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Ignatius, Erika

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Duplication/triplication mosaicism of *EBF3* and expansion of the EBF3 neurodevelopmental disorder phenotype

Erika Ignatius [a, b], Riina Puosi [a], Maarit Palomäki [c], Noora Forsbom [d], Max Pohjanpelto [b], Tiina Alitalo [e], Anna-Kaisa Anttonen [e, f], Kristiina Avela [f], Leena Haataja [a], Christopher J. Carroll [g], Tuula Lönnqvist [a], Pirjo Isohanni [a, b, *]

[a] *Department of Child Neurology, Children's Hospital, Pediatric Research Center, University of Helsinki and Helsinki University Hospital, Helsinki, Finland*
[b] *Research Programs Unit, Stem Cells and Metabolism, Faculty of Medicine, University of Helsinki, Helsinki, Finland*
[c] *Department of Radiology, HUS Medical Imaging Center, University of Helsinki and Helsinki University Hospital, Helsinki, Finland*
[d] *Department of Ophthalmology, University of Helsinki and Helsinki University Hospital, Helsinki, Finland*
[e] *Laboratory of Genetics, HUS Diagnostic Center, University of Helsinki and Helsinki University Hospital, Helsinki, Finland*
[f] *Department of Clinical Genetics, HUS Diagnostic Center, University of Helsinki and Helsinki University Hospital, Helsinki, Finland*
[g] *Genetics Research Centre, Molecular and Clinical Sciences Research Institute, St. George's, University of London, London, United Kingdom*

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ABSTRACT

Deleterious variants in the transcription factor early B-cell factor 3 (*EBF3*) are known to cause a neurodevelopmental disorder (EBF3-NDD). We report eleven individuals with *EBF3* variants, including an individual with a duplication/triplication mosaicism of a region encompassing *EBF3* and a phenotype consistent with EBF3-NDD, which may reflect the importance of *EBF3* gene-dosage for neurodevelopment. The phenotype of individuals in this cohort was quite mild compared to the core phenotype of previously described individuals. Although ataxia tended to wane with age, we show that cognitive difficulties may increase, and we recommend that individuals with EBF3-NDD have systematic neuropsychological follow-up.

1. Introduction

Heterozygous variants in the transcription factor early B-cell factor 3 (*EBF3*) are reported to cause a neurodevelopmental disorder which is also called hypotonia, ataxia and delayed development syndrome (HADDS) [1–3]. EBF3 is a member of the highly evolutionarily conserved EBF- transcription factor family, members of which have a variety of developmental roles [4]. *EBF3* is widely expressed throughout the body, including prenatally expressed in the brain, and may be a major regulator of many neurodevelopmental disorder genes [5]. In mice, *EBF3* is highly expressed in Cajal−Retzius-cells [6] which have an important role in mammalian cortical development. It is estimated that pathogenic *EBF3* variants could be the underlying cause in 1:1000 individuals

with unexplained neurodevelopmental disorders [2] and as such, EBF3 neurodevelopmental disorder (EBF3-NDD) is likely vastly underdiagnosed. As a growing number of individuals are described [1−3,5,7−14], the *EBF3*-associated phenotype is expanding and new disease features continue to be reported.

EBF3-haploinsufficiency is reported to be a likely pathogenic mechanism for EBF3-NDD [12], although dominant-negative and gain-of-function mechanisms have also been proposed [1,3]. In individuals with EBF3-NDD most reported variants are de novo missense or nonsense variants, but other variant types, such as deletions, have been reported. *EBF3*-haploinsufficiency likely at least partially explains the phenotype of previously reported individuals with large terminal 10q26 deletions [12]. To our knowledge, gross duplications limited to only *EBF3* have not been reported.

We report a cohort of individuals with *EBF3* variants, including an individual with a duplication/triplication mosaicism encompassing *EBF3*, and expand on the *EBF3* phenotypic spectrum and cognitive trajectory in EBF3-NDD.

* Corresponding author. Department of Child Neurology, Children's Hospital, Helsinki University Hospital, P.O. Box 347, 00029, HUS, Finland.
E-mail address: pirjo.isohanni@helsinki.fi (P. Isohanni).

2. Subjects and methods

We studied 11 individuals from six families with *EBF3* variants. The Helsinki University Hospital ethics review board approved the study. Individuals and/or their legal guardians gave written informed consent in accordance with the Declaration of Helsinki.

A study clinician examined all individuals and reviewed available clinical, laboratory and imaging data. Ataxia severity was evaluated using the Scale for Assessment and Rating of Ataxia (SARA) [15].

The *EBF3* variants of families 1–4 were identified by exome sequencing and those of families 5 and 6 by array comparative genomic hybridization (array-CGH; Supplementary Methods). The mosaic duplication/triplication in P11 was confirmed with fluorescence *in situ* hybridization (FISH), and somatic mosaicism in the mother of P8 was quantified using droplet digital PCR (Supplementary Methods). Family 1 has six individuals with a pathogenic *EFB3* variant and the other families have one affected individual each. Individuals P5, P7, P8 and P10 have previously been published in a cohort study of childhood-onset ataxias [16]. Variants reported in this study have been submitted to ClinVar [17,26] (SCV001547519 − SCV001547524) and sequence variant classification was based on the American College of Medical Genetics and Genomics (ACMG) guidelines for the interpretation of sequence variants [18].

The study neuropsychologist reviewed all available written reports (n = 25) and raw data (n = 19) from neuropsychological examinations. Data from formal neuropsychological examinations were available for all individuals except P9 and P11. Different tests of the Wechsler Scales and The Bayley Scales of Infant Development were used for evaluation of cognitive capacity depending on the individual's age at time of testing (Supplementary Methods). Finnish norms and versions were used for all the scales.

3. Results

Table 1 shows clinical findings of the individuals in this study as well as 34 previously published individuals (last column). Strabismus was the most common presenting symptom in our cohort and specifically infantile strabismus stood out as a common feature in our case series. SARA [15] score was above the mean in all cases, but mostly within the range of unaffected adults or typically developing children.

Fig. 1 shows MRI-images from individuals with abnormalities detected. The brain MRI of P9 showed a small area of polymicrogyria, a malformation of cortical development, which may represent an additional feature associated with EBF3-NDD.

In four families, the variant arose *de novo*, and family 1 shows dominant inheritance. In family 3, P8 was heterozygous for the NM_001005463.2:c.1183C>T; :p.(Arg395Ter) variant. P8 inherited the variant from her clinically unaffected mother, who carries the variant in a mosaic state (fractional abundance was 22%, 22% and 33% in leukocytes, buccal cells and urine cells respectively, see Supplementary Methods).

3.1. Duplication/triplication mosaicism of EBF3

Individual P11 was investigated for motor delay, hypotonia and asymmetric tone at four months of age. Brain MRI at 11 months revealed pontine and cerebellar hypoplasia and dysplastic foliation of the cerebellar hemispheres (Fig. 1). In childhood, P11 had ataxia and tremor, but tone asymmetry had normalized. P11 had mild dysmorphic features including hypertelorism, small nose, long philtrum, open mouth appearance, everted lower lip, and small nails (detailed clinical features see Table 1).

Array-CGH and FISH analyses revealed an 888 kb *de novo* tandem duplication/triplication mosaicism (40%/60% of cells) on chromosome 10q26.3, NC_000010.10:g.(131225843_131243689)_(132131959_132151948)dup/[3] (Supplementary Fig. 1). The region covers the genes *EBF3*, *GLRX3*, *MGMT* and *C10orf143*. Clinical trio exome sequencing revealed no other pathogenic or likely pathogenic variants. To our knowledge, duplications or triplications of *EBF3* have not been previously reported to cause EBF3-NDD.

3.2. Neuropsychological profiles

Fig. 2 shows the results of cognitive assessments for which raw data was available. Individuals in this cohort with deleterious variants in *EBF3* showed heterogeneous and uneven cognitive profiles. At a younger age, full-scale intelligence quotients were mostly within the average or low average range, despite varied performance in different cognitive indexes. Cognitive difficulties seem to increase with age, although individuals did not lose knowledge or skills. At an older age, the performance across different cognitive indexes varied mostly from low average to extremely low performance. Some of the individuals were functioning within the extremely low range of intelligence but at the time did not fulfill the diagnostic criteria for intellectual disability. This is due to lack of severe impairments/disabilities in adaptive functions and academic skills; two individuals performed worse than expected due to co-operation and concentration difficulties. Behavioral and/or emotional difficulties may explain poor performance in some individuals. Six individuals had difficulties in concentration or were diagnosed with attention deficit hyperactivity disorder. Four of the school-aged children attended full-time special education with normal or adjusted syllabus and two attended part-time.

One individual in their thirties had a full-scale intelligence quotient in the average range, whereas the individual's intellectual abilities were above average in a childhood evaluation. P9 has not yet been evaluated by a neuropsychologist but seems to be more severely affected than other individuals in the cohort.

4. Discussion

We identified a duplication/triplication mosaicism of the *EBF3* gene as a possible genetic mechanism in *EBF3*-related disease. We describe individuals with pathogenic *EBF3* variants without a diagnosis of intellectual disability and analyze the cognitive trajectory of individuals with EBF3-NDD.

In the Database of Genomic Variants [19,27], there are no reports of duplications covering the entire *EBF3* gene and which are interpreted to be normal variation. We have not seen *EBF3* duplications in 13 000 patient/parent samples (array-CGH *in-house* data). Multiple individuals with distal trisomy 10q syndrome have been described [20] and pathogenic/likely pathogenic gross copy number gains including *EBF3* are found in DECIPHER [21,27] (1.2−24 Mb) and ClinVar [17,26] (4.7−135 Mb), but none including only *EBF3*. DECIPHER includes two individuals with intellectual disability/global developmental delay and duplications covering the same genes as in P11. *EBF3* is the only one of these genes currently linked to human disease in OMIM [28]. Multiple individuals in DECIPHER with copy number gains covering *EBF3* and reported individuals with a diagnosis of EBF3-NDD share features such as intellectual disability, delayed speech and language development, hypotonia, low-set ears, high palate and cryptorchidism.

A possible disease mechanism in P11 is increased gene dosage and an associated increase in *EBF3* expression. As patient cells were unavailable, we were unable to analyze *EBF3* expression and measure the functional consequence of the duplication/triplication. However, previous experimental evidence derived from an *in-vitro*

Table 1
Clinical findings in individuals with *EBF3* variants.

Variant type	Deleterious variant in *EBF3*								Deletion of *EBF3*	Duplication/ triplication of *EBF3*	Deleterious variant or deletion of *EBF3*
Family	F1	F1	F1	F1	F1	F1	F2	F3	F4	F5	F6	
Individual	P1	P2	P3	P4	P5	P6	P7	P8	P9	P10	P11	34 previously reported individuals [1−3,7,8,10−13]
DNA NM_001005463.2	c.622dup	c.622dup	c.622dup	c.622dup	c.622dup	c.622dup	c.625C>T	c.1183C>T	c.530C>T	deletion[c]	duplication/ triplication mosaicism[d]	26 variants
Protein NP_001005463.1	p.(Met208 AsnfsTer56)	p.(Met208 AsnfsTer56)	p.(Met208 AsnfsTer56)	p.(Met208 AsnfsTer56)	p.(Met208 AsnfsTer56)	p.(Met208 AsnfsTer56)	p.(Arg209Trp)	p.(Arg395Ter)	p.(Pro177Leu)	?	?	missense, nonsense, splice, frameshift, 9-bp duplication or whole gene deletion
Classification; previously published by other group	pathogenic; no	pathogenic; no	pathogenic; no	pathogenic; no	pathogenic; no	pathogenic; no	pathogenic; yes [2]	pathogenic; no	pathogenic; yes [2,3]	pathogenic	VUS	—
Inheritance	unknown	inherited	inherited	inherited	inherited	inherited	*de novo*	inherited from mosaic mother	*de novo*	*de novo*	*de novo*	*de novo* or inherited from affected or mosaic parent
Sex	female	female	female	female	female	female	female	female	male	female	male	male 15/34, female 19/34
Age of presentation	infantile	infantile	neonatal	infantile	infantile	infantile	neonatal	infantile	neonatal	infantile	infantile	congenital, neonatal or infantile presentation (n = 15)
Presenting features	strabismus	strabismus	tremor	motor delay	strabismus	strabismus, hypotonia	motor asymmetry	strabismus	neonatal respiratory distress, feeding difficulties, vomiting	motor delay, ataxia	hypotonia, asymmetric tone, motor delay	hypotonia, developmental/ motor delay, ataxia, poor feeding, hypermobility, urogenital anomaly and/or infection (n = 15)
Age at last evaluation	adult	adult	adult	juvenile	juvenile	childhood	juvenile	juvenile	under 2 y	juvenile	childhood	15 m to mid-thirties (n = 33)
Height	normal	normal	normal	normal	normal	−2,0 SD	normal	normal	normal	normal	normal	short stature 11/28
Microcephaly	no	no	no	no	no	no	no	no	no	no	no	5/27
Hypotonia	yes	yes	no	yes	no	yes	yes	yes	yes	yes	yes	28/33
Motor delay	no (clumsy)	yes	no (clumsy)	yes	yes	yes	yes	yes	yes	yes	yes	33/33
Independent walking	15 m	24 m	14 m	21 m	20 m	28 m	22 m	18 m	no at 17 m	18 m	24 m	14 m to 5 y, 7 individuals unable to walk independently (n = 22)
Ataxia	no	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	20/30
Tremor	yes	yes	yes	yes	yes	yes	yes	yes	no	yes	yes	3/14
	3 (0.4, 0−7.5)[a]	4 (0.4, 0−7.5)[a]	5 (0.4, 0−7.5)[a]	4 (0.1, 0.0−1.4)[b]	5 (1.9, 0.1−17.0)[b]	NA	4 (0.1, 0.0−1.4)[b]	9 (1.9, 0.1−17.0)[b]	NA	4 (1.4, 0.0−11.3)[b]	15 (2.6, 0.2−26.7)[b]	NA

(continued on next page)

Table 1 (*continued*)

Variant type	Deleterious variant in *EBF3*								Deletion of *EBF3*	Duplication/ triplication of *EBF3*		Deleterious variant or deletion of *EBF3*
Family	F1	F1	F1	F1	F1	F1	F2	F3	F4	F5	F6	
Individual	P1	P2	P3	P4	P5	P6	P7	P8	P9	P10	P11	34 previously reported individuals [1−3,7,8,10−13]
SARA score total when last tested												
Abnormality of tone	no	transient mild asymmetry	no	no	transient mild asymmetric increased tone	no	transient motor asymmetry, spasticity and increased tone	transient increased tone and spasticity	transient dystonia and athetosis	no	transient tone asymmetry	hypertonia in 1 individual, dystonia in 1 individual
Delayed speech and language development or language impairment	no	yes	yes	yes	yes	no	yes	no	yes	no	yes	30/32
Intellectual disability	no	no	no	no	no	no	no	no	no (global developmental delay)	no	no	28/30
Strabismus	infantile onset alternating esotropia, surgery +	infantile onset alternating esotropia with abduction weakness, surgery +	childhood onset alternating esotropia, surgery -	intermittent esotropia, surgery -	infantile onset alternating esotropia, surgery -	infantile onset alternating esotropia, cross fixation, surgery +	infantile onset alternating esotropia, surgery +	infantile onset alternating esotropia, surgery +	no	no	infantile onset alternating exotropia, surgery +	26/31
Abnormality of the genitourinary system[e]	vesicoureteral reflux, recurrent UTI	ND	renal cyst, UTI	ND	right kidney slightly smaller than left, UTI	UTI	ND	ND	hydrocele testis	ND	ND	19/32
MRI brain (age imaged)	normal (34 y)	normal (age 3 y, images no longer available for independent review)	not imaged	not imaged	normal (5 y)	normal (8 m)	slightly hypoplastic cerebellar hemispheres and lower part of the vermis (10 y)	normal (4 y)	dysplastic and slightly hypoplastic vermis, slightly enlarged lateral ventricles and subarachnoid spaces, unilateral perisylvian polymicrogyria (9 m)	dysplastic upper part of the vermis (2 y)	pontine and cerebellar hypoplasia, dysplastic foliation of the cerebellar hemispheres (11 m)	abnormality of the brain on MRI 10/28
Other features	behavioral and/or emotional difficulties, vertigo, high narrow palate	behavioral and/or emotional difficulties, congenital calcaneovalgus, pes planus, high narrow palate	behavioral and/or emotional difficulties, accessory spleen, vertigo	behavioral and/or emotional difficulties, pes planus	behavioral and/or emotional difficulties, long philtrum, limited elbow extension due to abnormality of the proximal radius, pes planus	pes planus	pes planus	pes planus	weak cry	behavioral and/or emotional difficulties, pes planus, muscle weakness	pes planus	

n number of individuals for whom the information was available, *NA* not available/not applicable, *ND* not detected, *m* months, *UTI* urinary tract infection(s), *VUS* variant of uncertain significance, *y* years, *neonatal* first 28 days of life, *infantile* 28 days to 1 year, *childhood* 1−5 years, *juvenile* 5−15 years, *adult* 16 years or older.

[a] Scale for Assessment and Rating of Ataxia mean score and range in unaffected adults [15].

[b] Age-related predictive values for Scale for Assessment and Rating of Ataxia total in typically developing children, mean score and 95% prediction interval [24].

[c] NC_000010.10:g.(131529025_131542049)_(132107231_132131900)del.

[d] NC_000010.10:g.(131225843_131243689)_(132131959_132151948)dup/[3].

[e] Individuals have not been routinely examined for abnormality of the genitourinary system.
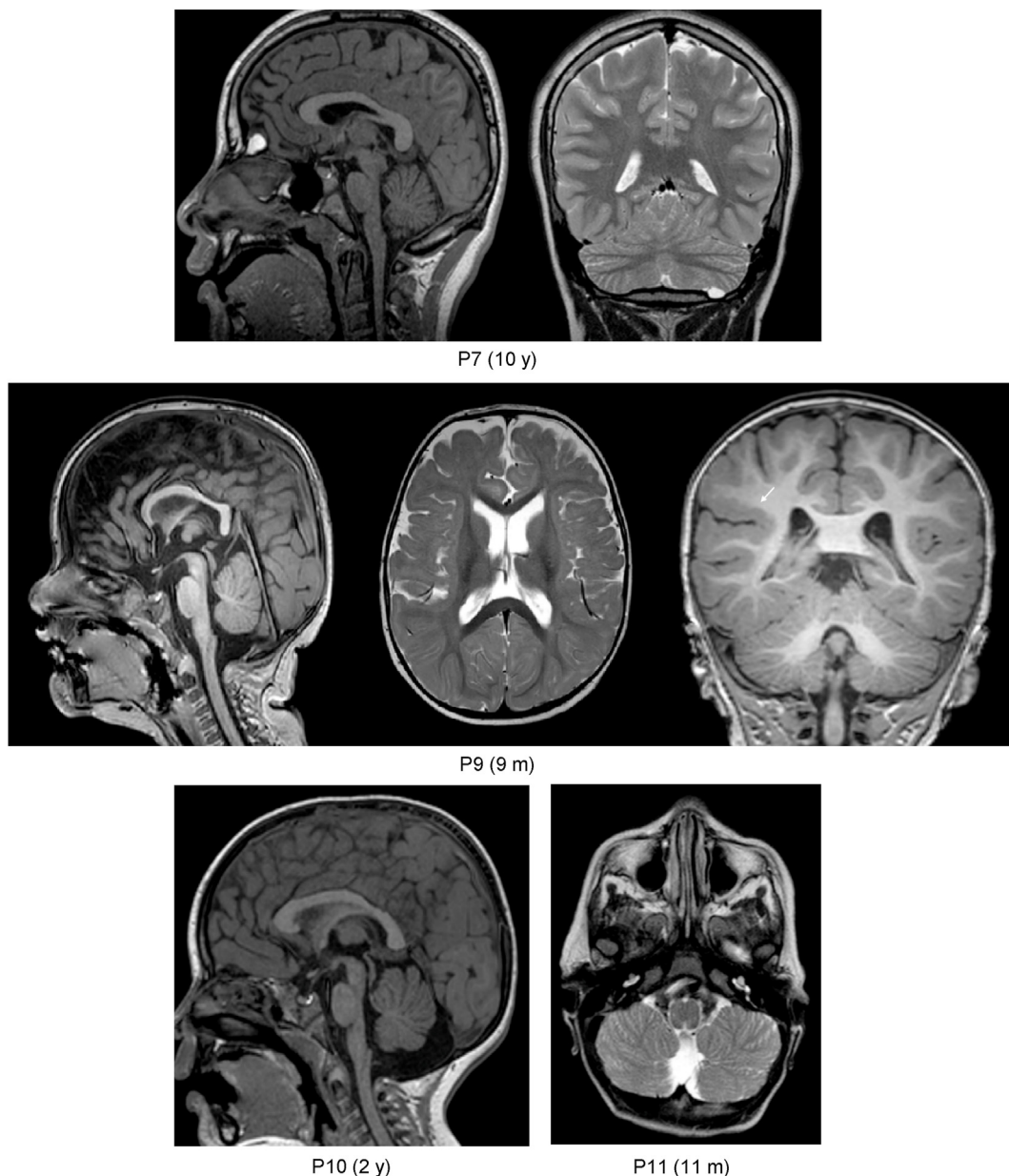
Fig. 1. Brain MRI in individuals with abnormal imaging.
P7: The cerebellar hemispheres and lower part of the vermis are slightly hypoplastic (3D T1 sagittal and T2 coronal images).
P9: The upper part of the vermis is dysplastic and the lower part slightly hypoplastic (T1 sagittal image). The lateral ventricles and subarachnoid spaces are slightly enlarged (T2 axial image). An arrow marks right perisylvian polymicrogyria (T1 coronal image).
P10: The upper part of the vermis is dysplastic (3D T1 sagittal image).
P11: Dysplastic foliation of the cerebellar hemispheres (T2 axial image), pontine and cerebellar hypoplasia (not shown).
m months, *y* years.

assay that measures transactivation abilities of EBF3 has suggested dose-dependent inhibitory effects of EBF3 function at high concentrations [3].

Pathogenic mechanisms involving EBF3 are not fully understood. Most individuals in this cohort had a presumed loss-of-function variant. Neither of the missense variants found in this cohort were located in the EBF3 "zinc knuckle" motif reported to be essential for DNA-binding but they might indirectly affect the binding affinity of EBF3 for DNA [2,3].

Cognitive profile in previously reported individuals with EBF3-NDD varies. The severity of cognitive delay can vary vastly even between individuals with near-identical genetic findings; P10 has a de novo deletion with the same gene content as an individual with a diagnosis of severe intellectual disability [12], however P10 has full scale IQ in the average range. We found individuals in this cohort to have a milder cognitive profile than most previously described individuals who have mostly been reported to have intellectual disability. We note with interest a recent publication by Padhi et al., describing three individuals with *de novo* non-coding variants in the brain-specific enhancer hs737 that targets the *EBF3* gene and a phenotype of autism without intellectual disability [5]. In our cohort cognitive difficulties seemed to increase with age. Our cohort is small, and this preliminary finding should be explored in a larger follow-up study. We recommend that individuals with
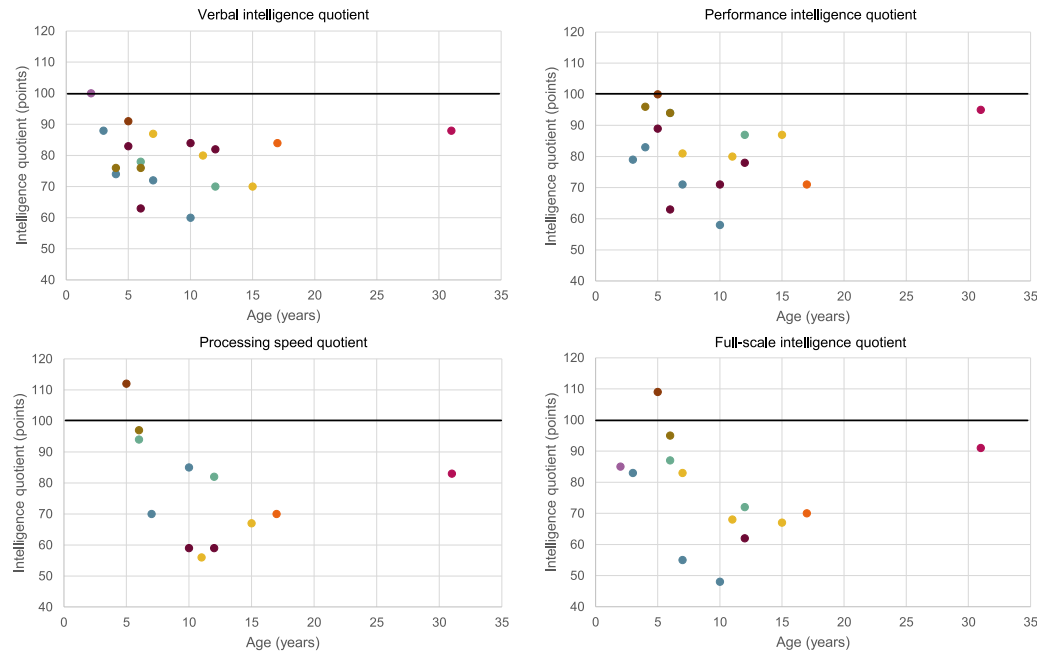
Fig. 2. Cognitive trajectory of individuals with deleterious *EBF3* variants.
x-axis: age (years), y-axis: intelligence quotient; average 90−109, low average 80−89, borderline 70−79, extremely low 69 and below. Individuals are not specified for privacy reasons.

EBF3-NDD have systematic neuropsychological follow-up even when cognitive skills are within normal range. Neuropsychiatric symptoms, such as difficulties with attention, were common in this cohort and it is important that adequate support is given.

In most individuals in this cohort, ataxia and hypotonia seemed to wane with age, and improvement has also been reported by Beecroft et al. [7]. Previous publications have described hypertonia and dystonia in a minority of individuals [2,13]. 6/11 individuals of the cohort showed increased tone and/or asymmetric movement patterns that largely resolved during childhood, including significant infantile dystonia in P9. Strabismus is seen in 84% of the previously published individuals we reviewed [1−3,7,8,10,12,13] and 82% of individuals reported in this study, whereas in a series of pediatric patients with different chronic ataxias, only 29% exhibited strabismus [22].

The polymicrogyria detected in one individual with EBF3-NDD may imply a role of *EBF3* in cortical development. In addition to our patient with polymicrogyria, an individual with a small schizencephalic cleft has been previously reported [13]; schizencephaly can be considered a related type of cortical malformation. The etiologies of polymicrogyria are heterogeneous and it is thought that nongenetic and genetic etiologies, including germline and mosaic variants, can underlie the malformation [23].

Pathogenic *EBF3* variants seem to be a surprisingly common cause of childhood ataxia and neurodevelopmental syndrome, and more information on the disease mechanism and phenotype are required. Larger cohorts of individuals with deleterious variants in *EBF3* are needed to fully characterize the cognitive trajectory in EBF3-NDD. Future research should explore factors modifying the severity of disease in individuals with pathogenic *EBF3* variants.

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Declaration of competing interest

None.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejpn.2021.12.012.

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