Expanding the Allelic spectrum in ATP1A3-related disorders with 3 novel mutations and clinic features

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ABSTRACT

الأهداف: وصف النمط الظاهري المعقد لجين ATP1A3، ومن ثم تقديم تقرير عن الطفرة الجديدة للجين.

المنهجية: مثل هذه الورقة دراسة مرجعية لسبعة مرضى تم تشخيص إصابتهم بطفرة في جين ATP1A3، بناءً على نتيجة فحص تسلسل الإكسوم الكامل والبيانات التالية التي تم جمعها، مثل العمر وسن ظهور المرض والقدرة على التعافي ونوع النوبة والتاريخ المرضي العائلي وأشعة الرنين المغناطيسي وتقرير فحص تسلسل الإكسوم الكامل، فقد بدأ جمع البيانات منذ عام في يناير 2021 بمستشفى الملك فيصل التخصصي ومركز الأبحاث في الرياض بالمملكة العربية السعودية، حيث وافق مكتب شؤون الأبحاث على النشر بموجب رقم 2225429.

النتائج: كان سن ظهور المرض بالنسبة لخمسة إناث واثنين من الذكور يتراوح بين 0–3 سنوات (18 شهر)، فقد عانى جميعهم من نفس درجة ضعف الإدراك، حيث يعاني ستة منهم من نوبات (85%)، وأربعة يعانون من شذوذات عصبية، وواحد يعاني من سمات توحدية، وآخر يعاني من ارتخاء عضلي خفيف.

الخلاصة: تؤكد مجموعتنا الصغيرة من الملاحظات أن طفرات جين ATP1A3 تعبر عن مجموعة واسعة من الأنماط الظاهرية، بما في ذلك، والتي تشمل عادةً وجود درجة معينة من الخلل الوظيفي للسلوك المعرفي (100% من المرضى) والنوبات (85% من المرضى) وشلل نصفي تناوبي في مرحلة الطفولة (71% من المرضى)، وعلاوة على ذلك، عملت مجموعتنا على التوسع في طيف تواتر الأليل المتطور لهذه الاضطرابات عن طريق تحديد ثلاثة طفرات جديدة.

Objectives: To describe the complex phenotype of ATP1A3 and second to report new mutation of ATP1A3.

Methods: This is a retrospective chart review of 7 patients who was diagnosed with ATP1A3 mutation based on whole exome sequencing (WES) result and the following information were collected; age, age of onset, developmental ability, seizure type, family history, MRI, WES report. The data collection started a year ago January 2021 in King Faisal Specialist Hospital and Research Centre, Riyadh, KSA. This has been cleared for publication by the Office of Research Affairs, and the Publication Number is 2225429.

Results: Five females and 2 males had onset ages of 0–3 years (mean=18 months). All had some degree of intellectual dysfunction, 6 had seizures (85%), 4 had neurologic abnormalities, 1 had autistic features and one had mild dystonia.

Conclusion: Our small-cohort observations confirm that ATP1A3 mutations express a wide range of phenotypes, usually including some degree of cognitive-behavioral dysfunction (100% of patients), seizures (85% of patients), and AHC (71% of patients). Moreover, they further expand the evolving allelic spectrum of these disorders by identifying 3 novel mutations.

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Since the availability of exome-sequencing technology several, human genome discoveries that advance our knowledge of disease-specific pathophysiology and enable connections between genetic variants and clinical phenotypes. An example is the recent identification of variants in the ATPase Na+/K+ transporting subunit alpha 3 gene (*ATP1A3*), which encodes the α3 isoform for the Na+/K+ pump.

The Na+/K+ pump is heterodimeric and contains α and β subunit globular proteins. The β subunit's main function is folding, targeting, and anchoring α into the plasma membrane, whereas the α subunit performs the

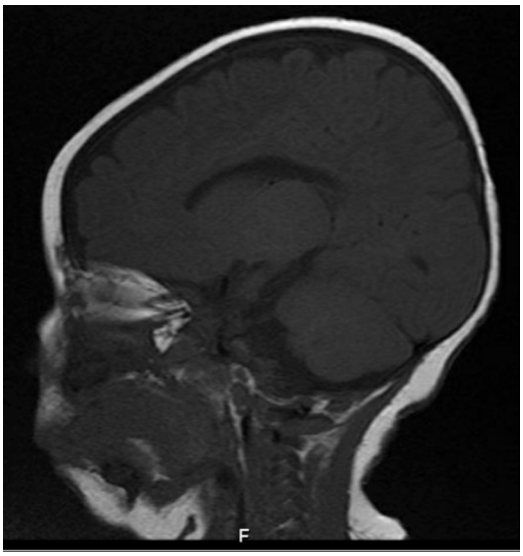

Figure 1 - brain MRI showing atrophy of corpus callosum (Patient 6).

main pump function. In neurons, the α3 isoform is found mostly in axons, although cell body expression has also been observed.

Variants of *ATP1A3* produce a wide variety of neurological disorders. The most common symptoms are alternating hemiplegia of childhood 2012; rapid onset dystonia-Parkinsonism 1999; cerebellar ataxia, areflexia, pes cavus, optic atrophy, and sensorineural deafness 2014; relapsing encephalopathy with cerebellar ataxia; fever-induced paroxysmal weakness and encephalopathy; and early infantile epilepsy and encephalopathy 2017. Indeed, the spectrum of disorders due to *ATP1A3* variants continues to evolve, and the objective of this study is to contribute additional genotype–phenotype observations.

Methods. This is a retrospective chart review of 7 patients who was diagnosed with *ATP1A3* variant based on whole exome sequencing (WES) result and the following information were collected; age, age of onset, developmental ability, seizure type, family history, MRI, WES report. The data collection started a year ago January 2021 in King Faisal Specialist Hospital and Research Centre, Riyadh, KSA. This has been cleared for publication by the Office of Research Affairs, and the Publication Number is 2225429.

Results. Five females and 2 males had onset ages of 0–3 years (mean=18 months). All had some degree of intellectual dysfunction, 6 had seizures (85%), 4 had neurologic abnormalities, 1 had autistic features, and one had dystonia. Group 1 consisted of 3 females and 2 males, with mean onset age of 24 months (**Table 2**). The hemiplegic episodes remitted in all of them except one (patient 5), who had the worst neurological impairment in this group, either spontaneously or after low-dose carbamazepine or flunarizine therapy. Two had mild neurologic abnormalities. Group 2 consisted of 2 females with mean onset age of 12 months (**Table 3**). One presented at birth with severe cognitive impairment and neurologic abnormalities, a phenotype compatible with EIEE (but no seizures), and died of apnea at 17

Table 1 - Summary of phenotypes associated with *ATP1A3* gene mutation.

Classical distinct phenotypes			Emerging new phenotypes		
AHC	**RDP**	**CAPOS**	**EIEE**	**RECA/FIPWE**	**Intermediate phenotypes**
6–18 months	Childhood to adulthood	6 months–5 years	Neonatal period	Childhood	Childhood
Paroxysmal episodes of hemiplegia, bilateral hemiplegia, or quadriplegia Abnormal eye movements, monocular nystagmus, dystonia, autonomic disturbance	Abrupt onset dystonia with prominent dysarthria and dysphagia postural instability bradykinesia Rostro-caudal gradient	Cerebellar ataxia, areflexia, pes cavus, optic atrophy, and sensorineural hearing loss	Early-onset epileptic encephalopathy, catastrophic epilepsy, refractory	Abrupt-onset ataxia after febrile illness, resembling encephalitis, relapsing course and then stable Evolution can be a mixed phenotype ataxia-dystonia	Paroxysmal episodes of weakness, strabismus resembling AHC spells; ataxia, dystonia with rostro-caudal gradient as in RDP
E801N, E815K, G947R, S811P	T613M, D903N	E818K	G358C, G358V, I363N, E815K	R756, E818K	R756

AHC - alternating hemiplegia of childhood, RDP - rapid-onset dystonia parkinsonism, CAPOS - cerebellar ataxia, areflexia, pes cavus, optic atrophy, and sensorineural hearing loss, EIEE - early infantile epilepsy and encephalopathy, RECA - relapsing encephalopathy with cerebellar ataxia

Adapted from A. Capuano et al (The Cerebellum 2018)[2]

Table 2 - Patients with AHC phenotype

Patient	Sex	Age of onset	Phenotype	Presenting symptoms						
				AHC			Dystonia	Cognition and Behavior	Seizures	Other
				Onset	Offset	Duration				
1	F	3 years	c.998T>A: p.Val333Asp *de novo* Pathogenic (PS2;PP3;PM1;PM2;PP5)	3 years	7 years controlled by carbamazepine	last for hours		Impaired speech mild intellectual disability	none	
2	F	2 years	c.2435A>T: p.D812Val *de novo* Pathogenic (PM1;PS2;PM5;PP3;PM2)	2 years	11 years	hours to days		Global developmental delay + Autistic features	At 2 years, intractable, Atonic and Generalized Tonic/Clonic	
3	M	15 months	c.1198G>A: p.Glu400Lys *de novo* Likely Pathogenic (PS2;PM2;PP5)	15 months	3 years	hours to days		Global Developmental Delay	At 34 months Focal seizure	Nystagmus
4	M	3 years	c.2284G>T: p.Gly762Cys *de novo* Pathogenic (PM2;PS2;PM5;PP3;PM5)	3 years	6 years	15-30 mins		Aggressive and hyperactive	At 8 years Focal secondarily generalized. Controlled on Topamax.	
5	F	2 months	c.2434G>A: p.D812N *de novo* Pathogenic (PM1;PS2;PS3;;PM5; PP3;PM5;PM2)	2 months	1-2 months triggered by emotional stress treated by flunarizine and currently by carbamazepine	hours to days	Mild dystonia	Global Developmental Delay, aggressive and hyperactive	At 2 months Focal with secondarily generalized	Spasticity L>R

Mean=24 months age of onset, Group 1 participants 60% female and 40% male; mean age=24 months. AHC-alternating hemiplegia of childhood, L-left, R-right

Table 3 - Group 2 patients without AHC phenotype.

Compatible Phenotype	Patient	Sex	Age of onset	Phenotype	Presenting symptoms		
					Cognition and Behavior	Seizures	Other
EIEE	6	F	at birth	c.2440G>A: p.G814S de novo	Severe Global Developmental Delay. Died at 17 months	At 6 weeks Generalized Tonic + Cyanosis	Nystagmus, Axial Hypotonia and perpendicular hypertonia, decelerated head circumference
RECA/ FIPWE	7	F	2 years	c.2300G>A: p.R767H de novo Episodic encephalopathy, ataxia, movement disorder	Mild intellectual disability	At 1 year focal motor with impaired awareness	Features of cerebellar involvement

Mean= 10.25 months, All Group 2 patients female; mean age=12 months. AHC - alternating hemiplegia of childhood, EIEE - early infantile epilepsy and encephalopathy, RECA - relapsing encephalopathy with cerebellar ataxia, FIPWE - fever-induced paroxysmal weakness and encephalopathy

months old. The other presented at 2 years old with mild cognitive impairment, neurologic abnormalities, seizures, and a phenotype compatible with RECA. Notably, MRI was unremarkable in 6 patients and in one patient (patient 6) thinking of Corpus Callosum (**Figure 1**). Consanguinity present in 70% of parents (patient 1,2,3,6 and 7) although no positive family history of similar cases in the families, the genotype differed in all 7 patients, and 3 previously unreported de novo variant appeared (Patients 1, 3, and 5).

Discussion. The clinical features in this small cohort concur with previous reports indicating that ATP1A3 variants cause a wide range of phenotypes, frequently including intellectual dysfunction, seizures, and neurologic abnormalities. Although, it is not possible to generalize from only 7 patients, the results may suggest that patients with AHC might tend to present later and have milder neurological signs than patients without AHC, and that they usually show resolution of hemiplegic episodes spontaneously or

after anticonvulsant treatment and in one patient persistence of AHC seem to be associated with severe neurological dysfunction. The fact that both Group 2 patients were female while the Group 1 sex distribution was approximately equal does not necessarily indicate a gender predilection. In agreement with previous reports of genotypic variability, every patient had a different genetic abnormality, and we discovered 3 new variants.

Our small-cohort observations confirm that *ATP1A3* variants express a wide range of phenotypes, usually including some degree of cognitive-behavioral dysfunction (100% of patients), seizures (85% of patients), and AHC (71% of patients). Moreover, they further expand the evolving allelic spectrum of these disorders by identifying 3 novel variants.

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