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SHORT REPORT

Expanding the Phenotypic Spectrum of the Recurrent De Novo *FBXO31* p.Asp334Asn Variant: Evidence for a Novel Neurodevelopmental Disorder (Kruer Syndrome)

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ABSTRACT

Biallelic loss-of-function variants in *FBXO31* cause autosomal-recessive intellectual disability. A recurrent de novo variant, c.1000G>A(p.Asp334Asn), has been described in association with an autosomal-dominant phenotype. To refine this phenotype and its clinical implications, we re-evaluated three published cases and ascertained four additional probands via advocacy networks, GeneMatcher, and clinician referral. Phenotyping included neurologic, behavioral, and dysmorphology assessment. All seven individuals carried the recurrent de novo *FBXO31* p.Asp334Asn variant. A core neurodevelopmental profile was observed and included cerebral palsy (mixed hypotonia, spasticity, and dystonia), global developmental delay/intellectual disability, and speech impairment. Neuropsychiatric features were sometimes prominent and included attention-deficit/hyperactivity disorder, anxiety, stereotypies, autistic features, and behavioral dysregulation. Neuroimaging often showed a hypoplastic corpus callosum and posterior-predominant white-matter changes. In one individual, gray matter heterotopias were also observed. A subtle but consistent facial gestalt was noted. Recurrent *FBXO31* p.Asp334Asn variants lead to a recognizable neurodevelopmental syndrome. Based on our findings, we recommend including *FBXO31* in diagnostic algorithms for cerebral palsy and neurodevelopmental disorders. We propose the descriptive term "autosomal dominant FBXO31-associated neurodevelopmental disorder," and—consistent with the validating laboratory and with support from the FBXO31 Foundation—propose the eponym "Kruer syndrome."

1 | Introduction

Biallelic loss-of-function variants in *FBXO31*, which encodes an F-box protein of the Skp1-Cullin-F-Box (SCF) E3 ubiquitin-ligase complex, are known to lead to autosomal-recessive intellectual disability (ARID) (OMIM 615979) [1, 2]. More recently, an autosomal-dominant (AD) phenotype linked to the recurrent de novo variant, *FBXO31* c.1000G>A(p.Asp334Asn), was identified in two individuals with a spastic-dystonic cerebral palsy (CP) and intellectual disability (ID) phenotype, with in vitro evidence supporting a gain-of-function mechanism [3]. Recent work identified endogenous C-terminal amides within the cellular proteome as chemical indicators of protein damage arising from spontaneous radical-mediated reactions [4].

The authors found that FBXO31 serves as a C-terminal amide clearance factor, with SCF-FBXO31 complexes specifically recognizing C-terminal amidated peptides and marking them for proteasomal degradation via ubiquitylation. The p.Asp334Asn variant replaces a negatively charged asparagine within the substrate-binding pocket of FBXO31, abolishing normal binding to C-terminal amide peptides [3, 4]. Evidence shows that the p.Asp334Asn variant also leads to recognition of neosubstrates containing a [Lys/Arg]-X-Φ-COOH motif that is not recognized by the wild-type protein. *FBXO31* p.Asp334Asn therefore represents a neomorphic mutation, conferring recognition of an entirely new set of targets [4].

In this study, we describe the phenotypic spectrum associated with this variant by reporting the clinical features of 7 individuals (three previously published [3, 5]) harboring the same de novo missense variant. We highlight neurologic and neuropsychiatric features, brain MRI findings, and an emerging facial gestalt supported by Face2Gene [6] analysis.

2 | Materials and Methods

2.1 | Recruitment and Enrollment

Participants were ascertained through the FBXO31 Foundation, GeneMatcher [7], the CP Research Network, and referrals from treating clinicians. All families were enrolled under a research protocol approved by the Phoenix Children's Institutional Review Board (IRB-15-080). Written informed consent permitting publication of clinical data and identifiable photographs was obtained from all legal guardians, with assent when appropriate, in accordance with the Declaration of Helsinki.

2.2 | Phenotyping and Genomics

Trio exome sequencing (ES) was performed for all newly reported patients in CLIA-certified laboratories. Participants' medical records and photographs were collected through collaboration with treating clinicians. Human Phenotype Ontology (HPO) terms were coded. Photographs were reviewed by a trained dysmorphologist (CIGM) and two-dimensional (2D) facial similarity analyses among probands were performed. A prepubertal composite image from all probands was created with Face2Gene [6].

3 | Results

Patients 1–3 were previously reported with a focus on neurologic findings [3, 5]. We expand phenotypic descriptions and we report four new cases. *Patient 4* is a 6 year-old male who presented in early childhood with hypotonic CP, ID, expressive language disorder, behavioral dysregulation, stereotypies, and autism spectrum disorder (ASD); he exhibited aggressive outbursts beginning around age four. *Patient 5* is a 4 year-old male who presented at birth with severe hypotonia. He was diagnosed with spastic-dystonic CP with axial hypotonia, Gross Motor Function Classification System (GMFCS) level V, ID, expressive-receptive language disorder, hyperopic astigmatism, and bilateral *coxa valga*. *Patient 6* is a 3 year-old male who presented at 8 months of age with motor delay and was diagnosed with hypotonia and GDD. He was later diagnosed with a language disorder and stereotypies. *Patient 7* is a male who presented with GDD in infancy and was diagnosed with hereditary spastic paraplegia (HSP) together with mild ID and a language disorder. He currently functions at GMFCS II.

In all four newly reported cases, trio ES identified a heterozygous de novo *FBXO31* variant, c.1000G>A(p.Asp334Asn). Detailed clinical descriptions, neuroimaging findings, and facial morphology analysis are shown in Table 1 and Supporting Information S1.

Neuroimaging (brain MRI) revealed white matter and structural abnormalities, including hypoplastic corpus callosum (CC) in 4/7 patients and white matter abnormalities (3/7), gray matter heterotopias (1/7), and ex vacuo ventriculomegaly (3/7) (Figure 1).

A subtle, consistent facial gestalt was observed across reported and newly identified probands. Facial features seen in nearly all individuals include a high, broad, prominent forehead; thin/sparse, widely spaced eyebrows; periorbital fullness; small nose; thin upper lip; and retrognathia. Other frequent features include inferiorly displaced inner canthus, downslanting palpebral fissures, and broad nose. Orofacial findings include palatal and dental abnormalities (Figure 2).

4 | Discussion

The recurrent de novo *FBXO31* p.Asp334Asn variant leads to a recognizable neurodevelopmental syndrome. The core manifestations include GDD and dystonia/spasticity, often accompanied by neuroimaging findings of hypoplastic CC and less commonly featuring periventricular white matter hyperintensities, gray matter heterotopias, and/or ventriculomegaly.

After re-evaluating the previously reported cases with new affected individuals, we confirm prior phenotypic observations [3, 5] and note that prominent behavioral and neuropsychiatric features can occur. In some cases, family members emphasized that dysregulated behaviors represent the most challenging aspect of the disorder and often disrupt family functioning and limit community participation. Stereotypies were common, self-injury, ADHD, and anxiety were sometimes present, and ASD was confirmed in one patient.

Movement disorders are another variably expressed feature. The motor phenotype was clinically diagnosed as CP in most (5/7).

These data expand the neuroimaging spectrum to include brain anatomic anomalies, supporting a common upstream disruption of neuroglial development perhaps related to altered protein turnover [4, 8].

Craniofacial features show a recognizable facial gestalt across the probands. Although palatal anomalies were seen in some cases (3/4), palatal photos were unavailable for 3 cases.

TABLE 1 | Clinical manifestations of patients with p.Asp334Asn variant in FBXO31.

	Previously reported			New cases			
References	*Nat Genet* 2020; 52, 1046–1056		*Neurology* 2021; 8 (4): 951–955				
Patient	1 (F218)	2 (F699)	3	4	5	6	7
Sex	Female	Male	Male	Male	Male	Male	Male
Age at last evaluation (years)	9	10	9	7.8	4	3	13
Pregnancy and birth history							
Pregnancy complications	DFM	n/a	n/a	–	Breech presentation	–	–
Gestational age (weeks)	40	36.4	38	41.2	38.3	39.2	39
Birth weight (g)	4220	2620	n/a	4090	3740	3900	3220
Birth length (cm)	n/a	46	n/a	52	55.9	53.3	49
Birth HC (cm)	n/a	32.5	n/a	37.6	34.5	35.5	34.5
Apgar	n/a	n/a	n/a	9.9	9.9	n/a	n/a
Age of onset	Birth	n/a	Infancy	Infancy	Birth	Infancy	Infancy
Neurological features							
CP diagnosis	+	+	+	+	+	–	–
HSP diagnosis	–	–	–	–	–	–	+
Diplegic spasticity	+	+	+	+	+	–	+
Dystonia	–	–	+	–	+	n/a	–
Hypotonia	+	–	+	+	+	+	–
Clonus	–	–	+	–	+	–	–
GMFCS	III	III	IV	IV	V	II	II
Abnormal EEG	–	n/a	n/a	+	n/a	n/a	–
Neurodevelopmental/behavioral							
GDD	+	+	+	+	+	+	+

(Continues)

TABLE 1 | (Continued)

	Previously reported			New cases			
ID	+	+	+	+	+	+	+
Language disorder	+	+	+	+ (Expressive)	+ (Expressive/ receptive)	+	+
ASD	−	−	−	+	−	−	−
ADHD	+	+	−	−	−	−	−
Anxiety disorder	+	+	−	+	−	−	−
Stereotypies	+	+	−	+	+	+	+
Aggressive behavior	−	+	−	+	−	−	−
Self-injury	−	n/a	n/a	+	−	−	−
Happy demeanor	+	n/a	n/a	+	+	+	+
Brain imaging characteristics							
Thin or hypoplastic corpus callosum	−	+	−	+	+	−	+
Ventriculomegaly	−	+	−	−	−	+	+
White matter (WM) abnormalities		−	+ (Abnormal myelination; reduced volume of WM and WM hyperintensities)	+ (Leukomalacia and WM hyperintensities)	−	−	+ (Leukomalacia)
Other CNS MRI findings	−	−	−	Ovoid T2/FLAIR-hyperintense lesion in the right thalamus (low-grade neoplasm vs. inflammatory/ demyelinating)	Transmantle gray matter heterotopias; frontal malformation with abnormal gyral contours	Arachnoid cyst	−
Facial morphology							
Strabismus	+	+	+	−	+	−	+
Long face	+	+	+	+	+	+	+
Prominent forehead	+	+	+	+	+	+	+

(Continues)

TABLE 1 | (Continued)

	Previously reported				New cases		
Broad forehead	+	+	+	+	+	+	+
Sparse eyebrows	+	+	+	+	+	+	+
Laterally displaced medial eyebrow	+	+	+	+	+	+	+
Down slanting eyebrows	+	−	+	+	−	−	+
Down slanting palpebral fissures	+	−	+	+	−	−	−
Up slanting palpebral fissures	−	+	−	−	−	+	−
Inferior displacement of the inner canthi	+	+	−	+	+	+	+
Periorbital fullness	+	+	−	+	+	+	+
Eyelid skin redundancy	+	+	+	+	+	+	+
Straight nasal dorsum	+	+	+	+	+	+	+
Short nose	+	−	−	−	+	+	+
Depressed nasal bridge	+	−	−	−	−	+	+
Hanging columella	−	+	+	+	−	−	−
Bulbous nasal tip	+	+	−	+	+	+	+
Thin upper lip	+	+	+	+	+	+	+
Cupid's bow	+	+	+	+	−	−	+
Prominent nasolabial fold	+	−	−	+	+	+	−

(Continues)

TABLE 1 | (Continued)

	Previously reported			New cases			
Retrognathia	+	+	+	+	+	+	+
Prominent antihelix	+	+	+	+	−	+	+
Abnormality of the teeth	+	+	+	+	+	+	+
Macrostomia	−	+	+	−	+	+	−
Other features							
Congenital anomalies	Cleft palate, intestinal malrotation Hallux valgus Brachydactyly	Thoracic syrinx	−	Lumbarization of S1	Bilateral *coxa valga*		−
Multiple nevi	+	+	+	−	−	−	+
Gastrointestinal symptoms	Mid gut volvulus, severe reflux, severe constipation	Severe constipation	n/a	Severe constipation	Severe constipation	Severe constipation	−
Other	Dysfunction vesical voiding; allergy to latex and cefdinir		Speech regression	Hypothyroidism	Henoch-Schönlein purpura		Persistent fetal finger pads

Abbreviations: −, feature absent; +, feature present; ADHD, attention deficit with hyperactivity disorder; ASD, autism spectrum disorder; CP, cerebral palsy; DFM, decreased fetal movements; EEG, electroencephalogram; GDD, global developmental delay; GMFCS, gross motor functional classification system; HSP, hereditary spastic paraplegia; ID, intellectual disability; n/a, not available.

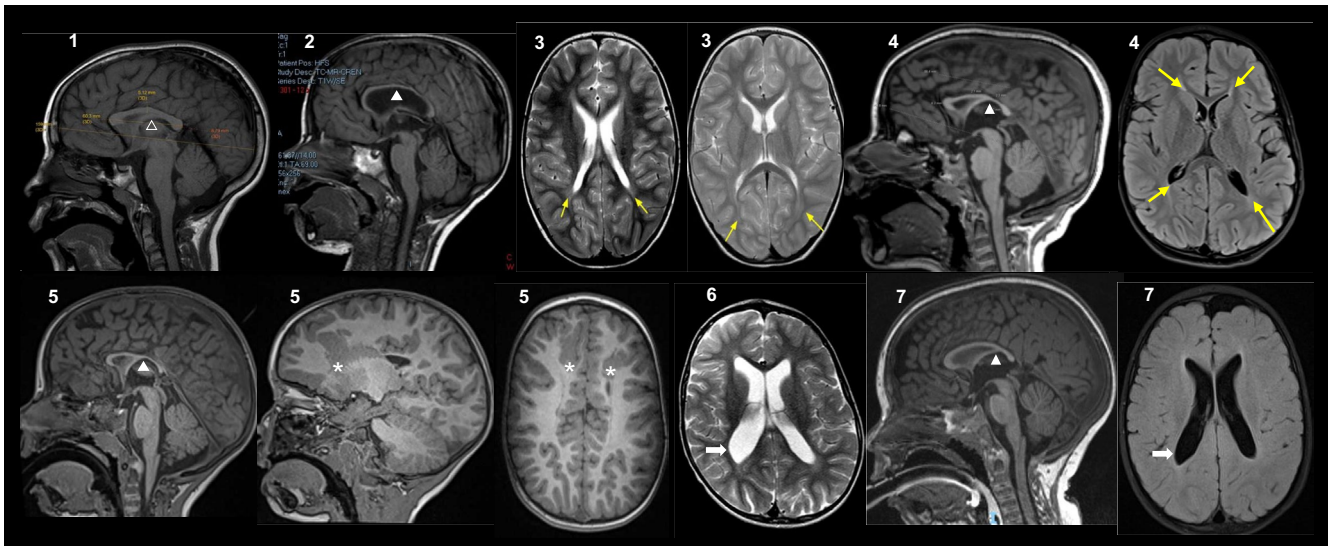

FIGURE 1 | Neuroimaging findings: Brain MRI images labeled with the corresponding patient identifier. Open triangle, normal CC; solid triangle, hypoplastic CC; yellow arrows, white matter hyperintensities; *, gray matter heterotopias; white arrows, ventricular dilatation. Detailed findings provided in Table 1 and Supporting Information S1. [Colour figure can be viewed at wileyonlinelibrary.com]

FIGURE 2 | Dysmorphology characterization: Probands photographs labeled with the corresponding patient identifier. (A) Craniofacial features are described in Table 1 and Supporting Information S1. †Composite facial representation generated with Face2Gene (version 17.6.1) from 2D photographs of pre-puberal probands (two per proband). (B) Evolution of the facial phenotype after puberty is described in Supporting Information S1. (C) High arched palate. (D) †Persistent fetal finger pads; ‡brachydactyly. (E) Low set ears (black line is highlighting the low position). [Colour figure can be viewed at wileyonlinelibrary.com]

FBXO31 is known to control axonal outgrowth and is essential for dendrite growth and neuronal migration in the developing brain [8]. The p.Asp334Asn variant changes the FBXO31-binding pocket, enabling recognition of neosubstrates, consistent with a neomorphic mechanism [4]. This has important therapeutic implications, making AD FBXO31-associated neurodevelopmental disorder a potential candidate for gene-knockdown approaches such as antisense oligonucleotide (ASO)—based therapies. Moreover, the ARID phenotype associated with biallelic loss-of-function variants—and the presence of healthy heterozygous carriers—argues against haploinsufficiency as a mechanism of disease for this gene [1, 2]. However, three reported 16q24 microdeletion cases proposed *FBXO31* as a potential candidate gene for the associated phenotype, suggesting the possibility of haploinsufficiency as a mechanism [9–11].

Somatic *FBXO31* dysregulation has been linked to several cancers [12]. While no malignancies were reported in this small series, *FBXO31* can function as either a tumor suppressor or

an oncogene depending on cellular context, with key roles in DNA damage response and cell cycle regulation [12]. Current evidence remains insufficient to support a standardized cancer surveillance protocol in affected individuals.

The male to female predominance in our series (6:1) may reflect sex-modulated penetrance/survival or simple ascertainment bias. All patients share the same de novo variant; thus, it remains unclear whether other dominant variants exist and if they cause similar phenotypes, or whether this represents a mutational hotspot analogous to achondroplasia, where ~98% of patients share the same variant [13].

Although multiple studies support a genetic approach to investigate the etiology of CP, genetic testing is still not uniformly incorporated into CP evaluations [14, 15], and *FBXO31* is absent from clinical multigene panels. As a result, individuals with pathogenic variants in *FBXO31* are at risk of remaining undiagnosed. Therefore, a key objective of this study is to raise awareness of this entity to improve diagnosis and patient care. Based on these data, we propose that AD FBXO31-associated neurodevelopmental disorder should be considered in patients with GDD/ID, CP, and neurodevelopmental disorders.

This study has limitations due to its remote, retrospective phenotyping and modest cohort size. Neuroimaging protocols and timepoints were not uniform. We hope to establish an FBXO31 registry with longitudinal follow-up for a natural history study to better understand the phenotypic spectrum. Future work should include standardized behavioral metrics and deep phenotyping.

Finally, in acknowledgement of the research laboratory that reported the first cases and provided in vitro evidence that p.Asp334Asn disrupted normal protein function, and with the support of the FBXO31 Foundation patient advocacy group, we propose and introduce the eponym "Kruer syndrome" as a synonym that can also help to distinguish this condition from allelic disorders like the ARID phenotype.

Author Contributions

C.I.G.-M., M.C.K., S.A.L., P.B., P.T.S., S.B., and H.M.: Study design and data interpretation. C.I.G.-M., S.B., K.B., B.K., A.A., M.S., M.Z., I.M.W., C.A.G., and W.K.C.: Cohort ascertainment and phenotypic characterization. C.I.G.-M., P.C., and M.C.K.: Clinical analyses. C.I.G.-M., M.K.G., and M.C.K.: wrote the initial manuscript. C.I.G.-M., M.K.G., S.A.L., S.B., and M.C.K.: Reviewed and edited the manuscript. All authors have read and approved the final manuscript.

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Conflicts of Interest

I.M.W. is an employee of and may own stock in GeneDx. The other authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Peer Review

For transparency, the peer review documents associated with this article are available at https://doi.org/10.1111/cge.70166.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Data S1:** Expanded clinical descriptions of the individuals in the cohort, including detailed dysmorphologic features.