


Original research

ACTB deletions or single-nucleotide loss-of-function variants: expansion and further delineation of the phenotype and review of the literature

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ABSTRACT

Background Pathogenic gain-of-function or dominant-negative effect missense variations in *ACTB* are associated with a neurodevelopmental disorder characterised by intellectual disability (ID), seizures, sensorineural hearing loss, cerebral, renal and ocular abnormalities and dysmorphic features (Baraitser-Winter cerebrofrontofacial syndrome). *ACTB* encodes beta-actin, a highly conserved protein involved in cell motility, structure and integrity. Deletions including *ACTB*, and, more rarely, single-nucleotide loss-of-function variants in *ACTB* have been described in patients with a distinct phenotype including developmental delay, ID, microcephaly, growth restriction, cardiac and renal abnormalities and dysmorphic features.

Methods We collected 14 individuals and 1 fetus carrying a heterozygous deletion including *ACTB*, and 4 individuals with a heterozygous truncating variant. Genotypic and phenotypic data were analysed. Furthermore, a comprehensive review of all cases reported to date was also undertaken.

Results Twelve out of 17 individuals presented with ID, and 3 out of 17 with learning disabilities. Speech delay and behavioural abnormalities were observed in 15 out of 17 and 12 out of 17 individuals, respectively, motor delay in 9 out of 17 and growth restriction in 9 out of 18. Most of the individuals (13/18) had recognisable dysmorphic features. 11 anomalies were de novo, except for 1 deletion inherited from the mother. The size of the deletion varied from 125 kb to 1.6 Mb and could result from a fork stalling and template switching.

Conclusion This study allowed us to better characterise the phenotype associated with the haploinsufficiency of *ACTB*, underlying the high prevalence of neurodevelopmental disorders (ID, speech and motor delay, behavioural abnormalities) and growth restriction in this recognisable syndrome.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ It is well documented that pathogenic gain-of-function or dominant-negative effect missense variations in the *ACTB* are associated with Baraitser-Winter cerebrofrontofacial syndrome (BWCF). More recently, deletions of *ACTB* and loss-of-function variants have been associated with a distinct phenotype with only a small number of patients with point mutations.

WHAT THIS STUDY ADDS

⇒ This study broadens the genotypic and phenotypic spectrum of *ACTB* haploinsufficiency, highlighting that the clinical features differ from those observed in BWCF and are less severe. In addition, four novel truncating variants and the first fetus are reported.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ It is recommended that caution be taken in the context of genetic counselling of *ACTB* families, given that carriers may exhibit a highly variable phenotype, which can range from moderate to normal cognitive development.

INTRODUCTION

The *ACTB* gene encodes beta-actin protein, which is a critical component of the cytoskeleton. It is involved in several essential cellular processes, including cell motility, structure, integrity and inter-cellular signalling.¹ Pathogenic gain-of-function or dominant-negative effect missense variants in this gene are responsible for Baraitser-Winter cerebrofrontofacial syndrome (BWCF) (OMIM#243310), a rare genetic disorder that is characterised by striking facial dysmorphism (metopic ridging/trigonocephaly, bilateral ptosis, hypertelorism),



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microcephaly, iris or retinal coloboma, epilepsy, sensorineural hearing loss and cortical malformations (pachygyria/lissencephaly). Congenital heart defects and renal malformations are also common.² The severity of intellectual disability (ID) is correlated with the specific type of brain abnormality.³ More recently, patients with heterozygous variants clustered in the 3'-encoding region of *ACTB* (exons 5 and 6) and presenting with syndromic thrombocytopaenia have been reported.⁴ It is noteworthy that another condition, distinct from BWCFF, has been described in patients with heterozygous *ACTB* gene deletions and loss-of-function (LoF) variants (including frameshift and nonsense mutations).^{1,4-7} The clinical presentation of these patients is highly variable, ranging from mild-to-severe phenotypes. The most common features include developmental delay, ID, microcephaly, dysmorphic facial features, growth retardation and skeletal abnormalities such as scoliosis. Furthermore, patients may also present with cardiac, renal and cerebral anomalies, as well as ocular abnormalities.

To date, the number of cases in the literature is limited with only five patients harbouring truncating point variants. In this study, we report on a series of 19 cases (18 individuals and 1 fetus) with deletions or truncating variants of the *ACTB* gene. Our objective is to provide insights into the phenotypic spectrum and further characterise the clinical features of this condition.

METHODS

Thanks to national networks AchroPuce (<https://acpa-achropuce.com/>) and AnDDI-Rares (<https://anddi-rares.org/>), and GeneMatcher (<https://genematcher.org/>), we collected 14 individuals and 1 fetus carrying a heterozygous deletion including *ACTB*, and 4 patients with heterozygous truncating variants. All cases were identified with routine genetic testing by chromosomal microarray analysis (CMA), exome sequencing (ES) or genome sequencing (GS). Only patients with a truncating point variant (excluding missense variants) were included in our study. All cases were documented with respect to their clinical and genetic characteristics. The data from each centre were provided in the form of a spreadsheet. Fourteen of the 15 deletions encompassing the entirety of the gene were identified through CMA, while one was detected by ES. The laboratories employed different microarray platforms: Agilent CGH Microarray 60K/105K/180K, Illumina Human Cyto SNP12. To confirm the deletion, FISH, digital droplet PCR, quantitative PCR or targeted sequencing was performed. To determine the inheritance of the deletion, FISH analyses or quantitative PCR were performed on the parents. The genomic positions of the deletions are relative to the human genome assembly GRCh37/hg19. With regard to the four patients who were heterozygous for a truncating variant in the *ACTB* gene, ES or GS was performed with trios including the proband and both parents using genomic DNA isolated from peripheral blood. All patients and family members provided informed consent prior to undergoing genetic testing. Prior written consent was obtained from subjects for the publication of photographs.

RESULTS

A summary of the detailed molecular and clinical features for each individual is provided in online supplemental table S1. The subjects (11 females and 8 males) ranged in age from 6 weeks to 54 years and included one female fetus that was terminated at 30 weeks' gestation. A total of 14 patients and one fetus had a heterozygous deletion of *ACTB*. The size of the deletion varied from 125 kb to 1.6 Mb (4.3 Mb in the fetus) (figure 1). The

smallest deletion in our cohort is 125 kb in size. It encompasses two genes encoding proteins: *ACTB* and *FBXL18*. The *FBXL18* gene is not predicted to be intolerant to haploinsufficiency (gnomAD LOEUF Score=1.15) and has not been reported in human pathology. The remaining four patients of our cohort were found to carry heterozygous truncating variants in *ACTB*. Patients 1 and 2 have a *de novo* heterozygous variant in the *ACTB* gene, NM_001101.5:c.457_458insAT p.(Met153Asnfs*34) and NM_001101.5: c.262dup p.(His88Profs*6), respectively. Patients 3 and 4, who are sisters, harboured an intragenic deletion encompassing exons 2–6. To be noted, individual 4 carries an additional likely pathogenic heterozygous variant in *COL2A1*: NM_001844.4:c.953G>T, (p.Gly318Val) (OMIM#120140) (figure 2 and online supplemental table S3). These variants are presumed to trigger nonsense-mediated decay. It should be noted that none of these variants have been previously reported in the literature or in the ClinVar database (<http://www.ncbi.nlm.nih.gov/clinvar/>) and are absent from general population alleles in the Genome Aggregation Database (gnomAD v2 and v4, <http://gnomad.broadinstitute.org/>). They were classified as likely pathogenic in accordance with the ACMG guidelines.⁸

Of the abnormalities observed, 11 were *de novo*, and one deletion was inherited from the symptomatic mother who exhibited fewer symptoms than her offspring. In seven cases (patients 3, 4, 9, 11, 12, 15 and 17), the results from both parents were unavailable (online supplemental table S1). It is noteworthy that patients 3 and 4 are sisters. Their biological parents were unavailable for genetic testing, as the children have been adopted, but clinical reports were available. The biological mother exhibited learning disabilities and required special education. Additionally, she experienced depression and hallucinations. With regard to the biological father, he is diagnosed with depression and exhibits aggressive behaviour. It is then possible that one of patients 3 and 4's parents carries the same deletion.

The majority of individuals (12/17; 70%) presented with ID, while three individuals presented with learning difficulties alone. The severity of ID ranged from mild to moderate and was associated with speech and motor delay in 15 out of 17 cases (88%) and 9 out of 17 cases (53%), respectively. Two of the four patients who carried truncating variants did not have ID. Behavioural issues, including attention deficit hyperactivity disorder (ADHD), autism spectrum disorder (ASD), echolalia, self-aggression and agitation, were observed in 12 out of 17 individuals (71%). Nine of the 18 individuals (38%) exhibited postnatal growth failure. Intrauterine growth restriction was frequently observed in the prenatal period, occurring in 8 out of 19 cases (42%). The majority of individuals (13/18; 72%) displayed recognisable dysmorphic features, including interrupted eyebrows, thick eyelashes, a broad nasal base, a large mouth, a prominent chin and cheeks, thin lips and a triangular face (figure 3). Cardiac and renal abnormalities were identified in some patients (5/18 and 3/18, respectively). Eleven patients had available brain MRI, and 5 of them exhibited non-syndrome-specific abnormalities including vermis hypoplasia, arachnoid cysts, simplified gyral patterns and non-specific white matter signal abnormalities (online supplemental table S1). Only three patients (3, 4 and 15) had thrombocytopaenia, which was neonatal and transient, not consistent with the type of thrombocytopaenia reported previously by Latham *et al.*⁴

DISCUSSION

This article presents the clinical and genetic data on 19 cases (11 females and 8 males) with a heterozygous deletion that

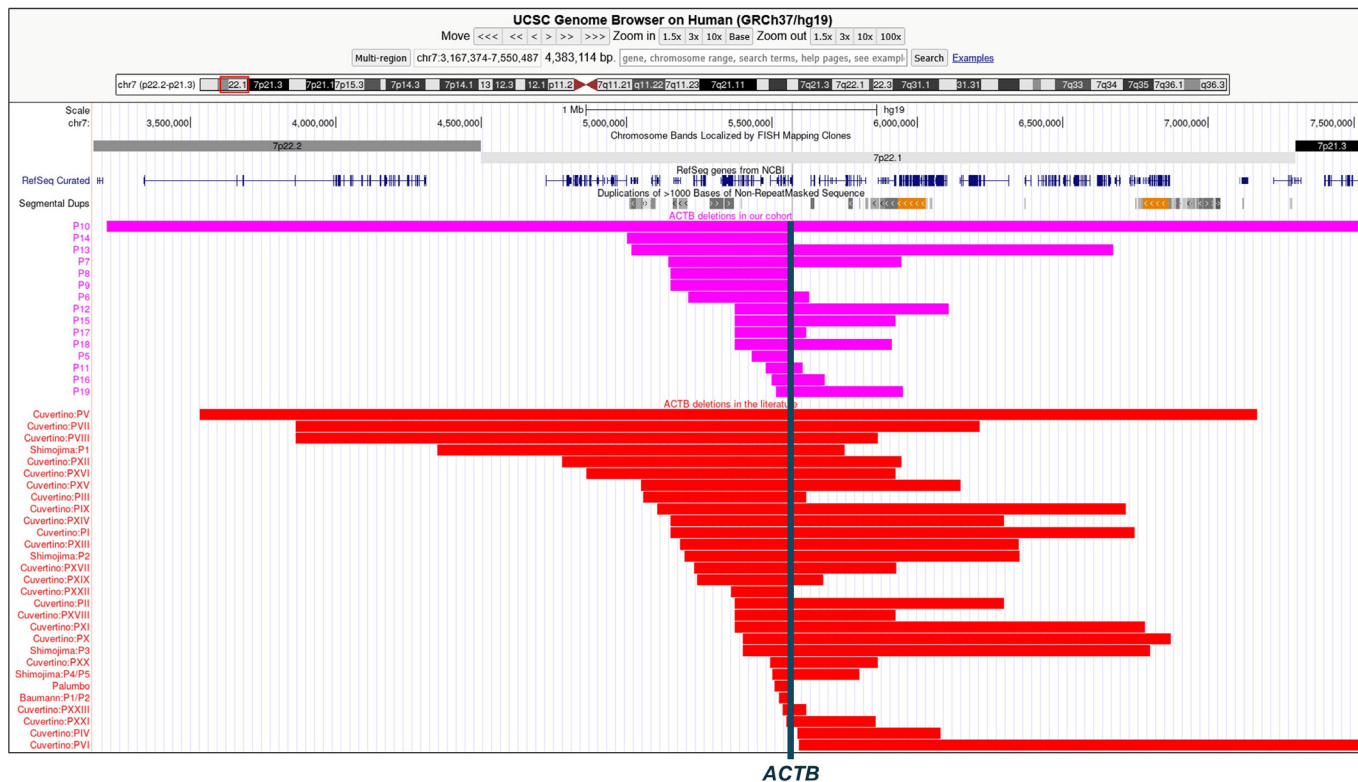


Figure 1 Schematic representation of the deletions identified in our cohort and in the literature, based on UCSC Genome Browser (<https://genome.ucsc.edu/cgi-bin/hgGateway>). The deletions identified in 15 out of the 19 patients included in our study are shown in fuchsia. The implication of *ACTB* was confirmed by a complementary analysis for patients 8, 9 and 14. In red are patients previously reported in the literature. The grey vertical bar indicates the position of *ACTB*. NCBI, national center for biotechnology information.

includes the *ACTB* gene or a heterozygous truncating variant in this gene, which have not yet been described. Caution should be taken in genetic counselling of *ACTB* families, as carriers may exhibit highly variable phenotypes, ranging from moderate to normal cognitive development. One deletion was inherited from the mother, who had fewer symptoms. This study includes the first prenatal diagnosis of a fetus with this condition. In addition, a review of the literature identified a total of 44 previously reported cases, which are presented in online supplemental table

S2: 39 deletions and only five sequence truncating variants. This brings the total number of cases in previous and current studies to 63. Patients with a deletion of *ACTB* and LoF variants in this gene present with a wide range of neurodevelopmental disorders. The most prevalent clinical manifestations are ID (48/60, 80%) and speech delay (47/54, 87%), with other common features including motor delay (36/60, 60%), behavioural abnormalities (31/54, 57%) and postnatal growth failure (32/62, 52%). Facial dysmorphism, including interrupted eyebrows, thick eyelashes,

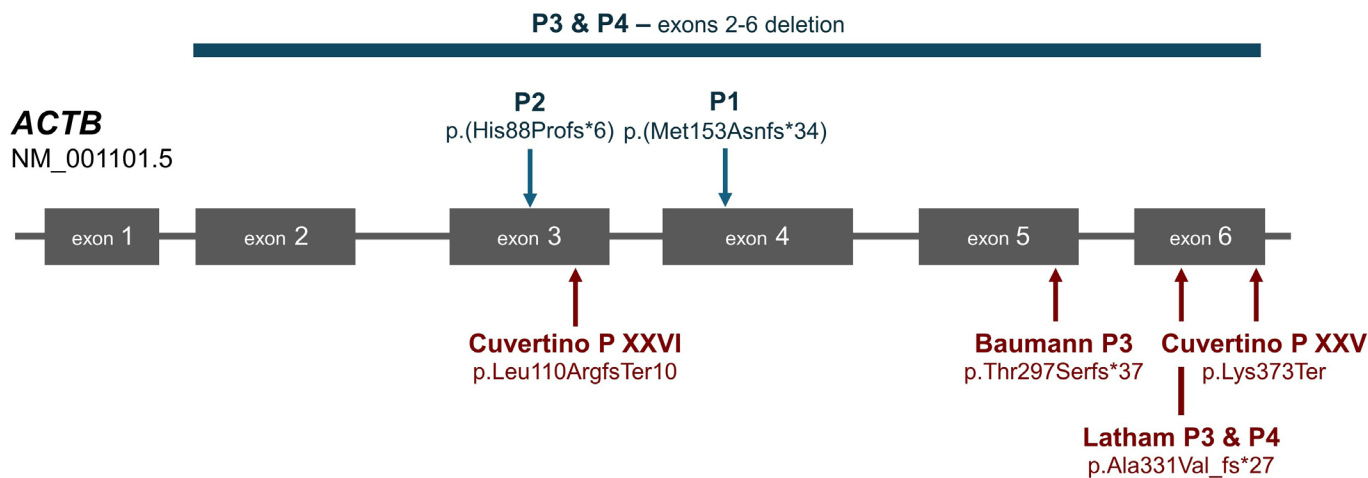


Figure 2 Schematic representation of the truncating variations identified in our cohort and in the literature. Patients from our cohort are shown in blue above the gene, while cases in the literature are shown in red below. The variant p.Ser368LeufsTer13 identified in patient XXIV from Cuvertino *et al*¹ and in patient six from Latham *et al*⁴ result in a protein elongated by a few amino acids. Therefore, these cases were not included, as it is unclear whether they lead to loss of function.



Figure 3 Photographs of seven individuals included in our study. P, patient. P2 has a point variant in *ACTB*. P3 and P4 (siblings) have an intragenic deletion in *ACTB*. The other individuals (P11, P12, P13 and P17) have a deletion including *ACTB*. The majority of individuals in our study (13/18; 72%) displayed recognisable dysmorphic features, including interrupted eyebrows, thick eyelashes, a broad nasal base, a large mouth, a prominent chin and cheeks, thin lips and a triangular face.

a prominent nasal bridge, a large mouth, a prominent chin and cheeks, thin lips and a triangular face, is commonly observed. Other, less common phenotypes include non-specific brain abnormalities (11/60; 18%), various congenital heart defects (10/62; 16%), horseshoe kidney (7/62; 11%) and seizures (4/62, 6%).

In our cohort, the incidence of microcephaly is lower than previously observed, as an occipital frontal circumference (OFC) strictly below 2 SD was observed in only two patients, whereas almost half of the individuals had an OFC measured at -2 SD, which is the cut-off. Regarding cognitive functions, five patients, including the mother of patient 8, do not have ID but present with additional neurodevelopmental disorders, including learning disabilities, ASD, ADHD and speech and motor delays. It should be noted that one individual was too young for ID assessment (patient 6), and patient 10 was a fetus with congenital malformations. In addition, the sisters' (patients 3 and 4) biological parents, who could not be tested, exhibited symptoms of psychiatric disorders. The mother also had learning disabilities.

The *ACTB* gene encodes a protein that is one of the two non-muscle cytoskeleton actins. It is a major constituent of the contractile apparatus and is ubiquitously expressed.¹ This gene is constrained to LoF with an LoF observed/expected upper bound fraction (LOEUF)=0.193, as well as to missense variations (gnomAD missense Z-score=7.69). Gain-of-function or dominant-negative effect heterozygous missense variations in *ACTB* are specifically associated with BWCFF (OMIM#243310). More recently, patients with deletions or truncating variants of the gene have been reported. The smallest deletion reported to date is confined to *ACTB*.⁷ These patients present with a wide range of clinical features, from mild-to-severe phenotypes.¹⁴⁻⁷

Our study emphasises that the phenotype associated with haploinsufficiency of the *ACTB* gene is highly variable and less severe than in BWCFF. Indeed, while epilepsy, coloboma, scoliosis and sensorineural hearing loss are prevalent in the BWCFF, they are either absent or observed rarely in patients with haploinsufficiency of the

ACTB gene. Congenital malformations are also less frequent. It is also noteworthy that ID is not a constant feature, as evidenced by the five individuals with *ACTB* LoF who do not have this impairment (patients 1, 2, 5, 9 and 16). Although not presenting with ID, each of these five individuals presented with either learning disability and/or behaviour disorders (ASDs, ADHD): 4/5 individuals without ID had speech delay, 3/5 motor delay and 3/5 dysmorphic features. Details are available in online supplemental table S1. Nevertheless, behavioural and psychiatric issues are generally present, although not constant, features of the syndrome. Considering our cohort and the patients reported in the literature, the phenotype associated with heterozygous truncating variants in the *ACTB* gene appears comparable to that of a deletion. However, our cohort is too small to enable us to compare the percentage of the main features between the two groups. This needs to be confirmed by more individuals with LoF variants.

In our study, one individual (patient 4) had a dual molecular diagnosis as she carries, in addition to an intragenic deletion of *ACTB*, a likely pathogenic heterozygous variant in *COL2A1*: NM001844.4:c.953G>T, (p.Gly318Val). Pathogenic monoallelic *COL2A1* variants are associated with multiple phenotypes, which are known to be associated with type II collagen disorders, with variable expressivity.⁹ Thus, the growth restriction observed in patient 4 might be due, at least partly, to this likely pathogenic *COL2A1* variation.

It is noteworthy that deletions of the *ACTB* gene account for 79% of patients in our cohort and 86% in all reported patients, whereas LoF point variants are rare. These deletions are of different sizes in each case and the breakpoints are not located within segmental duplications or in repetitive sequences. However, the *ACTB* locus appears to be a region prone to non-recurrent rearrangements. We could hypothesise that these deletions could be explained by the fork stalling and template switching/microhomology-mediated break-induced replication models.¹⁰ In this study, we present the first case of a fetus with haploinsufficiency of *ACTB* that was detected prenatally. At 22 weeks' gestation, a *de novo* heterozygous 7p22 deletion was identified by CMA following the detection

of intrauterine growth retardation (femoral length and OFC < 3rd percentile), partial corpus callosum agenesis (presence of genu and a third of the body) and large dysplastic ears by ultrasound examination. The deletion spanned 4.3 Mb and involved a total of 37 protein-coding genes in addition to *ACTB* (nomenclature details are available in online supplemental table 1). It is currently unclear what role these genes play in the phenotype of the fetus. Only four of these genes have an LOEUF Score < 0.3: *USP42*, *TNRC18*, *INTS15* and *RAC1*. None of these genes, except *RAC1*, is known to be associated with disease. Indeed, missense variants in *RAC1* with a pathogenic dominant-negative or activating effect have been found in patients presenting with a syndromic neurodevelopmental disorder with variable brain anomalies, including corpus callosum hypoplasia (OMIM#617751).¹¹ It is then possible that the loss of this gene has influenced the phenotype. Because of the ultrasound findings and the deletion of the *ACTB* gene detected in the fetus, a termination of pregnancy was performed at 30 weeks' gestation. The external examination revealed a head circumference of 35 cm, a weight of 1082 g and a height of 35.5 cm.

In conclusion, these cases extend the genotypic and phenotypic spectrum of *ACTB* haploinsufficiency and emphasise that the clinical features differ from those observed in BWCFF.

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