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CLINICAL REPORT

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Clinical spectrum of *KIAA2022* pathogenic variants in males: Case report of two boys with *kiaa2022* pathogenic variants and review of the literature

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KIAA2022 is an X-linked intellectual disability (XLID) syndrome affecting males more severely than females. Few males with *KIAA2022* variants and XLID have been reported. We present a clinical report of two unrelated males, with two nonsense *KIAA2022* pathogenic variants, with profound intellectual disabilities, limited language development, strikingly similar autistic behavior, delay in motor milestones, and postnatal growth restriction. Patient 1, 19-years-old, has long ears, deeply set eyes with keratoconus, strabismus, a narrow forehead, anteverted nares, café-au-lait spots, macroglossia, thick vermilion of the upper and lower lips, and prognathism. He has gastroesophageal reflux, constipation with delayed rectosigmoid colonic transit time, difficulty regulating temperature, several musculoskeletal issues, and a history of one grand mal seizure. Patient 2, 10-years-old, has mild dysmorphic features, therapy resistant vomiting with diminished motility of the stomach, mild constipation, cortical visual impairment with intermittent strabismus, axial hypotonia, difficulty regulating temperature, and cutaneous mastocytosis. Genetic testing identified *KIAA2022* variant c.652C > T(p.Arg218*) in Patient 1, and a novel nonsense *de novo* variant c.2707G > T(p.Glu903*) in Patient 2. We also summarized features of all reported males with *KIAA2022* variants to date. This report not only adds knowledge of a novel pathogenic variant to the *KIAA2022* variant database, but also likely extends the spectrum by describing novel dysmorphic features and medical conditions including macroglossia, café-au-lait spots, keratoconus, severe cutaneous mastocytosis, and motility problems of the GI tract, which may help physicians involved in the care of patients with this syndrome. Lastly, we describe the power of social media in bringing families with rare medical conditions together.

KEYWORDS
KIAA2022, X-linked intellectual disability

1 | INTRODUCTION

KIAA2022 is an X-linked gene that has been implicated in X-linked intellectual disability (XLID) (Athanasakis et al., 2014; Cantagrel et al., 2004; de Lange et al., 2016; Farach & Northrup, 2016; Kuroda et al., 2015; Moysés-Oliveira et al., 2015; Van Maldergem et al., 2013; Webster et al., 2016). Pathogenic variants in X chromosome genes are believed to account for 5–10% of intellectual disabilities (ID) in males, and to date over 100 XLID genes have been discovered (Lubs, Stevenson, & Schwartz, 2012). *KIAA2022* was first hypothesized by Cantagrel et al. (2004) to be an XLID gene after the identification of a family with two male patients with ID and an X chromosome pericentric inversion with *KIAA2022* and *P2RY8* interrupted by the breakpoints. Subsequently, five additional families with males with ID and *KIAA2022* pathogenic variants have been found (Kuroda et al., 2015; Van Maldergem et al., 2013). Van Maldergem et al. (2013) described truncating frameshift variants in *KIAA2022* in two families with males with ID, and a 70-kb microduplication in *KIAA2022* exon 1 in another family with a male with ID. Kuroda et al. (2015) identified two additional nonrelated males with ID and nonsense variants in exon 3 of *KIAA2022*. Recently, Charzewska et al. (2015) reported a family with two patients with whole gene duplication spanning a 384-kb segment, but interestingly with decreased expression

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of KIAA2022 protein in fibroblasts and lymphocytes. A recent paper described five females with *de novo* pathogenic variants in *KIAA2022*, most of them described as nondysmorphic and with mild to severe intellectual disability (Webster et al., 2016). Skewed X-inactivation in the brain was presented as the possible explanation for the differences. Interestingly all of the females reported had epilepsy as well. Given the small number of individuals found to have *KIAA2022* pathogenic variants, a precise description of morphological features and clinical spectrum delineation requires further case reports to be published. Further delineation of pathogenic variants in *KIAA2022* is important to the individuals and the families affected, as well as the physicians involved in the care of these individuals, and requires future research. We report two further unrelated male patients with nonsense *KIAA2022* pathogenic variants and provide an overview of the features of all male patients with *KIAA2022* pathogenic variants reported to date.

2 | PATIENT 1

Patient 1 is the first child of unrelated healthy Canadian parents of Western European descent. He was delivered at term after an uncomplicated pregnancy, and weighed 3,430 g (mean) with length unknown. Early developmental delays were observed; he was not able to crawl until 2 years and walk unaided until 5 years. The patient was completely nonverbal until the age of five. On the Vineland Adaptive Behavior Scale, a standardized test designed to measure adaptive behavior and day-to-day functioning, at 5 years of age, the patient scored in the bottom 0.1–0.3%ile in the areas of communication, socialization, daily living skills, and motor skills.

The patient was first seen by another genetics clinic at 2 years of age for global developmental delay and underwent chromosomal and metabolic workups, which were reported as normal at that time. The patient has been seen at our genetics clinic since 11 years of age for a profound ID and autistic behavior. At his most recent assessment at the age of 19 years, he continues to have difficulties in control of both bowel and bladder function. His medical issues include chronic constipation and flatulence, gastroesophageal reflux, large adenoids, mild scoliosis and kyphosis, metatarsophalangeal, interphalangeal and large joint hypermobility, pes planus, difficulty regulating temperature as evidenced by intolerance to temperature extremes, and a history of one grand mal seizure. He also has a high pain tolerance. For aggressive behavior toward others, he was prescribed the maximum dose of risperidone, which has markedly reduced these behaviors. He has approximately 4 words and 20 signs in his vocabulary, but is primarily nonverbal and has limited social interactions. He engages in self-injurious behaviors including head banging and eye poking. He has restricted interests to small and tactile objects, and is fascinated by blocks and spoons. He also looks at objects through the side of his eyes. Other sensory issues include repetitive rubbing and smelling objects.

On examination, his head circumference is 55.5 cm (-1 *SD*), height is 154 cm (-3 *SD*), and weight is 43 kg (<-4 *SD*). His dysmorphic features include long ears (7 cm in length, $>+2$ *SD*), a narrow forehead, deeply set eyes, severe keratoconus in both eyes, with in his left eye requiring a corneal transplant, strabismus, anteverted nares, four frontal hair upsweeps, a double hair whorl, several café-au-lait spots on his back, macroglossia, thick vermilion of the upper and lower lips, and prognathism (Figure 1; Patient 1). He continues to be hypotonic. He

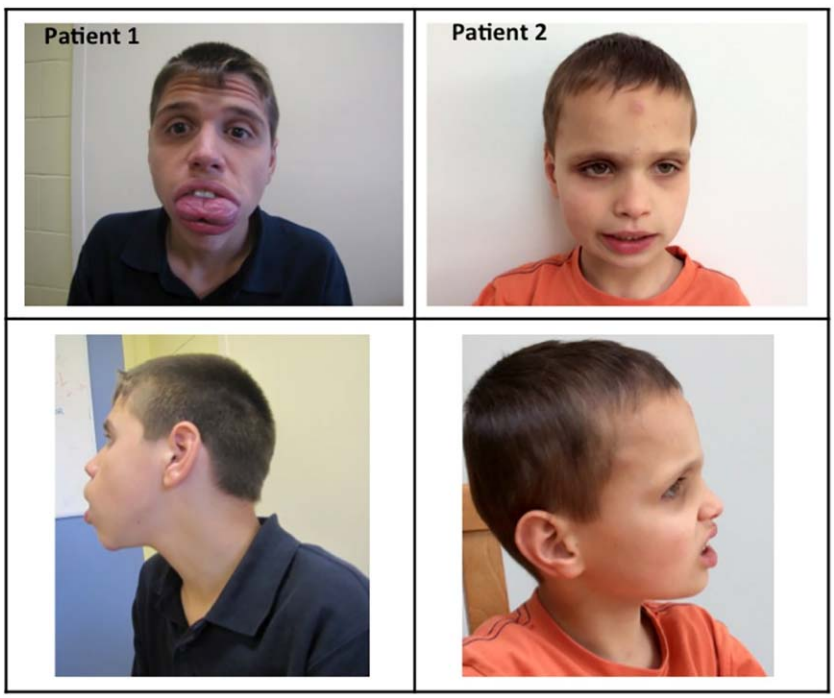


FIGURE 1 Photograph of the patients. Patient 1 with a narrow forehead, frontal hair upsweeps, long ears, deeply set eyes, anteverted nares, hypotonia, macroglossia, thick vermilion of the upper and lower lips, and prognathism. Patient 2 with deeply set eyes and a thick vermilion of the lower lip

walks uncoordinated, with pronation of his feet. His fine motor skills are also limited. The patient has many repetitive motor movements including rocking, hand flapping, and flicking his fingers in front of his eyes.

Little information could be provided on the patient's mother, as she is estranged from the patient's father and has not been involved in the patient's care since he was an infant. However, the patient's father was able to confirm that the patient's mother had a learning disability and completed high school in a special needs program. It is also known that she has two other daughters fathered from two different males, and one of the daughters has an ID. This daughter, the patient's biological half-sister, was seen as a follow-up in our clinic and was found to be carrier of the same pathogenic variant. As described previously for other females in literature, she is nondysmorphic with a moderate intellectual disability and a history of grand mal seizures. The other half-sibling is reportedly doing well. Patient 1's mother has not shown an interest to attend the clinic for genetic testing.

Patient 1's initial investigations included a normal XY karyotype, microarray, *PAK3* and *ATRX* gene sequence analysis, and Fragile X Syndrome test (PCR amplification of the CGG repeat region in *FMR1* gene). He had a normal metabolic screen, which included testing for urine organic acids (UOA) and amino acids (UAA), plasma amino acids (PAA), acylcarnitines profile, mucopolysaccharides and oligosaccharides screened for using thin-layer chromatography, ammonia, and lactate. He also had normal endocrine tests including cortisol, insulin like growth factor, and thyroid function. Brain-imaging tests included a normal CT at 11 years, and normal magnetic resonance imaging (MRI) at 14 years. An 18 channel electroencephalography (EEG) at 11 years demonstrated generalized low-voltage 15-Hz beta activity, with intermittent bifrontal 1-Hz delta slow wave activity and left temporal 5- to 6-Hz theta slow wave activity. Gastrointestinal (GI) studies for abdominal distension completed from the age of 12–14 years revealed a normal abdominal ultrasound, normal anorectal manometry, distension of the large bowel to the rectum found on an upper GI series and contrast barium enema, and a delayed rectosigmoid colonic transit time. A skeletal survey performed at 16 years showed a bone age of 13 years (-2 *SD*). An echocardiogram performed at 18 years was normal except minor mitral insufficiency.

3 | PATIENT 2

Patient 2 is the third child of unrelated healthy Dutch parents. During the pregnancy, his mother reported reduced fetal movements. He was born at 40 weeks by cesarean section, and weighed 3,120 g (-1 *SD*) and was 49 cm (mean) in length. The first years of his life were complicated by failure to thrive, intractable vomiting, disturbed temperature regulation (episodes of hypothermia and hyperthermia without organic causes), and cutaneous mastocytosis. He was hypotonic and had problems with muscle tone regulation, which included episodes of hypertonia and sudden clenching of his jaws during feeding. The patient was first referred to genetics at the University Medical Center Groningen, Netherlands for severe developmental delay at 8 months of age characterized by poor eye contact, poor head control, and no smiling, interest in grasping objects, or attempts to roll over. He was able to sit unaided at 20 months of age, and to walk independently at 6 years. He had two episodes of generalized tonic-clonic seizures during periods of fever at approximately 12 months of age. At the age of 7 years he was diagnosed with cortical visual impairment (0.15) with intermittent strabismus, there were no structural ophthalmological abnormalities. At the most recent assessment at 10 years of age, his main medical problem remains extreme and persistent vomiting that began at a very early age. The vomiting has been resistant to all forms of therapy. Although it was deemed medical, attempts at behavioral therapy were made and found to be unsuccessful. Constant one-to-one feeding has provided some weight gain. He still has difficulty regulating temperature as evidenced by intolerance to temperature extremes. He is incontinent in both bowel and bladder function and has mild constipation. The patient has no language ability and has limited social interactions. He has a high pain tolerance and engages in self-injurious behaviors including head banging, biting hands, and eye poking.

On examination, his head circumference is 51 cm (-3 *SD*), height is 122 cm (-3 *SD*), and weight is 20 kg (<-4 *SD*). He has deeply set eyes and a thick vermilion of the lower lip (Figure 1; Patient 2). His skin shows signs of cutaneous mastocytosis. He is generally hypotonic. He walks uncoordinated and his fine motor skills are limited. His behavior is characterized by hyperactivity, contact avoidance, repetitive behaviors, and stereotypic movements including rocking and hand flapping.

The patient had a normal XY karyotype, FISH for 22q11.2 deletion, and FMR1, *CDKL5*, *MECP2*, *MEF2C*, *FOXG1*, *RAI1*, and *KIT* gene testing all proved to be negative in the past. He had normal thyroid function and a normal metabolic screen, which included urine testing for UOA, UAA, purines/pyrimidines, mucopolysaccharides and oligosaccharides screened for using thin-layer chromatography, sialic acid, creatine, and guanidinoacetate. Plasma testing for PAA, sialotransferrin profile, fatty acid profile, 7-dehydrocholesterol, 8-dehydrocholesterol, lactate, and pyruvate were also normal.

Imaging tests included a normal brain MRI at 19 months. He had a normal echocardiogram at 20 months. Three 20-channel EEG registrations were also performed. Background activity was normal at 2–7 Hz with good differentiation in all three registrations, sporadic peak activity, and two bifrontal and bitemporal peak-wave complexes. A sleep registration in the afternoon showed a remarkable period of 20 seconds duration with theta–delta activity 3–4 Hz and voltage 100–250 μV, with no significant clinical correlation seen on simultaneous video-registration.

Repeated studies for gastroesophageal reflux showed no abnormalities. GI studies at 4 years demonstrated a large stomach with diminished movement and delayed gastric emptying.

4 | MATERIALS AND METHODS

Consent was obtained from the patients' parents in accordance with Queen's University Health Sciences Research Ethics Board. Peripheral blood was collected from the patients and DNA collection and a

targeted panel using next-generation sequencing for XLID genes was performed by Greenwood Genetic Center's molecular diagnostic laboratory for Patient 1. Whole exome sequencing was performed by Radboud University Medical Center Netherlands for Patient 2 (Dr. R. Pfundt). The pathogenic variants were confirmed by Sanger sequencing.

5 | RESULTS

Targeted sequencing identified a nonsense pathogenic variant of *KIAA2022*: c.652C > T(p.Arg218*) [NM_001008537.2] in exon 2 of Patient 1. His biological mother could not be reached for testing, but his biological half-sister also had the same pathogenic variant.

Whole exome sequencing identified a novel nonsense pathogenic variant of *KIAA2022*: c.2707G > T(p.Glu903*)[NM_001008537.2] in exon 3 of Patient 2. Exome sequencing and Sanger sequencing analysis of the mother did not detect the pathogenic variant, suggesting the change arose *de novo* in this patient.

6 | DISCUSSION

We report two nonsense pathogenic variants, one being a novel, in two unrelated male patients with profound ID. These represent the seventh and eighth reported families with males with ID and a *KIAA2022* pathogenic variant (Cantagrel et al., 2004; Kuroda et al., 2015; Van Maldergem et al., 2013). Patient 1 shares many of the same features as the previously studied 10 male patients including narrow foreheads, anteverted nares, long ears, hypotonia, postnatal growth restriction, strabismus, seizures, gastroesophageal reflux, limited language development, delay in motor milestones, autistic behavior, and ID (Table 1) (Cantagrel et al., 2004; Kuroda et al., 2015; Van Maldergem et al., 2013). Patient 1 has musculoskeletal issues including metacarpophalangeal, interphalangeal and large joint hypermobility, pes planus, and spinal curvatures, which have only been reported in two other patients with a duplication of the gene, but decrease in the KIAA2022 protein (Charzewska et al., 2015). His bone age was less than 2 *SD*, which can be seen in many genetic syndromes, but may require further endocrinological workup including for hypogonadotrophic hypogonadism. Moreover, he is the first patient with a *KIAA2022* pathogenic variant to have macroglossia and more than one café-au-lait spots as dysmorphic features. Patient 1 is also the first reported individual to have keratoconus. His keratoconus is so severe that the right eye has required surgery and the left eye, a corneal transplant. These features may represent features of the *KIAA2022* loss of function; however it is possible that this patient could have an additional genetic condition that has not been tested for.

The pathogenic variant found in Patient 1, c.652C > T(p.Arg218*), was previously reported in a female patient described by de Lange et al. (2016) and Webster et al. (2016). When comparing our patient to the female patient, the two share some of the same features including hypotonia, a broad-based gait, and postnatal growth retardation. However, as compared to the female patient, our patient walked at a later age (5 years vs. 15 months), has a more severe language delay, a more profound intellectual disability, and features not present in the female patient such as frontal hair upsweeps and double hair whorl, long ears, macroglossia, café-au-lait spots, delayed bone age, delayed rectosigmoid colonic transit time, joint hypermobility, scoliosis, strabismus, and keratoconus. Moreover, the female patient began having generalized tonic-clonic seizures at 2 years of age, and continues to have approximately 10–15 seizures a day whereas our patient has had only one episode of a grand mal seizure at 14 years of age.

Patient 2 also shares similar features as other reported male patients including hypotonia, postnatal growth restriction, strabismus, absent language development, delay in motor milestones, autistic behavior, and ID (Table 1). Patient 2 is the first patient to have demonstrated therapy resistant intractable vomiting and severe cutaneous mastocytosis. Both patients share strikingly similar autistic and behavioral features including rocking and hand flapping, high pain tolerance, self-injurious behaviors, and restricted interests to inanimate objects. They also display issues with motility of the stomach and gut, including diminished movement and delayed gastric emptying of the stomach, and delayed rectosigmoid colonic transit time. Both patients demonstrate difficulty regulating their body temperature, a feature which has only been reported in one other patient with a *KIAA2022* pathogenic variant (Cantagrel et al., 2004).

Recent publications have mainly focused on female patients with *KIAA2022* pathogenic variants described to have ID and seizures as the main presenting features, but provide limited information on the symptomatology in males (Athanasakis et al., 2014; de Lange et al, 2016; Farach & Northrup, 2016; Moysés-Oliveira et al., 2015; Webster et al., 2016). Thus, we have focused on summarizing the male patients. From the reported male patients with *KIAA2022* pathogenic variants to date, for which sufficient data is available, it can be summarized that patients with pathogenic variants may have dysmorphic features including narrow foreheads, anteverted nares, round faces, and long ears (Table 1). These patients are typically hypotonic and have postnatal growth restriction. Developmentally, these individuals tend to have delayed motor milestones, lack of language development, autistic behavior and stereotypic movements, and moderate to profound ID. In terms of health concerns, the majority of patients have a history of seizures, gastrointestinal issues, and strabismus. There have also been reported musculoskeletal concerns including pes calcaneovalgus, pes planus, metacarpophalangeal, interphalangeal and large joint hypermobility, as well as spinal curvatures (Cantagrel et al., 2004). Patients may less commonly have shawl scrotum, oculogyric crisis, keratoconus, or central hypothyroidism (Cantagrel et al., 2004; Kuroda et al., 2015). It is also known that these individuals live at least into their midlives, as the oldest known patient with a *KIAA2022* pathogenic variant is in his 40s (Cantagrel et al., 2004).

In conclusion, these nonsense *KIAA2022* pathogenic variants discovered in two male patients with severe ID lend further support to the gene's role in XLID, as do the previously described families with ID and *KIAA2022* pathogenic variants (Athanasakis et al., 2014; Cantagrel et al., 2004; de Lange et al., 2016; Farach & Northrup, 2016; Kuroda et al., 2015; Moysés-Oliveira et al., 2015; Van Maldergem et al., 2013;

TABLE 1 Summary of clinical characteristics of male patients with *KIAA2022* variants

Clinical report	Cantagrel et al. (2004) and Van Maldergem et al. (2013)		Van Maldergem et al. (2013)		Van Maldergem et al. (2013)	Van Maldergem et al. (2013)			Kuroda et al. (2015)	Kuroda et al. (2015)	Current paper	Current paper	Charzewska et al. (2015)	
Family	Family 1		Family 2		Family 3	Family 4			Family 5	Family 6	Family 7	Family 8	Family 9	
Patient	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8	Patient 9	Patient 10	Patient 11	Patient 12	Patient 13	Patient 14
Age of evaluation	12 years	5 years	6 years	4 years	8 years	14 years	10 years	40 years	3 years	5 years	11 years and is now 19 years	8 months and is now 10 years	–	–
KIAA2022 variants	46,Y, inv(X) (p22.3q13.2)		c.3597insA (p.Ser1200 Tyrfs*5)		46,Y,dup(X) (q13.3q13.3), 70 kb exon 1	c.183 delC (p.Arg62 Glufs*22)			c.2113C>T (p.Gln705*)	c.964C>T (p.Arg322*)	c.652C>T (p.Arg218*)	c.2707G>T (p.Glu903*)	Duplication of entire gene and large intergenic flanks, and decreased KIAA2022 protein expression	
Neonatal and early fetal concerns														
Hypotonia	+	+	–	+	–	–	–	–	+	+	–	–	–	–
Reflux	+	+	+	–	–	–	+	–	+	–	–	–	–	–
Other	Poor visual pursuit	C-section for acute fetal distress.	Infantile spasms seizures.	Poor eye contact	Mother had relapsing Crohn's disease in pregnancy	Repetitive attitudes and bulimia noted in infancy	–	–	Born at 33 weeks due to premature rupture of membranes	–	–	Reduced fetal movements in pregnancy	–	–
Dysmorphic features														
Microcephaly	–	+	+	+	–	–	–	–	–	+	–	–	–	–
Round face	–	+	–	+	–	+	+	–	–	–	–	–	–	–
Narrow forehead	–	–	+	+	–	–	–	–	+	+	+	–	–	–
Hair	–	–	–	–	–	–	–	–	Upswept	Upswept	4 frontal upsweeps, double hair whorl	–	–	–
Prognathism	–	+	–	–	–	–	–	–	–	–	+	–	–	–
Macroglossia	–	–	–	–	–	–	–	–	–	–	±	–	–	–
Short philtrum	+	–	–	–	–	–	–	–	–	–	–	–	–	–
Anteverted nares	–	–	–	–	–	–	–	–	+	+	+	–	–	–
Long ears	–	–	–	–	–	–	–	–	+	+	+	–	–	–
Postnatal growth restriction														
Height	−2.6 *SD*	−2.5 *SD*	−3.5 *SD*	−6.5 *SD*	–	–	+1 *SD*	−1 *SD*	−3.3 *SD*	−5 *SD*	−3 *SD*	−3 *SD*	–	–
Weight	−1 *SD*	−1 *SD*	–	−4.5 *SD*	–	–	+4 *SD*	+8 *SD*	−1.2 *SD*	−3 *SD*	−4 *SD*	−4 *SD*	–	–
Hypotonia	+	+	+	+	–	–	–	–	+	+	+	+	–	–
Motor														
Sitting	15 months	18 months	12 months	24 months	–	–	9 months	–	21 months	14 months	2 years (crawled)	20 months	–	–
Walking	3 years	3 years	34 months (lost after 6 months)	4 years	17 months	18 months	18.5 months	–	3 years	4 years	5 years	6 years	–	–

(Continues)

TABLE 1 (Continued)

Clinical report	Cantagrel et al. (2004) and Van Maldergem et al. (2013)		Van Maldergem et al. (2013)		Van Maldergem et al. (2013)	Van Maldergem et al. (2013)			Kuroda et al. (2015)	Kuroda et al. (2015)	Current paper	Current paper	Charzewska et al. (2015)	
Language	Absent	Absent	Limited to a few words	Absent	Limited to disyllabic repeats	Able to read and write	Delayed	–	Absent	Absent	Able to speak four words	Absent	–	Delay of speech
Intellectual disability	Profound	Profound	Profound	Profound	Mild	Mild	Severe	Moderate	Severe	Severe	Profound	Profound	Moderate	Severe
Behavioral and social														
Autistic behavior	+	+	+	+	+	–	+	–	+	+	+	+	+ (atypical)	+
Stereotypic movements	+	+	+	+	+	–	+	–	+	–	+	+	–	–
Other	Grunting, aggressiveness, anxiety	Self-injury, hyperactivity	Outbursts of laughing and screaming	–	Pervasive disorder	Hyperactivity, low attention span	Aggressiveness, hyperactivity, low attention span	Hyperactivity and bulimia at 3 years	Tongue protrusion	–	Aggression, flicking fingers in front of eyes, rubbing and smelling objects, self-harm	Hyperactivity, self-harm	–	–
Health issues														
Cutaneous	–	–	–	–	–	–	–	–	–	–	Multiple Café-au-lait spots	Cutaneous mastocytosis	–	–
Musculoskeletal	Pes calcaneovalgus quadriparesis, muscle wasting and spasticity of the lower limbs	Quadriparesis	Muscle wasting and spasticity of the lower limbs	Lower limb spasticity	–	–	–	–	–	–	Metacarpophalangeal, interphalangeal, and large joint hypermobility, scoliosis, kyphosis, pes planus.	None	Hyperextenion of the elbow joints and mobility of the metacarpoph-alangeal and interphalangeal joints, and lateral curvature of spine	Interphalangeal and hip joint mobility
Gastrointestinal														
Reflux	+	+	+	+	–	–	+	–	–	–	+	± (Treatment resistant emesis)	–	–
Others	–	–	–	–	–	–	–	–	–	–	Chronic constipation	Mild chronic constipation	–	–
Gentiurinary or kidney	Shawl scrotum	–	–	–	–	–	–	–	–	Steroid-dependent nephrotic syndrome	–	–	–	–

(Continues)

TABLE 1 (Continued)

Clinical report	Cantagrel et al. (2004) and Van Maldergem et al. (2013)		Van Maldergem et al. (2013)		Van Maldergem et al. (2013)	Van Maldergem et al. (2013)			Kuroda et al. (2015)	Kuroda et al. (2015)	Current paper	Current paper	Charzewska et al. (2015)	
Eye	Strabismus and oculogyric crisis	–	Strabismus	Strabismus	Right squint	–	–	–	–	–	Strabismus and keratoconus	Intermittent strabismus and cerebral visual impairment	–	–
Central Nervous system														
Seizures	Generalized	–	Flexor spasm	Flexor spasm	–	–	Lennox-Gastaut	Generalized	–	–	One episode of a grand mal seizure	Febrile	–	–
Temperature regulation	Several fevers of unknown origin	–	–	–	–	–	–	–	–	–	Difficulty regulating temperature	Difficulty regulating temperature	–	–
Imaging/other														
Brain MRI	Moderate brain atrophy, enlarged ventricles, Wirchow–Robin spaces, and thin corpus callosum	Small brain with mild enlargement of sulci in the frontal lobes	–	–	–	–	–	–	–	–	–	–	–	–
EEG (electro-encephalogram)	Bilateral marked slow dysrhythmia	–	Hypsarrhythmia	Hypsarrhythmia	–	–	–	–	–	–	Mild to moderate generalized slow wave excess	–	–	Generalized paroxysmal seizures
Gastrointestinal	–	–	–	–	–	–	–	–	–	–	Delayed rectosigmoid colonic transit time	Large stomach with diminished movement and delayed emptying	–	–
ECHO (echo-cardiography)	–	–	–	–	–	–	–	–	–	–	Minor mitral insufficiency	–	–	–
Skeletal Survey	–	–	–	–	–	–	–	–	–	–	Delayed bone age	–	–	–
Hypothalamic-pituitary-thyroid and gonadotropic	–	–	–	–	–	–	–	–	–	Central hypothyroidism	–	–	–	–

+ = a feature present in the individual; – = a feature either not present in the individual or not mentioned in the article; *SD*, standard deviation; Underlined = novel features.

Webster et al., 2016). This article describes new features likely to add to the spectrum of characteristics and medical issues these individuals face, including macroglossia, cutaneous mastocytosis, delayed gastric emptying, treatment resistant vomiting, and keratoconus, although future case studies will help in confirming this.

Both families of these individuals with *KIAA2022* pathogenic variants were engaged in bringing up a son with a profound intellectual delay, and challenging behavioral and medical problems. They met on the internet when searching for other patients with the same condition. From the start it was clear that both boys had an uncanny similarity in behavior and that the families faced similar problems, of which they alerted their physicians to. The families have established a strong long-distance relationship and they have become support systems for each other. This highlights the increasingly utilized role of social media in medicine amongst families, researchers, and physicians.

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CONFLICT OF INTEREST

None of the authors have any conflicts of interest to report.

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