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ORIGINAL COMMUNICATION

Genome sequencing identifies a novel mutation in *ATP1A3* in a family with dystonia in females only

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Abstract Dystonia is a movement disorder characterized by sustained or intermittent muscle contractions causing abnormal movements or postures. Several genetic causes of dystonia have been elucidated but genetic causes of dystonia specifically affecting females have not yet been described. In the present study, we investigated a large dystonia family from New Zealand in which only females were affected. They presented with a generalized form of the disorder including laryngeal, cervical, and arm dystonia. We found a novel, likely disease-causing, three base-pair deletion (c.443_445delGAG, p.Ser148del) in *ATP1A3* in this family by combining genome and exome sequencing. Mutations in *ATP1A3* have previously been linked to rapid-onset dystonia-parkinsonism (RDP), alternating hemiplegia of childhood (AHC), and CAPOS syndrome. Therefore, we re-examined our patients with a specific focus on typical symptoms of these conditions. It turned out that all patients reported a rapid onset of dystonic symptoms following a trigger suggesting a diagnosis of RDP. Notably, none of the patients showed clear symptoms of parkinsonism or symptoms specific for AHC or CAPOS. The *ATP1A3* gene is located on chromosome 19q13.2, thus, providing no obvious explanation for the preponderance to affect females. Interestingly, we also identified one unaffected male offspring carrying the p.Ser148del mutation suggesting reduced penetrance of this mutation, a phenomenon that has also been observed for other RDP-causing mutations in *ATP1A3*. Although phenotypic information in this family was initially incomplete, the identification of the p.Ser148del ATP1A3 mutation elicited clinical re-examination of patients subsequently allowing establishing the correct diagnosis, a phenomenon known as "reverse phenotyping".

Keywords Dystonia · Female · Next-generation sequencing · ATP1A3

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Introduction

Dystonia is a movement disorder characterized by sustained or intermittent muscle contractions causing abnormal, often repetitive, movements, postures, or both [1]. The prevalence of isolated dystonia is thought to be around 16

per 100,000 with maybe slightly higher prevalence in women compared to men (22 vs. 15 per 100,000) [19]. Several genetic forms of dystonia have been reported, all but one with autosomal inheritance affecting both males and females [12]. Only X-linked dystonia-parkinsonism is almost exclusively found in males due to the underlying X-chromosomal recessive inheritance [21]. No genetic cause of dystonia that specifically affecting females has been described to date.

Among the known dystonia genes, mutations in *ATP1A3* were reported to cause rapid-onset dystonia-parkinsonism (RDP) [5]. Dystonia in RDP has a characteristic sudden onset within hours to weeks, typically in adolescence or young adulthood, often in response to physical or mental stress or other triggers such as fever or injuries. Dystonic symptoms usually involve the bulbar region and are accompanied by symptoms of parkinsonism [4]. Recent clinical evaluation also demonstrated non-motor symptoms in RDP patients such as mood disorders and psychosis [3]. RDP is inherited in an autosomal dominant manner with reduced penetrance. Fourteen different mutations (12 missense mutations, a 3-bp deletion, and a 3-bp insertion) were identified in the *ATP1A3* gene in RDP patients and affect different parts of the gene [8, 16].

More recently, mutations especially in the C-terminal region of *ATP1A3* have been linked to two distinct phenotypes, namely alternating hemiplegia of childhood (AHC) [9, 17] and CAPOS syndrome [6], using next-generation sequencing. AHC is a mostly paroxysmal disorder characterized by the occurrence of frequent episodes of hemidystonia or hemiplegia together with other paroxysmal symptoms such as nystagmus, anarthria, dysphagia, hypersalivation, and seizures with a disease onset within the first 18 months of life [2]. The acronym CAPOS syndrome refers to the clinical features cerebellar ataxia, areflexia, pes cavus, optic atrophy, and sensorineural hearing loss [14]. Further, an intermediate RDP/AHC phenotype has been described in a girl with a missense mutation in *ATP1A3* [15]. While 32 different, mostly de novo mutations were reported in AHC patients [8, 16], a single, recurrent, and likely de novo mutation was described in three cases with the extreme rare CAPOS syndrome [6]. ATP encodes Na^+/K^+ ATPase alpha 3, the catalytic subunit of an ionic pump that uses ATP hydrolysis to exchange Na^+ and K^+ across the cell membrane to maintain ionic gradients [5].

In the present study, we elucidated the genetic cause in a large dystonia family from New Zealand using a combination of next-generation sequencing techniques. Remarkably, only females were affected in this pedigree. Our analyses imply that the disease is caused by a novel three base-pair deletion in the *ATP1A3* gene.

Patients and methods

Patients

The study was approved by the ethics committee at the University of Luebeck and was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. After obtaining informed consent, we investigated a family with dystonia from New Zealand with nine affected family members, all women, with an age at onset ranging from 15 to 41 years. The pedigree spans five generations with affected women in generations 2–4 (Fig. 1). Twenty-six family members were identified and DNA samples were obtained from nine family members including six affected. Neurological assessment and clinical history collection was performed by RW and TA. Examinations in L-3960 and L-4007 were videotaped and independently evaluated by NB. Several affected family members had regular Botulinum toxin injections (Table 1). One affected family member (L-4005) agreed to provide a blood samples for genetic analysis but declined formal neurological examination or treatment.

Genetic analysis

After exclusion of mutations in *TOR1A* and *THAP1* by Sanger sequencing of all coding exons and exon–intron boundaries, we initially performed whole genome sequencing in two affected cousins (L-3962 and L-3963). Sequencing was performed using Illumina short-read technology by Knome Inc. (Boston, MA) in 2011. Overall, this resulted in sequencing data of 30 × average coverage. Quality control and data processing such as alignment, variant calls, and selection of candidate variants was done using the "KnomeDiscovery kit" software. The "KnomeDiscovery Data Filtering dashboard" was used for filtering of potentially disease-causing variants. Since re-sequencing of 20 resulting candidate variants did not allow us to pinpoint the genetic cause in this family, we carried out exome sequencing in a third affected family member (L-4007) at Atlas Biolabs (Berlin, Germany) in 2013. Exome sequencing was performed as described [2] using the SeqCap NimbleGen EZ Exome 2.0 kit for exon enrichment.

Bioinformatic analysis

Subsequent bioinformatics analysis was performed based on the variant call files that were provided by the respective companies using an in-house pipeline. First, we annotated all three available exome and genome sequencing data files using the ANNOVAR software tool [20]. Next, we based our data filtering on the following four assumptions: (1)

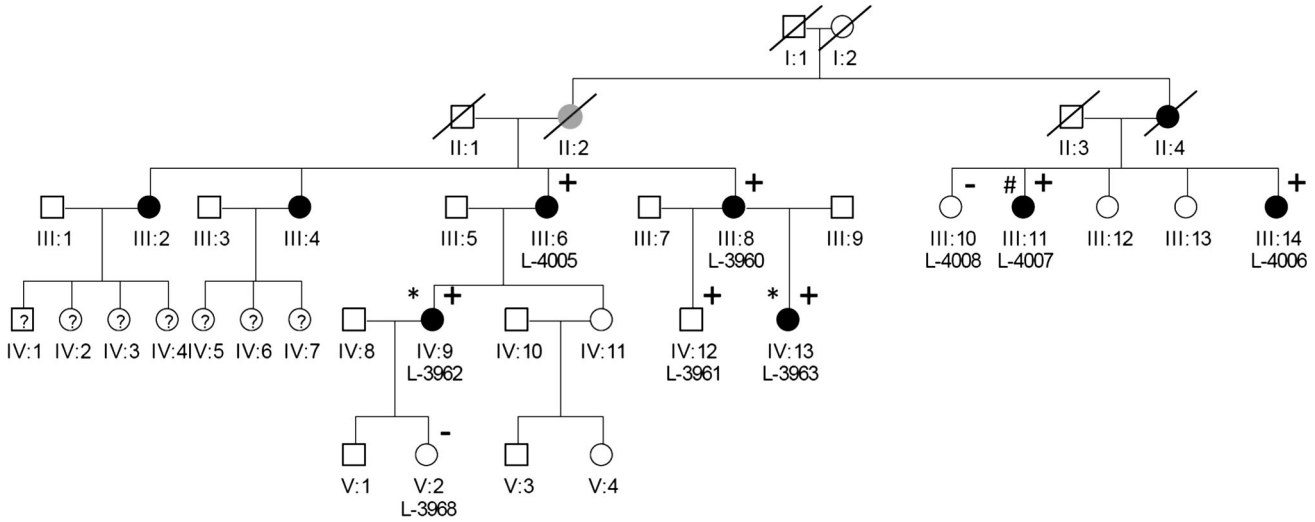

Fig. 1 Pedigree of the dystonia family from New Zealand. Affected individuals are marked by *black-filled symbols*, unaffected with *unfilled symbols*. A possibly affected family member is indicated in *gray*. Offspring without phenotypic information are marked by a *question mark*. Individuals for whom DNA was available are indicated by an *L-number*. Family members included in genome sequencing are highlighted with "*", the exome sequenced member with "#". Mutation carriers are marked with a *plus sign*. Deceased family members: *slashed*; females: *circles*; males: *squares*

We expected the disease-causing variant to be rare in the general population. Therefore, we excluded variants with a minor allele frequency (MAF) ≥1 % in the data from the 1000 genomes project (ANNOVAR version 1000g2012apr). We also excluded variants found in eight unrelated control samples. (2) As we expected the disease-causing variant to be shared by all sequenced affected individuals, we excluded all variants not fulfilling this criterion. (3) Given the apparent autosomal dominant mode of inheritance in this family, we also excluded all homozygous sequence variants from further analysis. (4) Finally, we removed all synonymous variants. Additional filtering steps included removing of all variants that were either not conserved (ANNOVAR version phastCons 46-way alignments), and those found in regions of segmental duplications (ANNOVAR version genomicSuperDups). The putative function of loci containing the remaining variants was evaluated by consulting the databases of PubMed (http://www.ncbi.nlm.nih.gov/pubmed), OMIM (http://www.omim.org/), and GeneCards (http://www.genecards.org).

Results

Genome and exome sequencing

In the whole genome sequencing data, about 89 % of the genome was covered resulting in about 4.5 million mismatches in each patient to the reference genome including 427,894 and 421,237 novel variants (Table 2). Since inheritance in the family followed a dominant pattern, we specifically looked for mutations among the 2.8 million heterozygous mismatches of which 80,000 were located on the X chromosome. Further filtering for variants (1) shared by the two affected individuals, (2) changing the protein sequence, (3) being novel or rare (reported MAF <1 %), and (4) exclusion of variants in genes with >2 variants fulfilling criteria 1–3 resulted in 52 candidate disease-causing variants. Based on their known function and expression pattern, 20 of these variants were selected for validation using Sanger sequencing in all available family members. However, none of these variants was present in the affected individuals L-4006 or L-4007 and thus failed to show the expected segregation with disease.

To further narrow the number of candidate variants, we performed exome sequencing in L-4007. Approximately 40,000 single base-pair substitutions were called of which 22,381 were within the coding region or affecting splice sites. We next removed all variants that were reported at a frequency ≥1 % in the 1000 Genomes project or were present in internal control samples leaving 2,804 variants. Among these, 18 were shared by the three sequenced family members. Application of region-based filtering (such as conservation and segmental duplication); resulted in seven candidate variants, two of which were non-synonymous changes. Using a similar filtering strategy on the total of 302 indels within the coding region revealed two additional shared deletions. Thus, our post-sequencing filtering strategy yielded four candidate variants (Table 3),

Table 1 Clinical features of carriers of the novel ATP1A3 mutation in the New Zealand family

ID	Age	Age at onset	Sex	First symptoms	Description of onset	Present symptoms	Progression	Non-motor symptoms	Epilepsy	Drug response[a]
L-3960	59y.	25y.	F	Dystonic posture of left hand, softening of voice	Rapid onset during delivery of first child	Prominent bibrachial and hand (asymmetric; left>right) and laryngeal (adductor) dystonia, mild lingual, jaw, facial (left blepharospasm), cervical (laterocollis) dystonia; reduced arm swing on right side	Plateau over several days, then slight improvement over several months after onset	Anxiety (occurred before onset of motor symptoms)	No	Propranolol (20 mg): +, Btx: not tried, Alcohol: (+), Dopamine: −, Tetrabenazine: −
L-3961	40y.	na	M	None	Not applicable	None	Not applicable	None	No	Not applicable
L-3962	54y.	16y.	F	Softening of voice	Rapid onset after domestic mental and physical abuse	Laryngeal dystonia, jaw-closing, mild orofacial and tongue dystonia, left hand and fingers and neck dystonia; reduced arm swing on the left side while walking, no parkinsonian symptoms	Stable but left hand dystonia worsened after a stressful event in her 30 s	Prominent anxiety Lorazepam responsive	No	Btx: +, Lorazepam: +, Alcohol: +, Dopamine: −
L-3963	34y.	19y.	F	Tremor of left hand	Rapid onset after operation on elbow (ulnar translocation)	Laryngeal dystonia, severe left hand dystonia and left hemifacial spasm	Unknown	Unknown	No	Btx +, Alcohol: +, Dopamine: −
L-4005	72y.	Unk.	F	Unknown	Unknown	Unknown	Unknown	Unknown	Unknown	Unknown
L-4006	62y.	41y.	F	Flexion dystonia in 5th finger	Rapid onset within hours of treatment with prochlorperazine	Right hand, forearm, arm and shoulder dystonia, no parkinsonian symptoms	Progressive over weeks and then stable for years	Unknown	No	Btx: +, Alcohol: +, Dopamine: −
L-4007	72y.	15y.	F	Severe generalized dystonia	Rapid onset immediately after awaking from anesthetic after an operation	Generalized dystonia with lingual, orofacial, and mild jaw dystonia, laryngeal dystonia (adductor), cervical, bibrachial and limb and torso dystonia, effective use of sensory trick, no parkinsonian symptoms	Progressive over several days and then stable for years	Unknown	No	Btx: +, Dopamine: −

[a] Alcohol+ indicates that alcohol improves the symptoms (alcohol-responsive dystonia)

Table 2 Results from genome and exome sequencing

	L-3962	L-3963	L-4007
Type of NGS	Genome	Genome	Exome
% of genome covered	89.5 %	89.6 %	94.3 % with
Mean coverage	47.4	47.2	≥30×
Called mismatches	4,441,763	4,525,906	39,843
Novel variants	421,237	427,894	2,397
Protein-changing variants	9,266	10,213	1,585
Shared, novel or rare (<1 %), and protein-changing variants	52		na
Shared, novel or rare (<1 %), and protein-changing variants	4		

including a novel three base-pair deletion (c.443_445delGAG, p.Ser148del) in *ATP1A3* in all three sequenced patients. This deletion was validated by Sanger sequencing and segregation analysis confirmed it to be present in all patients as well as one unaffected male (age at examination 40 years). The deleted residue is located near the N-terminus of the 1,013 amino acids spanning ATP1A3 protein, at the beginning of a cytoplasmic domain.

Clinical re-examinations

Since *ATP1A3* mutations were reported in RDP, AHC, and CAPOS syndrome, we re-examined our patients with a specific focus on symptoms typical for RDP (description of onset and parkinsonian features), AHC (episodic attacks), and CAPOS (cerebellar signs, hearing and/or problems with vision). The clinical features are summarized in Table 1. All patients for whom information on onset was available ($n = 5$) reported a rapid onset of symptoms following a specific trigger [delivery of a child, abuse, operation ($n = 2$), drug intake]. These characteristics together with prominent bulbar and upper body half dystonia strongly suggest a diagnosis of RDP in these family members. Patients presented with a unique hand/arm dystonia characterized by dystonic stiffness, swan-neck deformity of the fingers and problems to open the hand (see supplementary video). However, symptoms of parkinsonism were not reported except for reduced arm swing in two patients. However, this may be related to their arm dystonia. Notably, two patients reported anxiety. No characteristic symptoms of AHC were detected and age at onset was not in early childhood. Further, there was no hearing loss in our patients excluding a diagnosis of CAPOS syndrome.

Discussion

Using a combination of whole genome and exome sequencing in a large, multigenerational family with rapid-onset dystonia from New Zealand revealed a novel and likely disease-causing three base-pair deletion in *ATP1A3*. The variant results in an in-frame deletion of a single amino acid (i.e., serine at residue 148). While the pathogenic mechanism of this mutation within one of the cytoplasmic domains encoding part of the E1-E2 ATPase domain [16] remains to be elucidated, we believe it to be functional. This conclusion is based on the observation that the Ser148del mutation is located adjacent to a part of the *ATP1A3* gene that is known to contain three different AHC mutations leading to amino acid substitutions at residues Ser137 and Gln140 [16], all located within the second transmembrane domain. Another amino acid deletion (Leu327del) has previously been described in a patient with typical RDP with predominant generalized dystonia. This mutation also affects the E1-E2 ATPase domain [10].

The phenotype in our family was initially not recognized as RDP since specific information about the disease onset was not collected and parkinsonian features were not present. Parkinsonian features in RDP usually include bradykinesia and postural instability but do not comprise stooped gait or tremor [4]. After identification of the p.Ser148del variant, we carefully re-examined available patients and confirmed the expected rapid onset of dystonic symptoms. Establishing the correct diagnosis after re-evaluation of patients prompted by the genetic finding has been called 'reverse phenotyping' [7]. We here provide another example showcasing the power of next-generation sequencing in a clinical setting. For the clinical evaluation in our family, we were initially distracted by the apparent preponderance to females. If the history of the affected family members would have been taken in more detail, the primary care physicians might have had a clue pointing

Table 3 List of the candidate variants shared by all three genome/exome sequenced family members

Gene	Chromosome	Nucleotide position	Nucleotide change	Amino acid change	Frequency in 1000 genomes	dbSNP ID
KIAA0319	6	24566953	G > A	p.R133W	0.0027	rs113411083
BTN2A2	6	26392768	A > T	p.H172L	0.0014	rs142785600
GPX6	6	28472199	A > del	Unknown	Not reported	na
ATP1A3	19	42490327	AGG > del	p.148_149del	Not reported	na

toward a diagnosis of RDP based on the typical symptoms. However, for this, the physician has to be aware of this rare disorder. Especially for extreme rare diseases, next-generation sequencing can help in a diagnostic setting or may broaden phenotypes in already known diseases [13].

The identification of the putative disease-causing mutation in *ATP1A3*—a gene located on chromosome 19—provided a first indication that X-linked transmission is not the underlying cause of disease in this family. Notably, inspection of the pedigree reveals that almost all offspring in this particular family (at least in the first four generations) are female (regardless of disease state) except for IV.1 and IV.12 (L-3961). While there is neither genetic nor clinical information available for IV.1, IV.12 was identified as an unaffected mutation carrier. It is known that *ATP1A3* mutations may exhibit reduced penetrance in up to 30 % of carriers [11]. In our family, one of seven mutation carriers (14 %) represents with reduced penetrance which is, thus, in the expected range. The fact that the reduced penetrance occurs in the only male carrier might be attributable to chance or caused by as yet unknown modifying factors. However, based on a single individual, these putative protective factors cannot be elucidated with sufficient confidence.

Previous work suggests that carriers of mutations in *ATP1A3* represent with a broad phenotypic spectrum comprising patients with RDP, AHC, intermediate phenotypes [15], CAPOS syndrome [6], and even unaffected individuals due to reduced penetrance [4]. Interestingly, a recent paper that carefully evaluated the phenotypes of RDP and AHC patients and found several shared features of both conditions, including abrupt onset often after a specific trigger and a rostrocaudal gradient of involvement with prominent bulbar findings, suggesting that RDP and AHC may represent prototypic disorders within a continuous phenotypic spectrum [16]. This is further supported by the finding that the mutation Asp923Asn may cause RDP or AHC [18]. Notably, specific features of AHC such as onset in early childhood or episodes of hemiplegia have not been reported by our patients. Although visual acuity or hearing have not formally been tested in our family, major impairment of hearing and vision can be excluded based on the face-to-face clinical examination. Therefore, a diagnosis of CAPOS syndrome is also not supported. Reports on additional cases with *ATP1A3* mutations will further elucidate the whole clinical spectrum and provide information on overlapping phenotypic features such as the abrupt onset of symptoms.

From a technical point of view, our study underlines some important challenge when utilizing next-generation sequencing in the context of mutation screening. Initially, we had missed the three base-pair deletion in the genome data since this variant was not correctly annotated by a commercially available software package that was used for the analysis in 2011. Only subsequent analysis using an updated pipeline based on ANNOVAR [20] and inclusion of exome data generated in a third family member allowed us to pinpoint to the likely disease-causing and novel *ATP1A3* mutation.

Taken together, we identified a novel *ATP1A3* mutation in a family with RDP using a combination of whole genome and exome sequencing. Notably, the specific clinical diagnosis was established only after considering the molecular genetic findings, a procedure referred to as "reverse phenotyping". However, the mutation could have been identified using a conventional candidate gene approach if the history of the affected family members would have been taken in more detail underlining the importance of a comprehensive clinical examination. Our study further stresses correct annotation of variants as an essential prerequisite for the identification of a causative mutation.

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Conflicts of interest On behalf of all authors, the corresponding author states that there is no conflict of interest.

Ethical standards All patients and controls provided written informed consent and the local ethics committee approved the study which has been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

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