notable improvement in the signs and symptoms upon riboflavin supplementation clinically confirms a riboflavin transporter deficiency. At the first assessment, our patient was clinically undernourished but without the classical signs of vitamin B12 deficiency, such as pellagra. After four years of riboflavin suppletion, her nutritional condition and ocular ptosis had normalized, her muscle power was near normal, and she had reached a normal level of functioning by attending university and living independently. The precise contribution of improved nutrition versus the indirect effect stemming from the improvement in her muscle power or atrophy remains indistinct. The availability of riboflavin in resource-constrained regions remains as much of a challenge as genetic testing accessibility. Consequently, the continuity of our patient's treatment and her long-term prognosis are major concerns.

Acknowledgements

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Competing interests

None.

Author contributions

A. Sadiq, W. Howlett, M. Dekker, H. Waterham, J. Suleiman, D. Mavura, P. Shija, E. Assey, and M. de Bruin performed the clinical investigations and diagnostic workup. M. Dekker and A. Sadiq conceived and drafted the manuscript. B. Hamel and H. Waterham were responsible for the storage of the blood and the genetic analysis. All the authors critically reviewed the manuscript.

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Supplementary Table 1: Available clinical literature on BVVL

Authors, Year	Gene, RFT*	Consanguinity*	Location**	Sex	Sample size
Brown, 1894 [3]	-	No	Germany	M	1
Vialetto, 1936 [11]	-	-	Italy	F	3
van Laere, 1966 [12]	-	-	Belgium	F	4
van Laere ,1967 [13]	-	-	Belgium	M	1
Arnould et al., 1968 [14]	-	-	France	F	1
Trillet et al., 1970 [15]	-	-	France	M	1
Boudin et al., 1971 [16]	-	-	France	F	2
Serratrice & Gastaut, 1972 [17]	-	-	France	F	1
Lombaert et al., 1976 [18]	-	-	Belgium	F	1
Van Laere, 1977 [19]	-	-	Belgium	F	1
Alberca et al., 1980 [20]	-	No	Spain	F	1
Gallai et al., 1981 [21]	-	-	England	M, F	3 (1M, 2F)
Brucher et al., 1981 [22]	-	-	Belgium	F	2
Rosemberg et al., 1982 [23]	-	No	Brazil	F	1
Tavares et al., 1985 [24]	-	-	Brazil	F	1
Summers et al., 1987 [25]	-	No	England	F	1
Hawkins et al., 1990 [26]	-	No	Ireland	F	1
Abarbanel et al., 1991 [27]	-	No	Canada	F	1
Piccolo et al., 1992 [28]	-	-	Italy	M	1
Francis et al., 1993 [29]	-	No	England	M	1
Davenport & Mumford,1994 [30]	-	No	England	F	1
De Oliveira et al., 1995 [31]	-	No	Brazil	M, F	2
Puri et al., 1996 [32]	-	No	India	M	1
Sztajzel et al., 1998 [33]	-	No	Portugal	F	1
Mégarbané et al., 2000 [34]	SLC52A2 p.Gly306Arg	Yes	Lebanon	M, F	4 (3M, 1F)
Sathasivam et al., 2000 [35]		Yes	England	M	1
Urban & Hopf, 2001 [36]	-	No	Turkey	F	1
Voudris et al., 2002 [37]	-	No	Greece	M	1
Introini et al., 2003 [38]	-	-	Italy	M	1
Koç et al., 2003 [39]	-	-	Turkey	M	1
Aydin et al., 2004 [40]	-	Yes	Turkey	F	1
RamachandranNair et al., 2004 [41]	-	Yes	India	F	1
De Grandis et al., 2005 [42]	-	No	Italy	F	1
Dipti et al., 2005 [43]	-	Yes	Pakistan	M, F	4 (1 M, 3 F)
Nemoto et al., 2005 [44]	-	-	Japan	F	1
Prabhu & Brown, 2005 [45]	-	-	England	F	1
Descatha et al., 2006 [46]	-	-	Tunisia	F	1
Koul et al., 2006 [47]	-	Yes	Oman	M, F	3 (1M, 2F)
Malheiros et al., 2007 [48]	SLC52A3	Yes	Brazil	F	4
Miao et al., 2007 [49]	-	No	China	F	1
Fell, 2009 [50]	-	-	England	M	1
Dakhil et al., 2010 [51]	-	Yes	Libya	F	1

Green et al., 2010 [4]	C20orf54 - c.1048T>A (p.L350M) exon 3 - c.1325_1326 delTG (p.L442RfsX35) exon 5	Yes	Saudi Arabia	M	2
	- c.211G>T (p.E71X) exon 2	No	England	F	1
	- c.639C>G (p.Y213X) exon 3	No	India	M	1
	- c.394C>T (p.R132W) exon 2	Yes	Pakistan	F	2
	- c.670T>C (p.F224L) exon 3	Yes	Pakistan	F	1
	- c.1371C>G (p.F457L) exon 5	No	England	F	1
	- c.106G>A (p.E36K) exon 2	No	England	M	1
	- c.1237T>C (p.V413A) exon 5				
Johnson et al., 2010 [52]	C20orf54 - c.82C>A (p.P28T)	Yes	Turkey	F	3
	C20orf54 - c.82C>A (p.P28T)	No	USA (European/Asian)	F	1
	C20orf54	Yes	Turkey	F	3
	- c.639C>G (p.Y213X)	No	USA (European/Asian)	F	1
	C20orf54 - c.211G>A (p.E71K)	No	USA (European/Asian)	M	1
Bosch et al., 2011 [2]	C20orf54 - c.49T>C (p.W17R) - c.639C>G (p.Y213X)	No	Sudan	F	1
Silva-Junior et al., 2011 [53]	-	Yes	Brazil	F	1
Sinnathuray et al., 2011 [54]	-	-	Ireland	M, F	2
Dezfouli et al., 2012 [55]	C20orf54 - c.A62G (p.N21S) - c.C935T (p.A312V)	No	Iran	F	1
	- c.C659A/wt (p.P220H/wt)	No	Iran	F	1
	- c.G1124A/wt (p.G375D/wt)	No	Iran	F	1
Moustafa et al., 2012 [56]	-	Yes	Egypt	F	1
Yadegari et al, 2012 [57]	-	No	Iran	M	1
Gonzalez-Perex et al., 2012 [58]	UBQLN1 - c.162 G>T (p.E54D)	No	Italy	F	1
Anand et al., 2012 [59]	C20orf54	Yes	England	F	1
Koy et al., 2012 [60]	C20orf54 - c.989G>T (p.Gly330Val)	No	Morocco	F	1
Haack et al., 2012 [61]	SLC52A2 - c.368T>C (p.Leu123Pro) - c.1016T>C (p.Leu339Pro)	No	England	F	1
Ciccolella et al., 2012 [62]	hRFT2 - c.796C>T (p.R266W) - c.907A>G (p.I303V) - c.955C>T (p.P319S)	No	Italy	M	1

	- c.1296C>A (p. C432X) - c.173T>A (p.V58D) - c.1238T>C (V413A)			M F	1 1
Ciccolella et al., 2013 [63]	SLC52A2 - c.155C>T (p.S52F) - c.1255G>A (p.G419S)	No	Italy	M	1
Toopchizadeh et al., 2013 [64]	-	No	Iran	F	1
Bandettini di Poggio et al., 2013 [65]	C20orf54 - c.376A>G (p.Y376C) - c.361C>G (p.L361V)	No	Italy	M	1
Spataro et al., 2013 [66]	UBQLN1 - substitution E54D exon 1	No	Italy	F	2
Mahmoud et al., 2013 [67]	-	Yes	Saudi Arabia	M, F	3 (1M, 2F)
Salmina et al., 2014 [68]	-	No	Switzerland	F	1
Naik et al., 2014 [69]	SLC52A3 - p.Cys386Arg	No	Puerto Rico	F	1
Bandettini et al., 2014 [70]	C20orf54 - c.376A>G - c.361C>G	No	Italy	M	1
Foley et al., 2014 [71]	SLC52A2 - c.[916G >A]; p. [(G306R)]) - c.[92G >C]; p.[(W31S)] - c.[935T >C]; p.[(L312P)] - c.[700C >T]; p.[(Q234X)] - c.[1258G >A]; p.[(A420T)] - c.[916G >A]; p.[(G306R)] - c.[1016T >C]; p.[(L339P)] - c.[935T >C]; p.[(L312P)] - c.[1016T >C]; p.[(L339P)] - c.[916G >A]; p.[(G306R)] - c.[1258G >A]; p.[(A420T)] - c.[916G >A]; p. [(G306R)] - c.[916G >A]; p. [(G306R)] - c. [851C >A] p.[(A284D)] - c. [916G >A] p.[(G306R)] - c.[914A >G] p.[(Y305C)] - c. [916G >A] p.[(G306R)]	No No No No No No Yes Yes No No	Scotland Iceland England Scotland England England Lebanon Lebanon USA Ireland	F F F F F M F M M, F M	1 1 1 4 1 1 2 4 2 1
Srour et al., 2014 [72]	MAPK15 - c.419C>T (p.P140L) SLC52A2 - c.916G>A (p.G306R)	Yes	Lebanon	M, F	5 (3M, 2F)

Spagnoli et al., 2014 [73]	SLC52A3	No	England	F	1
Malafronte et al., 2015 [74]	C20orf54 - C106 G>A exon 2 - C639 C>G exon 3	No	USA	M, F	3 (1M, 2F)
Sasishekar et al., 2015 [75]	-	Yes	India	F	1
Petroski et al., 2015 [76]	SLC52A2 - c.1016T>C p.(Leu339Pro) - c.808C>T p.(Gln270*)	No	USA	F	1
Cosgrove et al., 2015 [77]	SLC52A3 - c.1292G>A exon 5 - c.383C>T exon 2	No	England	F	1
Chandran et al., 2015 [78]	-	Yes	India	M, F	4 (3M, 1F)
Davis et al., 2015 [79]	SLC52A3 - c.193C>T (Arg65Trp) exon 2 - c.1238T>C (Val413Ala) exon 5	No	England	F	1
Horoz et al., 2015 [80]	SLC52A3 - c.44G >T (p.Gly15Val)	Yes	Turkey	M, F	2
Menezes et al., 2016 [81]	SLC52A2 - p.G306R SLC52A2 - p.G306R - p.L339P	No	Australia	M, F F	5 (3M, 2 F) 1
Udhayabanu et al., 2016 [82]	SLC52A2 - c.C421A (p.P141T) exon 3 SLC52A3 - c.A62G (p.N21S) exon 2	Yes	India	M	1
Menezes et al., 2016 [83]	-	Yes	Australia	F	1
Thulasi et al., 2017 [84]	SLC52A3 - p.Cys386Arg (c.1156T>C) exon 4	No	Ecuador	F	1
Manole et al., 2017 [5]	SLC52A2 - c.935T>C p.Leu312Pro - c.[383C>T]; p.[Ser128Leu] - c.[1088C>T]; p.[Pro363Leu] - c.[1016T>C]; p.[Leu339Pro] - c.[935T>C]; p.[Leu312Pro] - c.[231G>A]; p.[Glu77Lys] - c.[865C>T]; p.[Ala288V] - c.1327T>C p.Cys443Arg SLC52A3 - c.1371C>G p.Phe457Leu - c.37G>A p.Gly13Arg - c.374C>A p.Thr125Asn - c.403A>G p.Thr135Ala	-	England Brazil England England Saudi Arabia England Brazil England England	F F M F M, F M M F F	1 1 1 1 2 1 2 1 1

	- c.58A>C p.Ile20Leu - c.[106G>A]; p.[Glu36Lys] - c.[1237T>C]; p.[Val413Ala] - c.[354G>A]; p.[Val118Met] - c.[1074G>A] [splice defect] - c.[1128-1129_insT]; p.[Tyr376fs] - c.[1294G>A]; p.[Trp431X] - c.[39G>A]; p.[Gly13Arg] - c.[1255G>A]; p.[Gly418Asp] - c.634C>T p.Arg212Cys		England England England England England Saudi Arabia	M M M M M M, F	1 1 1 1 1 3 (2M, 1F)
Çıralı et al., 2017 [85]	SLC52A2 - c.-110–1G>A - c.297G>C	Yes	Turkey	F	1
Khadilkar et al., 2017 [86]	SLC52A3 - c.935C>T (p.Ala312Val) exon 3	Yes	India	F	1
Allison et al., 2017 [87]	SLC52A2 - c.353C>A (p.Ala118Asp) SLC52A3 - c.106G>A (p.Glu36Lys) SLC52A2 - c.505C>T (p.Arg169Cys) SLC52A2 - c.916G>A (p.Gly306Arg) - c.935T>C (p.Leu312Pro)	No	England USA USA	F F M	1 1 1
Bashford et al., 2017 [88]	SLC52A3 - c.1237T>C/V413A - c.1381T>G/D461Y in exon 5	No	England	F	1
Nakou et al., 2017 [89]	SLC52A2	-	England	M, F	2
Set et al., 2017 [90]	SLC52A2 - c.1327T>C (p.Cys 443 Arg) ATP6V0A4 - c.1185delC TOP1MT - c.1030C>T) PLEC1 - c.5843 G>A	Yes	Yemen	M, F	2
Nimmo et al., 2017 [91]	SLC52A2 - c.917G>A; p. Gly306Glu	Yes	Canada	M	1
Garg et al., 2018 [92]	SLC52A3 - c20:742436A>G (p.L369P)	Yes	India	F	1
Woodcock et al., 2018 [93]	SLC52A2 - c.505C>T p.(Arg169Cys) SLC52A3 - c.1316G>A p.(Gly439Asp)	Yes Yes	Saudi Arabia Pakistan	M F	2 1

Bamaga et al., 2018 [94]	SLC52A2 - c.245G>C (p.Arg82Pro) - c.1140delG (p.Leu381CysfsX9)	No	USA	F	1
Camargos et al., 2018 [95]	SLC52A3	Yes	Brazil	F	1
Fan & Fogel, 2018 [96]	SLC52A2 - c.916G >A (p.Gly306Arg)	Yes	Lebanon	F	1
Forman et al., 2018 [97]	SLC52A2	-	Ireland	M	1
Chaya et al., 2018 [8]	SLC52A3 - c.639C>p.(Tyr213Ter) - c.374C>A p.(Thr125Asn)	-	South Africa	M	1
Mittal & Kamate, 2019 [98]	-	Yes Yes No	India	M	1 1 1
Anderson et al., 2019 [99]	SCL52A2 SCL52A3 SCL52A2 SCL52A2	No	England England England England	F F M F	1 1 1 1
Shi et al., 2019 [100]	SLC52A2 - c.917G>A; p.Gly306Glu	No	China	F	1
Abbas et al., 2019 [101]	SLC52A3 - c.106G>A (p.Glu36Lys) exon 2	Yes	Pakistan	M	1
Rabbani et al., 2019 [102]	SLC52A3 - c.394C >T (p.Arg132Trp) - c.502A >C (p.Asn168His)	Yes	Iran	F	1
Mutlu et al., 2019 [103]	SLC52A3	No	Turkey	M	1
Péréon et al., 2019 [104]	-	No	Morocco	F	1
Kranthi et al., 2020 [105]	SLC52A2 - c.1245C>T (p. Gly415) exon 5	No	India	M	1
Gayathri et al., 2020 [106]	SLC52A3 - c.710C>T (p.Ala237Val) exon 3 - c.62A>G (p.Asn21Ser) exon 3	Yes	India	M, F	3 (1M, 2 F)
Carreau et al., 2020 [107]	SLC52A3 - c.113G >C p.Trp38Ser	No	Mali	F	1
Carreau et al., 2020 [108]	SLC52A2 c.322C>T (p.Q108X) c.1088C>T (p.P363L) c.505C>T (p.R169C) c.863C>T (p.A288V) c.662del (p.L221Rfs*10) SLC52A3 c.634C>T (p.R212C) c.824G>T c.113G>C (p.W38S) c.374C>A (p.T125N)	- No No No No	France	F M F F M	1 1 1 1 1

	c.728G>A (p.R243H)	No		F	1
Pillai et al., 2020 [109]	SLC52A2 - c.1016T>C, p.Leu339Pro - c.405_407delCTT, p.Phe135del	No	USA	M	1
Yilmaz et al., 2021 [110]	SLC52A2 - c.1088C>T (p.363L)	Yes	Turkey	M	1
Khani et al., 2021 [111]	SLC52A3 - c.62A>G p.Asn21Ser - c.935C>T p.Ala312Val - c.1153C>G p.Pro385Ala - c.634C>T p.Arg212Cys - c.1285C>T p.Leu429Phe - c.986A>G p.Tyr329Cys - c.62A>G p.Asn21Ser - c.37G>A p.Gly13Arg SYCP1 - c.1918G>A (p.Glu640Lys) VCAN - c.3637A>G (p.Thr1213Ala) BAIAP2 - c.1516C>T (p.Arg539Trp) WDFY4 - c.8851T>A (p.Ser2951Thr)	No Yes Yes Yes No Yes Yes Yes Yes	Iran	F F F F F F M M M	1 1 1 1 1 1 1 1 1
Soyuyuce et al. 2021 [112]	SLC52A3	No	Turkey	M	1
Carey et al., 2021 [113]	SLC52A3 - c.1046C>T p.(Ser349Leu) SLC52A3 - c.1163T>G p.(Leu388Arg)	Yes No	France	M, F F	2 1
Belarbi et al., 2021 [114]		Yes	Algeria	F	1
Mir et al., 2021 [115]	SLC52A3 - c.1325_1326del	Yes	Saudi Arabia	F	1
Ma et al., 2021 [116]	SLC52A2 - c.75_c.76insCCTGG, p.A26Pfs*42 - c.832_c.833insGCCTGCTGG, p.C278delinsCLLG	-	China	F	1
Liu et al., 2021 [117]	SLC52A2 - c.350T >C, p.Leu117Pro - c.1135_1137delTGG, p.W379del	No	China	M	1

M=male; F=female

*In case of no information available: -

* *IIn case of no geographical origin mentioned we are assuming the author's country/affiliation country.

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