Supporting Information:

Patient synopsis and genetic findings

Genetic investigations

Patient 1

Trio-based WES was performed by Baylor Micra Genetics Laboratories (Texas USA). A novel *de novo* missense mutation in *GNAO1* gene, NM_020988 c.709G>A, (p.Glu237Lys) in exon 6. SIFT and PolyPhen-2 analysis predicted the mutation to be damaging and probably damaging respectively.

Patient 2

WES was performed by the Westmead Children's Hospitalutilizing Beijing Genomics Institute (Hong Kong). A *de novo* missense mutation in *GNAO1* gene, c.736G>A, (p.Glu246Lys) was identified. This mutation was confirmed by Amplexa Genetics (Odense, Denmark) via Sanger sequencing.

Patient 3

Trio-based exome sequencing was performed as part of the Deciphering Developmental Delay (DDD) Study as previously described[6,7]. Target capture using Agilent SureSelect 55 MB Exome Plus was performed on saliva- or blood-derived genomic DNA from each affected individual and their parents and sequenced on Illumina HiSeq A *de novo* missense mutation in *GNAO1* gene, c.625C>T, (p.Arg209Cys). SIFT and PolyPhen-2 analysis predicted the mutation to be damaging and probably damaging respectively.

Case description

Patient 1

Mild chorea and parkinsonian tremor, accompanied by global delays (mainly motor and language) and spasticity were noted in infancy. Episodic 'movement disorder crisis' lasting weeks to months were noted from age 8 years. On video review, these had variable elements of violently thrashing ballism, chorea, oro-facio-lingual dyskinesia and dystonia. Video examples are shown (Supporting Information). Complications included rhabdomyolysis, severe infections, shoulder dislocation, skin injuries, sacral ulceration, and 'cauliflower ear'. There was an incomplete response to all medical therapies, including intrathecal baclofen. Phenobarbitone at supratherapeutic doses and Tetrabenazine was felt to be most helpful, but with an incomplete response. Cumulative paediatric intensive care unit admission time was 14 months, with one admission lasting 11 months.

At age 11 a deep brain stimulator was placed into bilateral GPI (in partnership between St Andrew's private hospital and Royal Children's hospital, Brisbane). An immediate decrease in hyperkinetic movements enabled discharge from PICU then hospital within 3 months of DBS implantation. Current follow up time is 26 months. He has not required readmission to PICU or prolonged (>2 week) hospital admissions for exacerbations of his movement disorder. Episodic exacerbations have persisted, some requiring hospital admission, but occur mainly related to illness causing pain or fever, and include increased ballismic and oro-facio-lingual movement. Background medication continues at lower levels (phenobarbitone, clonazepam, Valproate and intrathecal baclofen) to treat intermittent exacerbations, and a persistent oro-facio-lingual movement with hypersalivation and vomiting triggering full body movements. At best, he has regained some voluntary purposeful movements, this depending on level of movement and tone, and when most functional he can drive a powered wheelchair.

Patient 2

At 6 months of age global developmental delay was noted with significant chorea and dystonic posturing, followed by progressive central hypotonia and peripheral spasticity. Expressive speech did not develop, she had non-verbal communication strategies including eye-pointing and gesturing, and was visually bright and interactive.

Intermittent severe exacerbations of hyperkinetic movements occurred from age 5 years, required prolonged hospitalizations and PICU admissions, at times triggered by intercurrent illnesses. Haloperidol transiently worsened orolingual-facial movements at age 2 years. An intrathecal baclofen pump provided some improvement in severity of movements, however improvements waned quickly and increasing doses were required leading to general decrease in tone and voluntary movements. Tetrabenazine was also effective in improving baseline movement disorder to some degree. Phenobarbitone in supra-therapeutic dosing was felt to be the most helpful as rescue therapy.

Movements and hyperkinetic status dystonicus with violent thrashing ballistic movements became progressively worse leading to prolonged PICU admissions with continuous intravenous sedation required. Complications included rhabdomyolysis and prerenal failure, injuries including skin abrasions, and respiratory infections related to the sedation required.

Bilateral GPI deep brain stimulator was placed at age 6 years (St Andrews private hospital). An immediate effect was noted with decreased hyperkinetic movements. The patient continues to have a baseline movement disorder involving proximal and distal chorea, and oro-facio-lingual movements, as well as exacerbations of her movements, but has not required prolonged hospital admissions nor PICU. Partial weaning of background medications was possible. She was slowly able to regain some voluntary purposeful movements, with non-verbal communication skills and oral feeding also improving. A worsening of background movements was noted again in the last 12 months of follow-up, with a new lead dislodgement noted on imaging. Following re-implantation, an improvement in background movements was again noted.

Patient 3

Symmetrical lower limb ‘spasticity’ evolved from late infancy, global developmental delay with prominent gross motor involvement was noted and the patient was non-verbal. Bradykinesia, rigidity and dystonia were noted from early life with parkinsonian features seen. A hyperkinetic movement disorder consistent of 4 limb choreoathetosis, dystonia and oro-facio-lingual dyskinesia was first noted at age 10, with episodes of worsening at times associated with intercurrent illnesses and exercise.

Generalized tonic-clonic seizures occurred from age 10, but EEG did not show epileptiform activity. Seizure remission occurred with carbamazepine and acetazolamide and further seizure exacerbations subsequently improved with Oxcarbazepine alone. A movement disorder crisis led to a 4 week PICU admission. DBS targeting the bilateral GPI was performed with instantaneous improvement noted. The patient could be discharged home, having been rapidly weaned off all anti hyperkinetic medications which were titrated against the extreme drowsiness evident after DBS management of the movement disorder. She has not been admitted to hospital for increase in movements since. A mild baseline movement disorder with dystonia persists, but the patient functions well and motor function includes the ability to kick a ball.

Table 1: Patient characteristics and Movement disorder phenomenology

Characteristics	**Patient 1 (M)**	**Patient 2 (F)**	**Patient 3 (F)**
Current age	12 y 4 m	8 y 2 m	14 y 7 m
Early central hypotonia, global developmental delay	Yes (from age 3 m)	Yes (from age 3 m)	Yes (from age 6 m)
Severe speech delay	Few words	Non-verbal	Few words
Feeding difficulties	Yes (PEG insertion age 9 y)	Yes (PEG insertion age 12 m)	Mild (tube dependence during exacerbation)
Ambulation	GMFCS V	GMFCS V	GMFCS II
Epileptic encephalopaty/neonatal seizures	No	No	No
Epilepsy	No	No	Generalized tonic-clonic seizures from age 10, well controlled on medication
MRI brain	Progressive global atrophy (8 y, 12y)	Progressive global atrophy (1 y, 5 y, 8y)	Normal (13y)
GNAO1 mutation	c.709G>A, (p.Glu237Lys), missense, *de novo*	c.736G>A, (p.Glu246Lys), missense, *de novo*	c.625C>T, (p.Arg209Cys), missense, *de novo*
<u>Movement disorder (MD) description</u>			
Age of onset (MD)	3 m	4 m	12 m
Primary MD (at baseline)	Chorea	Chorea	Dystonia
First crisis	8 y	5 y	11 y
Number of exacerbations	5 (lasting 2 w to 10 m)	21 (lasting 1 w to 1 m)	3 (lasting days to 2 m)
Secondary MD (in exacerbation)	Chorea, hemiballism, dystonia, Oro-facio-lingual dyskinesia	Chorea, hemiballism, dystonia Oro-facio-lingual dyskinesia	Chorea, dystonia, ballism Oro-facio-lingual dyskinesia
Autonomic features (in exacerbation)	Tachycardia, sweating, flushing, hyperthermia	Tachycardia, sweating, flushing, hyperthermia	Sweating, hyperthermia, tachycardia

PICU admissions (cumulative time)	5 (10 m)	6 (3 m)	1 (2 m)
Life threatening complications	Rhabdomyolysis, prerenal failure, pneumonia, joint dislocations, decubitus/severe skin breakdown and infection	Rhabdomyolysis, prerenal failure, pneumonia	Rhabdomyolysis, prerenal failure
Medications with partial effectiveness	Phenobarbitone, (Tetrabenazine)	Tetrabenazine, (Phenobarbitone)	Clonidine (high dose)
Response to DBS	Yes (slow over first 3 months) Functional improvement (able to sit in wheelchair and drive electrical wheelchair, improved feeding and communication, discharge from hospital, weaning of baseline medications)	Yes Functional improvement (able to tolerate sitting in wheelchair, improved feeding and communication, discharge from hospital, weaning of baseline medications)	Yes Functional improvement – improved mobility – GMFSC 5 to 2, improved communication and feeding, weaning of all baseline medications)
GPi DBS settings	Equal bilaterally, monopolar, current 6.6 mA, pulse width 280 US, rate 130 Hz, continuous cycle	Equal bilaterally, monopolar, current 4.4 mA, pulse width 100 US, rate 130 Hz, continuous cycle	Equal bilaterally, monopolar, current 0.5 mA, pulse width 450 US, rate 130 Hz, continuous cycle
Follow up post DBS	26 m	28 m	16 m
Remaining movement disorder	Oro-facio-lingual dyskinesia, chorea, dystonia – overall improved	Chorea, dystonia, oro-facio-lingual dyskinesia – overall improved	Dystonia – overall improved

Table 2: Medication Details and Response

Characteristics	Patient 1 (M)	Patient 2 (F)	Patient 3 (F)
Number of hospital admissions (exacerbation of MD)	5	21	3
Number of PICU admissions (duration)	5 (3 w, 1 w, 3 d, 1 w, 8 m), mean 55 d	6 (6w, 2d, 3d, 5d, 10d, 8d), mean 12 d	1 (2 m)
Medications			
Number tried prior to DBS	17 (8)	16 (5)	5 (4)
Medications for Primary MD	L-Dopa, Benzhexol, Diazepam, Clobazam, Clonidine, Prednisolone, oral Baclofen, Botulinum Toxin (local), Tetrabenazine, Clonazepam, Phenobarbitone, Sodium Valproate, Oxcarbazepine	L-Dopa, Benzhexol, Carbamazepine, Nitrazepam, Lorazepam, Clobazam, Acetacolamide, Clonidine, Biotin, Botulinum Toxin (local)	Benxhexol
No response (baseline or exacerbation)	L-Dopa, Benzhexol, Diazepam, Clobazam, Clonidine, Prednisolone, oral Baclofen, Midazolam infusion, Dexmedethomidine infusion, Ketamine infusion	L-Dopa, Benzhexol, Carbamazepine, Nitrazepam, Lorazepam, Clobazam, Acetacolamide, Clonidine, Biotin, Botulinum Toxin, Prednisolone, IVIG, Midazolam infusion	Chloral hydrate Morphine infusion Midazolam infusion
Some response (baseline or exacerbation)	Botulinum Toxin Tetrabenazine (1-5 mg/kg/day), Clonazepam (0.5 – 3 mg per day), Phenobarbitone (6 – 16 mg/kg/d), Chloral hydrate as rescue (10-30mg/kg/dose), Sodium Valproate (10-40 mg/kg/d) ITB	Tetrabenazine (1-5 mg/kg/day), Clonazepam (0.5 – 3 mg per day), Diazepam (0.5 - 1 mg/kg/d), Phenobarbitone (6 – 16 mg/kg/d), ITB	Clonidine (NG continuous, 4- 96 mcg/kg/d)

Causing side effects	Oxcarbazepine – liver dysfunction	Haloperidol – chorea improved, but increase in hypotonia and florid oro-facio-lingual dyskinesia Sodium valproate - some effect for chorea, but increase in oro-facio-lingual dyskinesia, sedation, decreased feeding	Benxhexol – worsening dyskinesia Gabapentin (seizures) – ?worsening dyskinesia, not recurring when re-introduced post DBS Botulinum toxin – bulbar palsy and need for NG tube, generalized muscle weakness and transient inability to walk Levetiracetam (for seizures) – worsening of parkinsonian features (freezing, hesitation, gait initiation), Topiramate (for seizures) – deterioration in thinking and processing Sodium valproate (for seizures) – initial benefits ?worsened dyskinesia
After DBS	4 and ITB	3 and ITB	none
Function after DBS	Discharge form PICU (6 w), then hospital (3 m), Functional improvement (able to sit in wheelchair and drive electrical wheelchair, improved feeding and communication, , weaning of baseline medications, less sedation)	Discharge from hospital (1 w), Functional improvement (able to tolerate sitting in wheelchair, improved feeding and communication, weaning of baseline medications, less sedation)	Functional improvement, improved mobility (GMFSC 5 improved to 2), improved communication and feeding, weaning of all baseline medications, improved sedation)
DBS complications	DBS site infection (long term Antibiotic required, with plan for replacement)	Lead dislodgement (replacement required)	none

ITB – Intrathecal Baclofen

Table 3 : Previous case reports of GNAO1 movement disorder

Case (ref)	Sex	Movement onset/ Age at follow up	Phenomenology	Treatment (DBS)	Mutation	MRI brain	Additional features
1[1]	F	4 y 13 y	Chorea, athetosis, dystonia with episodes of status dystonicus	Refractory to medications, (No)	c736G>A, p.(Glu246Lys)	Normal (5 m and 12 y)	Global delays, non-verbal, no epilepsy
2[1]	F	5 y 18 y	Athetosis, dystonia with episodes of status dystonicus	Refractory to medications, (No)	c.625C>T, p.(Arg209Cys)	Progressive atrophy (11 y, 14 y)	Global delays, few words, rare focal seizures, no epileptic encephalopathy
3[4]	M	3 y 6 y	Choreathetosis with intermittent severe life threatening exacerbations	Refractory to medications, (Yes)	c.626G>A (p.R209 H)	Normal (3 y, 7 yr) – note white matter changes at 3 y	Severe delays, central hypotonia, non-verbal, no epilepsy
4[4]	M	3 y 7 y	Orofacial dyskinesia, choreathetosis with intermittent life threatening exacerbations	Refractory to medications, (Yes)	c.626G>A (p.R209 H)	Normal (3 y, 6 y)	Severe delays, central hypotonia, non-verbal, no epilepsy
5[2]	M	4 y 5.5 y	Chorea, ballismus, intermittent mild exacerbations	Refractory to medications, (No)	c.736G>A	Normal (12 m)	Severe delays, central hypotonia, non-verbal, no epilepsy, dizygotic twin 1
6[2]	F	4 y 5.5 y	Chorea, ballismus, intermittent exacerbations	Refractory to medications, (No)	c.736G>A	Progressive global atrophy (12 m, 5.5 y)	Severe global delays, central hypotonia, non-verbal, no epilepsy, dizygotic twin 2
7[2]	F	3 y 10 m Deceased 4 y 7 m	Chorea, intermittent exacerbations	Refractory to medications, (No)	c.625C>G	Normal (13 m)	Severe delays, central hypotonia, non-verbal, no epilepsy
8[2]	F	6 m Deceased 10 y 3 m	Orofacial dyskinesia, chorea, intermittent exacerbations	Refractory to medications, (No)	c.736G>A	Global atrophy and T2 hypointensity in globus pallidi (4 y, 10 y)	Severe global delays, central hypotonia, few words, no epilepsy

9[2]	M	3 y 16 yr	Chorea, intermittent exacerbations	Refractory to medications, (No)	c.626G>A	Global atrophy (4 y, 16 y)	Severe global delays, central hypotonia, few words, no epilepsy, regression from age 6 years
10[2]	M	14 y 6 m 15 yr	Chorea, intermittent exacerbations	Refractory to medications, (No)	c.736G>A	Subtle hypo intensities in globus pallidi (14 y)	Global delays, few words, no epilepsy
11[3]	F	13 m 5 y	Chorea, athetosis, orofacial dyskinesia	Refractory to medications, (Yes)	c.698A>C p.(Q233P)	Normal (2 y)	Global delays, no epilepsy
12[8]	M	10 m 5 y	Chorea, dystonia	Refractory to medications, (No)	c.626G>A	Normal (2 y)	Global delays, central hypotonia
13[9]	M	1 y 6 m 3 y	Dystonia, myoclonus	No medications	c.626G>A	Normal (3 y)	Global delays, central hypotonia
14[9]	M	2 y 2 y	Dystonia, myoclonus	No medications	c.626G>T	Normal (2 y)	Global delays, central hypotonia

DBS – Deep Brain Stimulation, y - years, m - months

References:

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Movement Rating Proforma

MOVEMENT DISORDER PHENOTYPE

Dystonia *(if possible, also describe distribution)*	Y N
	symmetric UL Y N; LL Y N
	asymmetric Y N (please describe if yes)
Myoclonus *(if possible, also describe distribution)*	Y N
	symmetric UL Y N; LL Y N
	asymmetric Y N (please describe if yes)
Limb Dyskinesia *(eg. Chorea or stereotypical movements if possible, describe distribution)*	Y N
	symmetric UL Y N; LL Y N

asymmetric Y N (please describe if yes)

Orolingual dyskinesia Y N

Tremor *(if possible, also describe distribution)* Y N

Description:

Other movements*(eg stereotypies, bruxism)* Y N

Description:

have you seen similar movements in patients with an established diagnosis	Y N
	overlap with comparable patients with established diagnosis
	diagnosis
have you seen similar movements in patients without an established diagnosis	Y N
	overlap with comparable patients without established diagnosis