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Protein-Activated Kinase 3 (PAK3)-Related Intellectual Disability Associated with Combined Immunodeficiency: A Case Report

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

ABDEF 1 Ohood Almutairi
ABDEF 1 Hessah A. Almutairi
ADE 2 Maysoun Al Rushood

1 Faculty of Medicine, Kuwait University, Jabriya, Kuwait
2 Department of Pediatrics, Faculty of Medicine, Health Sciences Center, Kuwait University, Jabriya, Kuwait

Corresponding Author: Ohood Almutairi, e-mail: Ohoodkalmutairi@gmail.com
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Patient: Female, 10-year-old (5-year-old at diagnosis)
Final Diagnosis: Combined immunodeficiency
Symptoms: Infection
Medication: —
Clinical Procedure: —
Specialty: Genetics • Immunology

Objective: Rare co-existance of disease or pathology

Background: X-linked intellectual disabilities constitute a group of clinically and genetically heterogeneous disorders that are divided into syndromic and nonsyndromic forms. *PAK3* mutations are associated with X-linked nonsyndromic forms of intellectual disability, with the most common clinical features being cognitive deficit, large ears, oral motor hypotonia, and neurobehavioral abnormalities. These mutations have been reported to be associated with either loss of the PAK3 protein or loss of its kinase activity. We report a case with the novel PAK3 variant c.685C>T p.(Pro229Ser), which has not been previously described.

Case Report: We report the first case of a *PAK3* mutation to present with the common clinical features along with immunodeficiency resembling common variable immune deficiency. Our patient was a 10-year-old girl who had experienced septic shock with a rapidly deteriorating course when she was 5-years-old. The initial immune work-up showed lymphopenia affecting all cell lines, but preferentially the B-cell compartment. Further work-up of this patient revealed low levels of immunoglobulin (Ig) G, undetectable IgA, reduced IgG1 and IgG2 subclasses, and poor response to the diphtheria/tetanus vaccine. Lymphocyte function, tested as the response to the mitogen phytohemagglutinin, was low and fluctuated between 9% and 22% compared with control samples. The patient experienced recurrent respiratory tract infections, and she responded well to regular intravenous Ig treatment and antibiotic prophylaxis.

Conclusions: The current case might provide a new insight into *PAK3* gene function. Although further evidence is needed, it is worth considering that immunological abnormalities may be associated with *PAK3* gene mutations.

Keywords: Case Reports • Common Variable Immunodeficiency • Developmental Disabilities • Intellectual Disability • p21-Activated Kinases

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Background

X-linked intellectual disabilities constitute a group of clinically and genetically heterogeneous disorders that are divided into syndromic and nonsyndromic forms [1,2]. The syndromic form refers to cases that have recognizable dysmorphic features and other distinguishing symptoms and signs. To date, the number of genes associated with an X-linked intellectual disability has increased by 96% from 72 to 141 genes [3]. Among these genes is the protein-activated kinase 3 (*PAK3*) gene, which has been reported to have mutations in multiple families [4-10]. Mutations of this gene are associated with X-linked nonsyndromic forms of intellectual disability, with the most common clinical features being cognitive deficit, large ears, oral motor hypotonia, and neuropsychiatric abnormalities. Those abnormalities, which include symptoms such as aggression, hyperactivity, psychosis, and inattention, are shown and compared in **Table 1**, along with brain imaging changes reported in previous studies. Moreover, epilepsy was commonly reported in these patients [6,9-11].

PAK3 mRNA is highly expressed in the fetal human brain but is not found at detectable levels in other fetal organs [12]. The *PAK3* gene, which is located on the long (q) arm of the X chromosome at position 23 (Xq23), is a member of the p21-activating kinase gene family [4,13]. This family of serine/threonine kinases is mainly involved in cytoskeletal rearrangements. Rho guanosine triphosphatases (GTPases) are a group of molecular switches that are important in regulating transduction pathways in eukaryotic cells. They regulate the cytoskeleton, cell polarity, gene transcription, and multiple other cellular processes. Multiple kinases have been found to interact with the Rho GTPases, including the PAK family, thus showing the importance of the PAK genes in the involvement of complex cellular processes [14].

Here, we describe the first reported case presenting with immunodeficiency and X-linked intellectual disability associated with a novel *PAK3* gene mutation. To delineate the presentation related to the *PAK3* mutation, we compare this patient with previously reported individuals and families with this mutation.

Case Report

Our patient was a 10-year-old girl whose parents were nonconsanguineous. The parents were healthy, with no intellectual disability, and both were university graduates. The patient had 1 healthy older brother and no significant family history except for a resolved seizure disorder in 1 maternal cousin. The girl was born full term via spontaneous uncomplicated vaginal delivery, and the fetal and early neonatal periods were unremarkable. Birth weight, length, and head circumference were all within the normal limits.

At the age of 2 weeks, she began having feeding difficulties and was admitted to the hospital for pneumonia. Thereafter, the patient had recurrent lower respiratory tract infections that were attributed to severe gastroesophageal reflux disease and recurrent aspiration.

At the age of 2 years, she was evaluated for failure to thrive and was found to have microcephaly and developmental delay. In addition, hypothyroidism and growth hormone deficiency were diagnosed, and she received treatment for these conditions. Brain magnetic resonance imaging (MRI) revealed diffuse cerebral and cerebellar atrophy with thinning of the corpus callosum, while an electroencephalogram was normal.

At the age of 5 years, the patient developed septic shock with a rapidly deteriorating course. The initial immune work showed lymphopenia affecting all cell lines, but preferentially the B-cell compartment. The serum immunoglobulin (Ig) levels showed mildly decreased IgG level for age; however, vaccine-specific antibody titers were protective. Over the following 2 years, the patient's immune status deteriorated clinically and she experienced recurrent respiratory tract infections. Repeated immune work-up revealed low levels of IgG, undetectable IgA, reduced IgG1 and IgG2 subclasses, and poor response to diphtheria/tetanus vaccine. The patient continued to have lymphopenia, mainly affecting the B-cell compartment. Lymphocyte function, tested through response to the mitogen phytohemagglutinin, was low and fluctuated between 9% and 22% compared with control samples. The patient had normal complement levels (C3 and C4). The patient's work-up since her diagnosis is shown in **Table 2**. She was started on daily prophylactic sulfamethoxazole-trimethoprim as well as monthly intravenous Ig in 2018. Since then, the patient has improved.

Clinical examination revealed that the patient had microcephaly, bilateral long and low-set ears, an elongated face with oral motor hypotonia, a bulbous tip to the nose, and deep-set eyes. Her weight was just below the 50th percentile and her height was just below the 25th percentile based on age-related norms. In view of her immunodeficiency and dysmorphic features, clinical exome sequencing was carried out. It revealed a hemizygous missense variant in the *PAK3* gene c.685C>T [Pro229Ser] (NM_001128168.2); this gene encodes a p21-activated kinase 3 that is associated with X-linked mental retardation (OMIM 300558).

This variant is classified as being of uncertain significance by VarSome [15] based on American College of Medical Genetics and Genomics (ACMG) standards and guidelines for interpretation of sequence variants (PM2, PP2, PP3) [16]. This variant is not present in the genome aggregation database nor in the 1000 Genomes Project.

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Table 1. Summary of the clinical features of patients with protein-activated kinase 3 (PAK3) mutations.

Publication	Facial features/head circumference	Intellectual disability	Motor/language development delay	EEG/epilepsy	Imaging	Abnormal behavior
Allen et al [4]	Microcephaly	+	Motor/ language developmental delay	NA/–	Small brain, but otherwise normal architecture	Violence, hyperactive
Bienvenu et al [37]	NA	+	Motor/ language developmental delay	NA	NA	NA
Gedeon et al [38]	Microcephaly	Mild	Motor developmental delay, learning disability	+	NA	Psychiatric presentation: schizophrenia, psychosis, aggressive antisocial behavior, depression
Peippo et al [5]	In all patients (high-bridged nose, thin upper lip, high-vaulted palate)	Mild to moderate in all patients	Motor developmental delay, learning disability	+	Hydrocephalus in 1 patient	Aggression, inattentive, hyperactive, insomnia, agitation, psychotic features
Rejeb et al [39]	Microcephaly, flat face, low forehead, up-slanting palpebral fissures, short nose with large ears	Mild to moderate	Motor/ language developmental delay	–	NA	Hyperactivity, extreme agitation and aggression, psychotic features
Magini et al [40]	Microcephaly, left epicanthus, bilateral ptosis, convergent squint, depressed nasal bridge, broad nasal tip and long ears	+	Motor/ language developmental delay	+/+	Agenesis of the corpus callosum and cerebellar hypoplasia.	NA
Muthusamy et al [41]	Microcephaly, elongated face, bushy eyebrows, long and/or prominent low-set ears, short neck, and pes planus	Moderate	Motor/ language developmental delay	–	NA	Attention deficit, hyperactivity, aggression
Hertecant et al [42]	Macrocephaly	+	Motor/ language developmental delay	NA	NA	Temper tantrums

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Table 1 continued. Summary of the clinical features of patients with protein-activated kinase 3 (PAK3) mutations.

Publication	Facial features/head circumference	Intellectual disability	Motor/language development delay	EEG/epilepsy	Imaging	Abnormal behavior
Cartwright et al [7]	Bilateral low-set ears, a bulbous tip to the nose, deep-set eyes with accessory nipples	Mild	Motor/ language developmental delay	NA	NA	Autism
Horvath et al [6]	Facial asymmetry, long midface, full lips and a long jaw and a Marfanoid-like habitus.	Mild	Motor/ language developmental delay	+	Ventriculo-megaly, thin corpus callosum, multifocal areas of white matter cavitation of left temporal, left occipital, right parietal, and right occipital lobes	Anxiety, irritability, restlessness, aggression, self-abusive behavior
Iida et al [8]	Microcephaly	Severe	Motor/ language developmental delay	+	Cerebral white matter and midbrain atrophy, and a thin corpus callosum	Autistic stereotype movement
Qian et al [9]	Microcephaly, hypertelorism, mild nasal bridge depression, oral hypotonia, high palatal arch, large ears	+	Motor/ language developmental delay	+/–	Enlargement of the lateral ventricles, white matter decreased, and corpus callosum dysplasia	Hyperactivity, aggression
Nagy et al [10]	Microcephaly, large ears, prominent but not bulbous nose, low forehead, down slanting palpebral fissures, thin upper lip and high-arched palate	Mild to moderate	Motor/ language developmental delay	–	No abnormality	Severe attention deficit, mood imbalance, anxiety and autistic traits
This case	Microcephaly, bilateral long and low-set ears, elongated face with oral motor hypotonia, a bulbous tip to the nose and deep-set eyes	Mild	Motor/ language developmental delay	–/–	Diffuse cerebral and cerebellar atrophy along with thinning of the corpus callosum	None reported

EEG – electroencephalogram; NA – not applicable.

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Table 2. Selected laboratory test results of the patient.

Immune variant	Results			Reference range
	2016	2018*	2019	
IgG, g/L	3.91	4.39	6.17	4.9-16.1
IgG1, mg/L	2590	N A	NA	3060-9450
IgG2, mg/L	574	NA	NA	605-3450
IgG3, mg/L	381	NA	NA	99-1221
IgG4, mg/L	<71.4	NA	NA	18-1125
IgA, g/L	0.0859	<0.0667	<0.0667	0.4-2
IgM, g/L	0.266	0.615	0.302	0.5-2
Avg total $CD3^+$ T cells/µL (%)	746 (83.48)	766 (86.71)	478 (86.67)	1400-3700 (60-76)
$CD3^+$ $CD4^+$ helper T cells/µL (%)	172 (17.87)	179 (20.31)	148 (27.16)	700-2200 (31-47)
$CD3^+$ $CD8^+$ T cells/µL (%)	561 (58.41)	479 (54.42)	257 (47.19)	490-1300 (18-35)
$CD19^+$ B cells/µL (%)	84 (10.15)	83 (9.34)	41 (7.36)	390-1400 (13-27)
$CD16^+$ $CD56^+$ NK cells/µL (%)	50 (6.07)	47 (5.30)	28 (5.19)	130-720 (4-17)
Anti-diphtheria IgG, IU/mL	0.132	0.03 (Jan 2018); 0.06 (Feb 2018)	NA	0.01-0.1
Anti-tetanus toxoid IgG, IU/mL	0.143	0.11 (Jan 2018); 0.140 (Feb 2018)	NA	0.01-0.1
Anti-HIB IgG, mg/L	0.123	NA (Jan 2018); 0.027 (Feb 2018)	NA	0.15-1
Anti-PCP IgG, g/L	6.72	NA (Jan 2018); 0.936 (Feb 2018)	NA	10-30

HIB – *Haemophilus influenzae* type b; Ig – immunoglobulin; NK – natural killer; NA – not applicable; PCP – pneumocystis pneumonia.
* A diphtheria/tetanus vaccine booster was given in January 2018.

The variant was predicted to be pathogenic by 9 different computational programs (BayesDel addAF, DANN, FATHMM-MKL, LIST-S2, LRT, MutationTaster, PROVEAN, PolyPhen, and PrimateAI). Moreover, it has a genomic evolutionary rate profiling score of 5.8499, with a score of 6.17 being the most conserved.

Paternal carrier testing was recommended to the parents to know whether the variant was due to a de novo or an inherited mutation; however, they were reluctant. The patient was referred for X-chromosome inactivation analysis, but unfortunately, the test could not be done for many reasons.

Discussion

This report describes a case of intellectual disability linked to a mutation in the *PAK3* gene. The PAK3 variant c.685C>T p.(Pro229Ser) is novel mutation that has not been previously described. It is a missense mutation of uncertain significance, class 3 according to ACMG guidelines. Missense mutations constitute the majority of reported cases, with this case being the 12th to be reported. Other mutations included 1 nonsense, 1 splicing, and 1 frameshift. In addition, only 1 deletion has been reported so far [9].

This case is also the first to be reported with a *PAK3* mutation presenting with immunodeficiency alongside neurobehavioral deficits. The patient's immunodeficiency had features suggestive of common variable immunodeficiency syndrome, given her low IgG, low IgA, poor vaccine response, and low B-cell number and percentage. She also had chronic lymphopenia with variable T-lymphocyte function.

The patient had features similar to those reported for other families carrying a *PAK3* mutation, and comparisons are made in **Table 1** [6-8]. A previous study reporting a multiplex pedigree family with a point mutation in *PAK3* suggested that PAK

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signaling may be critical for neuronal connections underlying human cognitive function [4].

In a study of *PAK1*/*PAK3* double-knockout mice, the mice were born with a normal brain size but subsequently showed significant impairment of brain growth [17]. The results provided important evidence relating *PAK3* mutations to intellectual disability.

The most recent brain MRI in our patient predictably showed a small atrophied brain with grossly normal brain structures. Similar MRI findings were reported in mentally retarded male patients carrying a *PAK3* mutation in another family [4]. These results could suggest that PAK3 is not absolutely needed for neuronal proliferation or migration [4].

Our patient, similar to others with a *PAK3* mutation, had no history of seizures; however, other families had members with epilepsy, which shows the clinical heterogeneity of *PAK3* mutations [6-8].

To the best of our knowledge, our report describes the first case of combined immunodeficiency in a patient with this mutation. A relationship between PAK3 mutations and immunodeficiency has not been previously found, and limited studies have investigated the roles of PAK3 in immunodeficiency. However, the possibility exists that our patient's intellectual disability and immunodeficiency resulted from 2 different unrelated conditions. Another possibility is that the PAK3 variant could have interacted with another gene to cause the immunodeficiency. This could be supported by the fact that PAK3 can interact with Rac2, a member of the Rho GTPases, which play a pivotal role in regulating several vital cellular and immunological processes [18-20], including lamellipodia formation, chemotaxis, directed migration, and superoxide production in phagocytic cells [21]. Mutations within the encoding region of *Rac2* have been implicated in multiple immunodeficiency diseases such as neutrophil immunodeficiency syndrome and lymphopenia, which was present in our patient [22-24].

In innate immunity, Rho GTPases are involved in phagocytosis and regulation of leukocyte chemotaxis and motility [25-28]. Rho GTPases also play an important role in adaptive immunity by regulating the activation and migration of T and B cells and forming immunological synapses between dendritic cells and antigen-specific T cells, which are prerequisites for inducing an adaptive T-cell response [29-32]. Furthermore, mutations in Rho and Rho-modulating factors have been found to increase the risk of autoimmune diseases and hematopoietic malignancies [33-35].

One study found the expression of PAK1, another member of the PAK family, was detectable in both naive and activated T cells, while PAK3 was evident only in activated T cells [36]. That study also showed that the specific depletion of PAK3 reduces the elongation of activated T cells induced by activation-inducible lymphocyte immuno-mediatory molecule/inducible co-stimulator, a member of the CD28 co-stimulatory receptor family, as efficiently as PAK1. These findings indicated that both PAK1 and PAK3 are independently involved in this immunological process.

Moreover, a member of a family carrying a *PAK3* mutation previously presented with hypothyroidism due to childhood thyroiditis accompanied by alopecia and eczema, possibly linking *PAK3* mutation to immunological abnormalities [5]. Hypothyroidism was also present in our patient.

Conclusions

In conclusion, our report further confirms that subjects with a *PAK3* mutation share common features, including intellectual disability, microcephaly, and dysmorphic features. Although further evidence is needed, it is worth considering the possible association between immunological abnormalities and *PAK3* mutations, as highlighted in this case. This case, along with the previous reported studies, provides helpful information about the possibility of a new syndrome specific to *PAK3* mutation.

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Ethics approval

Ethics approval was obtained from the Ethics Committee of the Faculty of Medicine, Health Sciences Center, Kuwait University.

Conflict of interests

None.

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