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ORIGINAL ARTICLE

DYRK1A-related intellectual disability syndrome: a cohort of Portuguese patients

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Abstract

Introduction: *DYRK1A* heterozygous pathogenic variants have been shown to cause a syndromic form of intellectual disability (ID) with impaired speech development, features of autism spectrum disorder (ASD), microcephaly, and a recognizable facial gestalt that evolves with age. Patients can also present with gait disturbance or hypertonia, epilepsy, brain imaging, ocular, and foot anomalies. **Methods:** This is a cross-sectional study. Clinical data on patients with *DYRK1A* pathogenic variants identified at the Clinical Genetics Department of Santa Maria Hospital, in Lisbon, were retrospectively collected from medical records using a detailed clinical questionnaire. **Results**: We describe eight unrelated patients, six females and two males, aged 4 to 24. Fetal growth restriction (FGR) was present in 5/8, and microcephaly in 7/8. ID, ranging from mild to severe, and language impairment or absent speech were documented in all patients. ASD and/or stereotypic behavior were reported in 6/8. Five patients presented visual anomalies, most commonly optic disc pallor (in 4). Three main facial features were consistently reported: deep-set eyes, thin upper lip, and micro/retrognathia. Foot and hand anomalies were frequent. **Discussion/Conclusions:** Our cohort illustrates the variable degree of severity of a syndromic form of ID, which includes mild cases. Microcephaly and a typical neurobehavioral phenotype are in accordance with the literature, as well as some common dysmorphisms. Interestingly, optic disc pallor seems to be a frequent finding, highlighting the need for ophthalmological surveillance. Our study adds evidence to the existence of a consistent clinical phenotype of *DYRK1A*-related ID, hopefully contributing to increased awareness and improving the recognition of this entity.

Keywords: *DYRK1A*. Intellectual disability. Portuguese cohort.

Perturbação do desenvolvimento intelectual associada ao gene DYRK1A: uma coorte de doentes portugueses

Resumo

Introdução: Variantes patogénicas em heterozigotia no gene *DYRK1A* causam uma forma sindromática de perturbação do desenvolvimento intelectual (PDI) com comprometimento do desenvolvimento da linguagem, características de perturbação do espectro do autismo (PEA), microcefalia e um gestalt facial reconhecível que evolui com a idade. Os doentes também podem apresentar distúrbios da marcha ou hipertonia, epilepsia, alterações cerebrais estruturais, anomalias oculares e nos pés.

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Métodos: Trata-se de um estudo transversal. Os dados clínicos de doentes com variantes patogénicas no gene *DYRK1A* identificados no Departamento de Genética Clínica do Hospital de Santa Maria, em Lisboa, foram recolhidos retrospetivamente a partir de registos médicos através de um questionário clínico detalhado. **Resultados:** Descrevemos oito doentes não aparentados, seis do sexo feminino e dois do sexo masculino, com idades entre 4 e 24 anos. A restrição do crescimento fetal (RCF) esteve presente em 5/8 e a microcefalia em 7/8. PDI, ligeira a grave, com compromisso da linguagem ou a sua ausência, foi documentada em todos os casos. PEA e/ou comportamento estereotipado foram relatados em 6/8. Cinco pacientes apresentaram anomalias visuais, mais frequentemente palidez do disco óptico (em 4). Três características faciais principais foram consistentemente relatadas: olhos afundados, lábio superior fino e micro/retrognatia. Anomalias nos pés e nas mãos foram frequentes. **Discussão/Conclusões:** A nossa coorte ilustra o grau variável de gravidade de uma forma sindromática de PDI, que inclui casos ligeiros. A microcefalia e um fenótipo neurocomportamental típico estão de acordo com a literatura, assim como alguns dismorfismos comuns. Curiosamente, a palidez do disco óptico parece ser um achado frequente, destacando a necessidade de vigilância oftalmológica. O nosso estudo acrescenta evidências da existência de um fenótipo clínico consistente de PDI relacionada ao gene *DYRK1A*, contribuindo para aumentar e melhorar o reconhecimento desta entidade.

Palavras-chave: *DYRK1A*. Perturbação intelectual. Coorte portuguesa.

Keypoints

What is known
- *DYRK1A*-related intellectual disability syndrome is a rare condition with variable degrees of developmental delay reported.
- Loss-of-function DYRK1A pathogenic variants include disruptive balanced rearrangements, copy number variants, and single nucleotide variants (SNVs).
- No genotype-phenotype correlations could be consistently drawn.

What is added
- We report a new cohort of patients with *DYRK1A*-related intellectual disability syndrome.
- With advances on next-generation sequencing techniques, we expected an earlier diagnosis, raising awareness about common dysmorphic features, delineating a typical gestalt.
- Considering the prevalence of eye problems, namely optic disc pallor, a careful ophthalmological evaluation must be performed.

Introduction

DYRK1A (dual-specificity tyrosine phosphorylation regulated kinase 1A) is a protein kinase encoded on human chromosome 21[1-3]. The gene is dosage-sensitive with an impact on neurodevelopment[4]. *DYRK1A* is over expressed in Down syndrome (DS) and plays a relevant role in neuronal proliferation, differentiation, plasticity, and aging, making it a primary target for the development of DS therapeutics[2,5]. Dysregulation of *DYRK1A* levels also occurs in neurodegenerative diseases, such as Alzheimer and Parkinson[6].

Since 2008, the *DYRK1A* gene has gained attention in the clinical setting, starting with the description of two patients with microcephaly, fetal growth restriction, and febrile seizures. Both had a *de novo* balanced translocation that truncated the *DYRK1A* gene, suggesting *DYRK1A* haplo-insufficiency is associated with brain developmental changes[7].

In 2011, a *de novo* micro-deletion involving the last three exons of *DYRK1A* was described in a female with microcephaly and intellectual disability[8]. Considering these chromosomal rearrangements, as well as large deletions encompassing additional genes (that may contribute to extra-*DYRK1A*-related features)[9,10,11], van Bon et al. proposed that the heterozygous disruption of this gene causes a distinctive neuro-developmental syndrome, including mild to severe ID, microcephaly, and impaired speech[3].

One year later, Courcet et al. described a patient with an Angelman-like phenotype carrying a frameshift variant affecting the N-terminal part of the gene[12,13]. As more patients with single nucleotide variants in *DYRK1A* were documented, this gene was definitely placed on the list of genes responsible for syndromic ID. Furthermore, it has also been linked to autism spectrum disorder (ASD), with studies showing that *DYRK1A* syndrome accounts for 0.1-0.5% of individuals with ID and/or autism[3,12,14].

Core symptoms of *DYRK1A*-related ID syndrome (*OMIM#614104*) (also known as *DYRK1A*-haploinsufficiency syndrome or autosomal dominant mental retardation 7, MRD7) are ID with impaired speech development of variable degree, features of ASD with anxious and/or stereotypic behavior problems, microcephaly, and a recognizable facial gestalt that evolves with age[3,15]. Patients can also present with gait disturbance or hypertonia, epilepsy, brain-MRI anomalies, feeding issues, eye problems, and foot anomalies[15-17].

Loss-of-function *DYRK1A* pathogenic variants include disruptive balanced rearrangements, copy number variants, and single nucleotide variants (SNVs)[16]. About 500 families are part of the *DYRK1A* Syndrome International Association (DSIA). According to our acknowledge, there are around 112 patients reported in the literature[1,3,7,12-25] of whom with chromosomal abnormalities, including large deletions, translocations, inversions, inversion/deletions, and other complex rearrangements, and 87 patients harboring a SNV. Most reported SNVs were frameshift variants, followed by nonsense, missense, and splice site variants[16].

With this report, we aim to contribute to further delineating the phenotype of this still under-recognized but increasingly diagnosed condition.

Methods

This is a retrospective and cross-sectional study. Clinical data on patients with *DYRK1A* variants identified at the Genetics Department of Santa Maria Hospital, in Lisbon, were collected from medical records during 2022. We searched in our internal database (Microsoft® Office Access 2019) for patients with this diagnosis followed from January 2010 until December 2022 in our genetic service of a tertiary level hospital. Patient characterization was performed through a detailed questionnaire, completed by the clinician and organized into a standardized form designed in Microsoft® Office Excel 2010. This form was based on international registries and available literature, including information on the demographics, patient and family history, clinical and laboratory findings, genetic studies, and evolution. The molecular diagnosis was possible through whole exome sequencing (WES, CentoXome® from the Centogene laboratory in Germany) in all cases.

Results

A diagnosis of *DYRK1A*-related ID syndrome was made for eight unrelated patients, six females and two males, aged 4 to 24 years old, all representing simplex cases with a pathogenic or likely pathogenic variant in the *DYRK1A* gene. The summary of their main clinical features is shown in table 1.

FGR was present in 5/8. Further growth evaluation showed short stature in 4/8 and microcephaly in 7/8. ID, ranging from mild to severe, and language impairment (6/8) or absent speech (2/8) were documented in all patients. ASD and/or stereotypic behavior were present in 6/8. Only two patients had epilepsy, brain anomalies on MRI were present in 3/7, and 4/8 had gait disturbance (often ataxic) and hypertonic extremities, with no need to use support devices. Five patients had visual anomalies (strabismus, astigmatism, hypermetropia, optic nerve anomalies), with optic disc pallor present in four of them.

Characteristic facial features consistently reported were deep-set eyes (7/8), thin upper lip (8/8), and micro/retrognathia (5/8). Foot anomalies were described in 5/8 patients. Additional common features included thick eyebrows, prominent nose, large or dysplastic ears, and large mouth (Fig. 1).

The diagnosis was made on whole exome sequencing (WES) in all cases, but suspected clinically in four. *DYRK1A* variants were classified as pathogenic or likely pathogenic using ACMG criteria. All variants were located between exons four and ten, and 7/8 were loss of function, including three frameshift, two splicing, and two nonsense variants. There was only one missense variant not affecting the kinase domain. Parental segregation studies confirmed all cases were *de novo* (Table 1).

Patient 6 had an additional pathogenic variant in *PKD2* gene, explaining the presence of renal cysts.

Discussion

The purpose of this study was to characterize the *DYRK1A*-related ID syndrome patients diagnosed in our Medical Genetics Department. No Portuguese cohort has been published so far, and this syndrome is still unknown to many medical professionals dealing with ID/ASD patients. We have attempted to further delineate the phenotype of these patients by comparing them with those already described in the literature harboring a causative variant in *DYRK1A* gene. The clinical findings were consistent with the literature (Table 1).

Clinically, it is worth emphasizing the variable degree of severity of ID[3,6,15], which includes two mild cases in this cohort. Language impairment is seen in a significant proportion of patients[15,17], with completely absent speech in two of ours. ASD, stereotypes, anxious behavior, hyperactivity, and sleep disturbances have also been frequently observed[3,15], and were reported in all but two individuals in this cohort. Conversely, only two patients had epilepsy, which is lower than in the literature[12,17]. Seizures of the atonic, absence, and generalized myoclonic types have all been previously described[1,3,12,13]. FGR was present in 5/8 patients and can be a non-specific clue for the diagnosis of *DYRK1A*-related ID syndrome in the prenatal setting[3,13,20], but more reports are needed to reinforce this finding. Head circumference at birth is known to be between –1 and –4 SD, and abnormally slow head growth causes the

Table 1. Clinical characteristics of our cohort of Portuguese patients with *DYRK1A*-related intellectual disability syndrome and literature comparison

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8	Total n = 8 (%)	Patients in literature (%) 1,3, 7, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21,22, 23, 24
Age (years)	14	19	12	24	4	18	5	7	-	-
Genotype	c. 361C>T, p. (Gln121*)	c. 1405C>T, p. (Gln469*)	c. 665-9_ 665-5del	c. 562A>G, p.(Lys188Glu)	c. 336_348del, p.(Ala113Glufs*33)	c. 358del, p. (Gln120Asnfs*30)	c. 951+4_ 951+7del	c. 894del, p. (Lys299Asnfs*7)	-	-
Type of variant	Nonsense*	Nonsense	Splicing*	Missense	Frameshift	Frameshift	Splicing*	Frameshift	-	-
Classification	Likely pathogenic	Likely pathogenic	Pathogenic	Likely pathogenic	Likely pathogenic	Likely pathogenic	Pathogenic	Likely pathogenic	-	-
Inheritance	De novo	De novo	De novo	De novo	De novo	De novo	De novo	De novo	-	-
Sex	F	F	F	M	F	M	F	F	-	-
FGR	-	+	+	-	+	+	+	-	5/8 (63%)	33-64%
Microcephaly	-	+	+	+	+	+	+	+	7/8 (88%)	68-98%
Short stature	-	+	+	+	-	-	+	-	4/8 (50%)	10-41%
DD/ID	Mild-Moderate	Moderate	Mild	Severe	Moderate	Severe	Moderate	Moderate	8/8 (100%)	95-100%
Speech impairment	Impaired	Impaired	Impaired	Absent speech	Impaired	Impaired	Absent speech	Impaired	8/8 (100%)	96-100%
ASD/ Stereotypic behaviour	-	+	+	+	+	-	+	+	6/8 (75%)	29-50%
Feeding issues	-	-	-	+	-	-	+	+	3/8 (38%)	48-82%
Gait disturbance and/or hypertonia	-	-	-	+	+	-	+	+	4/8 (50%)	NA
Epilepsy	-	-	-	+	-	+	-	-	2/8 (25%)	20%-67%

(Continues)

Table 1. Clinical characteristics of our cohort of Portuguese patients with *DYRK1A*-related intellectual disability syndrome and literature comparison *(continued)*

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8	Total n = 8 (%)	Patients in literature (%) 1,3, 7, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21,22, 23, 24
Brain MRI anomalies	Megacisterna magna, hipoplasia of optic nerve and chiasma, corpus callosum agenesis	-	-	Cerebellar atrophy	-	-	NA	Bilateral ventricular enlargement	3/7 (43%)	31%-59%
Eye anomalies	Strabismus, astigmatism, hypermetropia, optic disc pallor, optic nerve bilateral atrophy	-	Strabismus, optic disc pallor	Strabismus, optic disc pallor	Temporal optic disc pallor	Strabismus	-	-	5/8 (63%)	46%-58%
Hand/feet anomalies	+	+	-	+	+	+	-	-	5/8 (63%)	37-50%
Deep set eyes	+	+	+	+	+	+	-	+	7/8 (88%)	10-29%
Large ears	+	+	+	+	-	-	-	-	4/8 (50%)	50-58%
Dysplastic ears	-	-	+	-	-	+	-	+	3/8 (38%)	NA
Long/flat filtrum	-	+	-	-	+	-	-	+	3/8 (38%)	NA
Thin upper lip	+	+	+	+	+	+	+	+	8/8 (100%)	NA
Micro/ retrognathia	+	-	-	+	+	+	-	+	5/8 (63%)	37%-54%
Additional features	Long eyelashes, bulbous nose tip, prominent supraciliary arch	Bitemporal narrowing, thick eyebrows, hypotelorism, malar hypoplasia, large mouth	Metopic prominence	Thick eyebrows, long nose, malar hypoplasia, large mouth		Renal cysts due to *PKD2* heterozygous pathogenic variant				

*Previously reported variants. ASD: autism spectrum disorder; DD: developmental delay; F: female; FGR: fetal growth restriction; ID: intellectual disability; M: male; NA: not available.

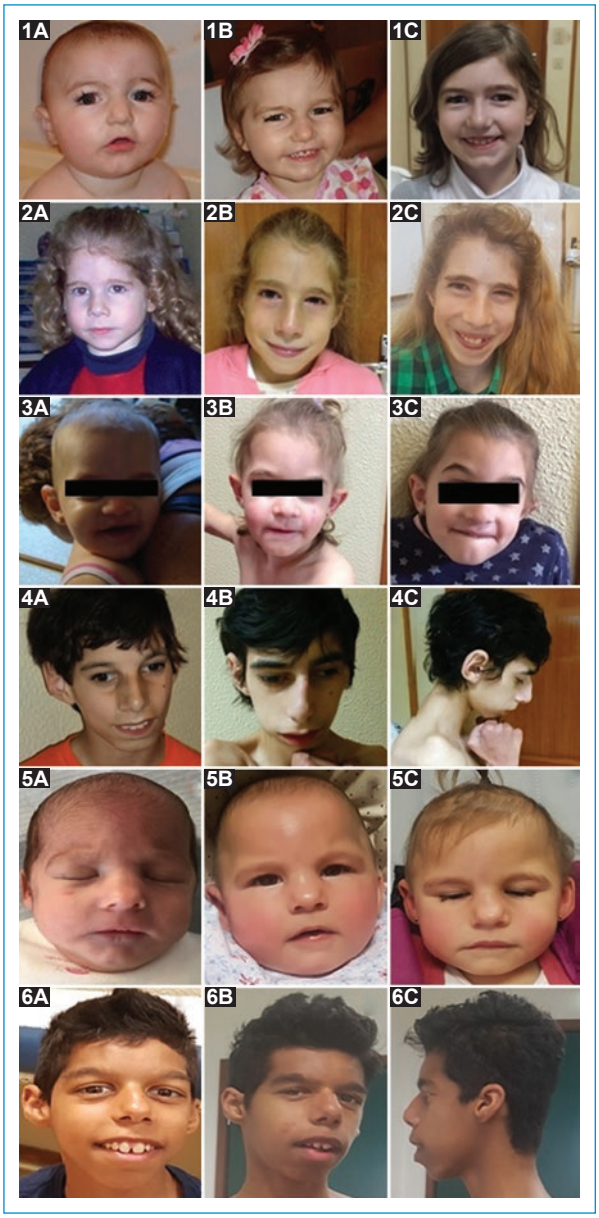

Figure 1. Images depicting similar and key dysmorphic features of presented cases, namely deep set eyes, thin upper lip and micro/retrognathia. **1A:** patient 1 at 11 months. **1B:** 5 years. **1C:** 10 years. **2A:** patient 2 at 3 years. **2B:** 11 years. **2C:** 13 years. **3A:** patient 3 at 1 year. **3B:** 3 years. **3C:** 6 years. **4A:** patient 4 at 13 years. **4B and C:** at 19 years. **5A:** patient 5 at 1 month. **5B:** 6 months. **5C:** 2 years. **6A:** patient 6 at 13 years. **6B and C:** 18 years.

deviation to further increase over time to –2 to –5 SD in the majority of individuals[3,15,17]. Accordingly, microcephaly was present in all but one patient in this report.

Gait disturbances, broad-based or stiffed, has been reported in a smaller fraction of individuals[17], with about half of the cases presenting this characteristic, very similar to what happens in our cohort.

Brain anomalies were described in 3/7 patients who had an MRI, including ventricular enlargement, sub-ependymal cysts, hypoxic-ischemic-like anomalies, corpus callosum agenesis, and cerebellar atrophy. Brain MRI anomalies are not well established in the literature, involving from grey matter to cerebral spinal fluid and ventricle anomalies[25,26].

Ocular anomalies were reported in five patients in our cohort, in line with Méjécase et al., who describe ocular features in 60.3% of patients with *DYRK1A* SNVs, predominantly refractive errors[16]. Optic nerve anomalies, including optic disc pallor, have been reported in 22.9% of patients[16], and were present in half of our cases.

Several publications refer to a typical gestalt or common dysmorphisms[1,3,13,15,18,20]. All patients in this report had a thin upper lip, and deep-set eyes were described in all but one (Fig. 1). Other frequent features include micro/retrognathia and large ears. In adulthood, the nasal bridge may become high and the alae nasi underdeveloped, giving the nose a more prominent appearance[3], as shown in patient 6 (Figs. 1-6 A, B, C).

Hand and feet anomalies were also frequent in our cohort and in previously reported patients[15,17], namely long splayed fingers, clinodactyly, mild cutaneous syndactyly of toes, hallux valgus, and short fifth toe.

The majority of variants elicited in our cohort were truncating, namely frameshift (Table 1), which is in accordance with previous reports[16]. Only three missense variants were previously reported in the literature[3,26]. No genotype-phenotype correlations could be consistently drawn. All cases were *de novo*.

From the above, it is clear that all *DYRK1A*-related syndrome ID patients need guidance for educational and behavioral problems, and should be regularly monitored for growth parameters and nutritional status, as well as have lifelong specialist follow up for issues affecting particular organs and systems[6,16,23]. Early motor intervention is also relevant regarding gait disorders and hypertonia, in order to avoid the use of a mobility device in the future[17]. Of note, taking into account the prevalence of eye problems, multidisciplinary care must include a careful ophthalmological evaluation.

All in all, national and international registries[27], and other forms of data sharing, are paramount in acquiring new insights into the pathophysiology and genetic mechanisms underlying this condition, which will ultimately contribute to improve patient management. In line with this endeavor, we hope this clinical review contributes to raise awareness of *DYRK1A*-related ID syndrome, namely among Portuguese doctors, so as to prompt the diagnosis of more patients.

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Conflicts of interest

None.

Ethical disclosures

Protection of human and animal subjects. The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki).

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author is in possession of this document.

Use of artificial intelligence for generating text. The authors declare that they have not used any type of generative artificial intelligence for the writing of this manuscript, nor for the creation of images, graphics, tables, or their corresponding captions.

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