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Seizures in trisomy 18: Prevalence, description, and treatment

Sue L. Jaspersen[1] | Deborah A. Bruns[2] | Meghan S. Candee[3] | Agatino Battaglia[4] | John C. Carey[5] | Kristen P. Fishler[6]

[1]Genetic Counseling Program, Department of Medical Sciences, College of Allied Health Professions, University of Nebraska Medical Center, Omaha, Nebraska, USA

[2]Special Education Program, School of Education, Southern Illinois University Carbondale, Carbondale, Illinois, USA

[3]Division of Pediatric Neurology, Department of Pediatrics, University of Utah School of Medicine, Salt Lake City, Utah, USA

[4]Department of Developmental Neuroscience, IRCCS Stella Maris Foundation, Pisa, Italy

[5]Division of Medical Genetics, Department of Pediatrics, University of Utah Health, Salt Lake City, Utah, USA

[6]Munroe-Meyer Institute for Genetics and Rehabilitation, University of Nebraska Medical Center, Omaha, Nebraska, USA

Correspondence
Sue L. Jaspersen, Genetic Counseling Program, University of Nebraska Medical Center, Omaha, Nebraska 68198.
Email: sjaspersen@unmc.edu

Abstract

Changes in medical intervention over the last decade have improved outcomes for individuals with trisomy 18, the second most common human aneuploidy syndrome at birth. As children with trisomy 18 live longer, a shared concern of medical experts and parents is the occurrence and treatment of seizures. Previously published surveillance guidelines for this condition have not addressed seizure management. Using parent-reported data collected as part of the Tracking Rare Incidence Syndromes project, we report on the prevalence, course, and management of seizures in individuals with trisomy 18. Twenty-eight percent (52/186) of individuals diagnosed with trisomy 18 in our retrospective cohort experienced generalized, focal, or mixed seizures at some point in their lifetime. For many individuals, seizures were effectively managed by broad-spectrum anti-seizure medications. Correlation analysis showed that focal and generalized seizures were more likely to occur in individuals who had previously experienced infantile spasms or central apnea. Electroencephalogram testing should be considered as part of a standard screening approach in individuals with trisomy 18 to enable early diagnosis and treatment of seizures. An international registry that incorporates parent-reported and clinical data for patients with trisomy 18 may facilitate ongoing research and recruitment into clinical trials for seizure management.

KEYWORDS
brain malformations, central apnea, epilepsy, infantile spasms, seizures, trisomy 18

1 | INTRODUCTION

Trisomy 18, also known as Edwards syndrome, is the second most common autosomal trisomy in newborns with a prevalence ranging from 1:3600–1:8500 (Crider et al., 2008; Embleton et al., 1996; Forrester & Merz, 1999; Irving et al., 2011; Rasmussen et al., 2003; Root & Carey, 1994). Caused by an additional full or partial copy of chromosome 18, trisomy 18 has long been considered to be a lethal condition, resulting in stillbirth or death in the first hours to days of life. Historically, only a small percentage of liveborn individuals with trisomy 18 (0%–8%) survived beyond their first year of life (Brewer et al., 2002; Carter et al., 1985; Embleton et al., 1996; Goldstein & Nielsen, 1988; Lin et al., 2006; Niedrist et al., 2006; Rasmussen et al., 2003; Root & Carey, 1994; Weber, 1967). Recent technological and medical innovations, including advances in cardiac surgery and respiratory support, have improved infant survival (Janvier et al., 2012). Internet-based social support networks have also led to increased parental awareness and advocacy for medical care options for children with trisomy 18 (Janvier et al., 2012). In the past decade, trisomy 18 survivorship has increased in many countries, although mortality remains high with at most 25% of individuals with trisomy 18 surviving beyond 1 year (Cortezzo et al., 2022; Goel et al., 2019; Hsiao et al., 2009; Meyer et al., 2016; Nelson et al., 2016; Neubauer & Boss, 2020; Rasmussen et al., 2003). More recently, 10% of individuals with this condition who underwent surgical interventions survived at least 10 years (Nelson et al., 2016). With more

children surviving past infancy, understanding trisomy 18 as a syndrome, including conditions with onset beyond the neonatal period, is important to provide the most optimal medical care.

Edwards syndrome can result from a full additional copy of chromosome 18 (full trisomy 18; 94%), a partial copy of chromosome 18 (partial trisomy 18; 2%), or mosaicism (4%–5%) (Carey, 2021). Partial trisomy 18 and mosaic forms of trisomy 18 have correlated with a less severe and less complex phenotype than full trisomy 18, including fewer anomalies and medical complications (Boghosian-Sell et al., 1994; Peron & Carey, 2014; Tucker et al., 2007; Wilson, 1993). However, the phenotypic spectrum of partial and mosaic trisomy 18 is extremely variable, presumably due to the number and types of tissues containing the extra copy of chromosome 18 and/or the duplicated segment (Cereda & Carey, 2012; Tucker et al., 2007).

Seizures are paroxysmal, stereotyped events involving sudden, involuntary, time-limited alterations in behavior, motor activity, autonomic function, consciousness, and/or sensation. Seizures are usually accompanied by abnormal electrical discharges in the brain that may or may not be associated with abnormal electroencephalography (EEG) patterns. Seizures may be provoked by acute events (e.g., fever or electrolyte disturbances), or they may be unprovoked. If an individual experiences recurrent, unprovoked seizures or has had an isolated seizure and an EEG suggestive of an underlying tendency for seizure, they are considered to have epilepsy. Infantile spasms are a specific type of seizure with onset typically in the first year of life, though it may occur later in certain genetic syndromes. Infantile spasms are associated with a specific, disorganized EEG pattern, that is, hypsarrhythmia, and are most commonly treated with high-dose steroids (Riikonen, 2020). The occurrence of infantile spasms in the general population has been linked to multiple etiologies ranging from ischemic perinatal brain injury to genetic mutations affecting neuronal migration and function (Berg et al., 2010; Scheffer et al., 2017). Left untreated, infantile spasms are associated with poor neurological outcomes, including other seizure disorders and delays or regression in development (Riikonen, 2020).

Individuals with trisomy 18 exhibit profound neurodevelopmental delays, including deficits in cognitive, motor, and other neurobehavioral functions. Few children attain milestones such as purposeful vocalizations and hand gestures to communicate, auditory comprehension, and voluntary mobility with or without adaptive equipment (Baty et al., 1994; Braddock et al., 2012; Bruns, 2015). Hypotonia and central apnea are common neurological conditions associated with the syndrome that can result in or be related to fatality in newborns (Cereda & Carey, 2012; Embleton et al., 1996; Kosho et al., 2013; Root & Carey, 1994). It has been theorized that a fraction of neonates diagnosed with trisomy 18 and central apnea may instead experience epileptic apnea (Fukasawa et al., 2015), a type of partial, temporal lobe, autonomic seizure (Fogarasi et al., 2006). Seizures were reported in half of all older children diagnosed with full trisomy 18 (Kosho et al., 2013; Kumada et al., 2013; Matricardi et al., 2016). In two studies, almost half of children with full trisomy 18 had intractable epilepsy (Kumada et al., 2013; Matricardi et al., 2016). Prior studies have suggested that the timing of onset, seizure severity, and response to anti-seizure medication in individuals with trisomy 18 may be linked to underlying brain malformations resulting from dysregulation of cortical development (Matricardi et al., 2016).

Neurological monitoring practices beyond birth have not yet been established for people with trisomy 18 (Kepple et al., 2021). This retrospective cohort study evaluates the prevalence and management of seizures in individuals with trisomy 18 using parent-reported data collected as part of the Tracking Rare Incidence Syndromes (TRIS) project. The TRIS project seeks to increase the knowledge base on rare incidence trisomy conditions, including trisomy 18, and to make this information available to families and interested educational, medical, and therapeutic professionals (https://tris.siu.edu). The project collects demographic, medical, and developmental information provided by parents or other caregivers (e.g., grandparents) who agree to share their family member's information by completing a baseline survey and annual follow-up surveys (see MATERIALS AND METHODS below).

The TRIS project baseline survey is sent to parents of individuals with trisomy 18 who survived more than 2 months. Items encompass many topics and include asking if the individual with the condition experienced seizures in the past or present and gathered information on brain malformations, apnea, and common anti-epileptic therapies such as anti-seizure medications, diet, and vagal nerve stimulation. We looked at seizure prevalence, seizure type, treatment, and assessed correlation with infantile spasms, central apnea, and brain malformations.

2 | MATERIALS AND METHODS

2.1 | Editorial policies and ethical considerations

Research reported here was approved by Southern Illinois University Carbondale and University of Nebraska Medical Center Institutional Review Boards. The authors declare no conflicts of interest.

2.2 | The TRIS project database

The TRIS project includes several surveys for parents or other caregivers of children and adults with rare trisomies, including trisomy 18. A baseline survey (TRIS Full survey) designed for children living 2 months or longer served as the basis for this project. As previously described (Bruns, 2008), the TRIS Full survey was developed based on medical literature from 1990 to 2005, rare trisomy specific websites, and materials from the Support Organization for Trisomy 18, 13, and Related disorders (SOFT, www.trisomy.org). An advisory committee of parents, medical professionals, and educational professionals participated in survey design and provided initial feedback.

The three-part TRIS Full survey collects pregnancy, birth, and demographic information (Part I); family support (Part II); health and medical needs, including medications, diagnoses, and surgeries (Part III) (Bruns, 2008). Recruitment included announcements to rare

trisomy-related websites, parent-to-parent communication, Facebook, SOFT conferences and newsletters, posts through the Global Genes project, and the TRIS project brochure. Data collection began in February 2007. The retrospective cohort described here included data collected from this timepoint until November 2021.

Participation in the TRIS project database does not have any pre-selection criteria. The natural history and prevalence of a variety of conditions is queried, with the caveat that the survey is retrospective and parent-reported. The 186 TRIS Full surveys completed on behalf of an individual with trisomy 18 make this one of the largest and most comprehensive collections of information on individuals diagnosed with trisomy 18.

2.3 | Data analysis

To maintain anonymity, the lead researcher for the TRIS project database (Deborah A. Bruns) provided the principal investigator (Sue L. Jaspersen) with de-identified information from the database for analysis. Data from a total of 186 participants who completed the TRIS Full survey on behalf of their child with a diagnosis of trisomy 18 was extracted. The specific items included in our dataset are listed in Supplementary Item 1 as they appeared to parents in the survey. These items relate to seizures, their etiology, and treatment. They also include questions about brain abnormalities and apnea.

The survey did not require parents to mark a positive (yes) or negative (no) response to each question. For the purposes of this analysis, positive (yes) answers were tallied and questions without a response were assumed to be negative (no) since parents were not recontacted to clarify responses. Seizure classification/nomenclature was updated since the start of the TRIS project as a result of new guidelines from the International League Against the Epilepsies (ILAE) (Scheffer et al., 2017). Many parents wrote in responses to seizure type using this new nomenclature. Seizures were therefore subdivided into generalized seizures (absence, petit mal, atonic, tonic, tonic–clonic, grand mal, and myoclonic): focal seizures (simple and complex partial); mixed (Lennox–Gastaut); and other (febrile, unknown).

Microsoft Excel was used to assemble the data, perform basic tabular and descriptive statistical calculations (e.g., sums, frequencies, percentages, median, minimum, maximum, etc.), and create charts and tables. Because the age distribution was skewed, median values are reported instead of the mean. GraphPad Prism was used for statistical hypothesis testing, including Fisher's exact test to compare variables. A p-value of 0.05 or less was considered to be significant.

2.4 | Demographics

Information on parent demographics has previously been reported (Bruns & Martinez, 2016; Donovan et al., 2016). Summary statistics showing the demographic information of individuals with trisomy 18 on whose behalf the baseline survey was completed are shown in Table 1. Twenty-eight individuals with mosaic full trisomy and four individuals with mosaic partial trisomy were included as part of the full T18 group and partial T18 group, respectively.

3 | RESULTS

3.1 | Seizure prevalence in individuals with trisomy 18

The TRIS project database includes TRIS Full survey information submitted by parents of individuals with a variety of types of trisomy 18, including full trisomy 18 and partial trisomy 18 involving 18q or 18p. Individuals represented in the database ranged from 2 months to more than 32 years, with more females (75.8%) than males (24.2%). Although the survey was available to parents worldwide, most participants were from the United States (Table 1).

Parents reported that 52 of 186 (28%) individuals experienced seizures at some point in the past (Figure 1; Table 2). Seizures were reported in 43 of 141 (30%) females and 9 of 45 (25%) males. The median age of individuals with seizures in the past was 5 years (range 0.3–33) while the median age of individuals without seizure was 2 years (range 0.2–27) (Table 2). Seven individuals experienced more than one type of seizures, but most had a single type. Generalized seizures were more frequently reported than focal seizures (Figure 1).

The percentage of individuals with mosaic full trisomy 18 who experienced seizures (28.7%) was not statistically different from individuals with full trisomy 18 (25.8%, $p = 0.8129$ Fisher's t-test). However, the percentage of individuals with partial trisomy 18 who experienced seizures (44.4%) was significantly higher than full trisomy 18 (full trisomy 18 and mosaic full trisomy 18 combined; 26.2%, $p = 0.0022$) (Figure 1; Table 2). Interestingly, of the individuals with partial trisomy 18 who reported seizures, 5 of 6 individuals with trisomy due to an extra copy of 18p reported seizures compared to just 1 of 4 individuals with an extra copy of 18q.

3.2 | Parent reported seizure management in individuals with trisomy 18

Data from the TRIS project survey showed that seizures were managed with a variety of anti-seizure medications, including broad spectrum anti-epileptic medications such as levetiracetam, lamotrigine, and phenobarbital (Table 3). Parents reported similar seizure management for individuals with full and partial trisomy 18. Other treatments designed to reduce seizure activity include the ketogenic diet and surgical implantation of a vagal nerve stimulator (VNS) (Martin-McGill et al., 2020; Toffa et al., 2020). Four parents reported the use of the ketogenetic diet while one child with myoclonic seizures had a VNS, a device that sends electrical impulses to the brain via the vagus nerve.

Of the 52 individuals reported to experience seizures, some did not use anti-seizure medications, diet, or VNS for management while others used up to six different therapies for seizure control. The average number of anti-epileptic treatments was 1.4 ± 1.4 (SD).

TABLE 1 Baseline survey demographics

	Median age (y)[c]	Min age (y)	Max age (y)	% female	% deceased	% mosaic	% US[a]	Number
All T18[b]	2.4	0.2	32.8	75.80%	16.70%	17.00%	79.60%	186
Full T18	2.3	0.2	32.8	78.60%	17.90%	16.70%	78.00%	168
Partial T18	6.4	0.2	25.7	50.00%	5.60%	22.00%	94.40%	18

[a]US, United States.
[b]Participants were grouped into three categories: any form of trisomy 18 (All T18), trisomy 18 caused by an extra copy of chromosome 18 in all or some cells (full T18), or trisomy 18 caused by an extra copy of a segment of chromosome 18 in all or some cells (partial T18). Twenty-eight individuals with mosaic full trisomy and four individuals with mosaic partial trisomy were included as part of the full T18 group and partial T18 group, respectively.
[c]y, age in years.

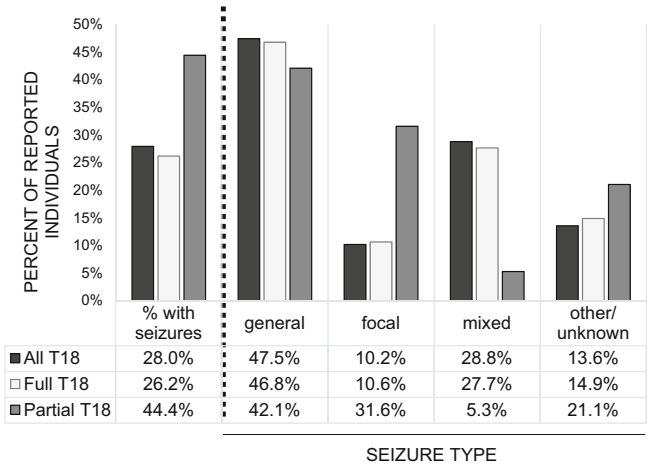

FIGURE 1 Seizures reported in individuals with trisomy 18. Fifty-two of the 186 (28%) participants reported seizures in the past, including 44 and 8 individuals with full and partial trisomy 18, respectively. Shown is the percentage of general, focal, and mixed seizures. In some cases, seizure type was unknown or not reported.

Levetiracetam was reported by the greatest number of parents as the most effective medication in seizure control although it is unknown if effectiveness was based on the number of perceived seizures, the side-effects of the medication, feedback from physicians based on differences in EEG paroxysms, or other criteria such as the child's alertness, mood, or personality. Parents were also satisfied with several other anti-seizure medications, although many were less frequently prescribed (Table 3). Five parents noted that a combination of medications was required for effective seizure control. Each combination was unique, but four of the five included levetiracetam and three of the five included lamotrigine. One combination also involved the ketogenic diet, but the diet alone was not reported as most effective at seizure control. Twenty parents reported adverse events associated with anti-seizure medications (Table 3). The most common adverse event was sleepiness/lethargy, which was observed with multiple agents.

3.3 | Infantile spasms are correlated with seizures in individuals with trisomy 18

Infantile spasms are an age-specific epilepsy characterized by clusters of brief spasms or stiffening. In the general population, approximately 1 in 1000 babies experience infantile spasms (Riikonen, 2020). Despite previous data linking infantile spasms and epilepsy in children with trisomy 18 (Kumada et al., 2013; Matricardi et al., 2016), parents often report that infantile spasms go undiagnosed or are dismissed in their child with trisomy 18.

Despite these concerns in diagnosis, parents reported that 11.8% (22/186) of individuals with trisomy 18 experienced infantile spasms, including 10.7% (18/168) of individuals with full trisomy 18 and 50.0% (4/8) of individuals with partial trisomy 18 (Figure 2a). Eighteen percent (30/164) of individuals without infantile spasms developed seizures, whereas 50% (11/22) of individuals with infantile spasms reported subsequent seizures (Figure 2b). These data suggest that infantile spasms are correlated with later seizure activity in individuals with trisomy 18 ($p = 0.0019$, Fisher's *t*-test).

3.4 | Brain anomalies and seizures in individuals with trisomy 18

Microcephaly was reported in 32/186 (17.2%) individuals with trisomy 18 while 33/186 (17.7%) reported specific structural brain anomalies including agenesis of the corpus callosum (16/33, 48.5%), hydrocephalus (7/33, 21.2%), choroid plexus or arachnoid cysts (7/33, 21.2%), cerebellar hypoplasia (4/33, 12.1%), holoprosencephaly (2/33, 6.1%), lissencephaly or Dandy-Walker malformation (1/33, 3.0% each) (Figure 3a). Five individuals had more than one structural brain malformation. The frequency and types of these structural brain malformations were similar in individuals with full and partial trisomy 18 (Figure 3a). In most cases, it is unknown from survey responses how brain anomalies were diagnosed (ultrasound, computerized tomography (CT), magnetic resonance imaging (MRI), etc.).

In our sampling of individuals with trisomy 18, an underlying brain malformation did not correlate with infantile spasms ($p = 0.7703$) or seizures ($p = 0.8300$) (Figure 3b).

3.5 | Relationship between central apnea and seizures

Central apnea is a common neurological symptom observed in individuals with trisomy 18 that has been linked to fatality in the newborn period (Cereda & Carey, 2012; Embleton et al., 1996; Kosho

TABLE 2 Seizures in individuals with trisomy 18

	% with seizures	Total individuals with seizures	Total individuals without seizures	Generalized	Focal	Mixed	Other/unknown
All T18[a]	28.00%	52	134	47.5% (28/59)	10.2% (6/59)	28.8% (17/59)	13.6% (8/59)
Full T18	26.20%	44	124	46.8% (22/47)	10.6% (5/47)	27.7% (13/47)	14.9% (7/47)
Partial T18	44.40%	8	10	42.1% (8/19)	31.6% (6/19)	5.3% (1/19)	21.1% (4/19)

[a]All T18, individuals with any form of trisomy 18; full T18, individuals with trisomy 18 due to a complete copy of chromosome 18; partial T18, individuals with trisomy 18 due to an extra copy of 18p or 18q.

TABLE 3 Anti-seizure medications used per parent report for seizure management in individuals with trisomy 18

Anti-seizure medication	Used ($n = 75$)[a]	Most effective ($n = 38$)	Parent reported adverse events ($n = 18$)
Levetiracetam	17 (22.7%)	7	Sleepiness, apnea, rage ($n = 5$)
Valproic acid	13 (17.3%)	3	Low platelets, low energy, elevated ammonia levels, increased seizures ($n = 2$)
Phenobarbital	11 (14.7%)	4	Gum overgrowth, elevated liver enzymes ($n = 2$)
Lamotrigine	8 (10.7%)	3	Sleepiness, rash (n = 2)
Carbamazepine	7 (9.3%)	2	sleepiness, rash ($n = 2$)
Topiramate	6 (8.0%)	4	Sleepiness, rash, kidney stones ($n = 1$)
Oxcarbazepine	3 (4.0%)	2	Sleepiness, rash ($n = 1$)
Clobazam	2 (2.7%)	1	Sleepiness, urine retention ($n = 1$)
Vigabatrin	2 (2.7%)	2	NR[b]
Acetazolamide	1 (1.3%)	0	NR
Clonazepam	1 (1.3%)	1	Overdose symptoms ($n = 1$)
Gabapentin	1 (1.3%)	0	NR
Lacosamide	1 (1.3%)	1	NR
Phenytoin	1 (1.3%)	1	Sleepiness, rash ($n = 1$)
Sultimine	1 (1.3%)	1	NR

[a]The total number of individuals who reported use of an anti-seizure medication or reported it at the most effective medication. Adverse events are also listed including the number of times (n) each was reported.
[b]NR, none reported.

et al., 2013; Root & Carey, 1994). Twenty-four percent (45/186) and thirty-six percent (65/186) of individuals with trisomy 18 had ever been diagnosed with central or obstructive apnea, respectively (Figure 4a).

Of the 45 individuals with central apnea, 18 (40%) also reported seizures compared to 32/144 (22.7%) of individuals without central apnea who reported seizures. In contrast, 34/121 and 18/65 (~28%) of individuals with and without obstructive apnea reported seizures (Figure 4b). This suggests that central ($p = 0.0328$) but not obstructive apnea ($p = 0.9999$) is correlated with seizures. Given the connection between infantile spasms and seizures, we also looked at whether central apnea correlated with infantile spasms, but the two appear to be unrelated ($p = 0.4230$).

4 | DISCUSSION

The TRIS project database is one of the largest and most comprehensive retrospective patient databases that includes individuals with trisomy 18. Unlike previous studies of seizures in individuals with trisomy 18 (Fukasawa et al., 2015; Kumada et al., 2013; Matricardi et al., 2016), recruitment into the TRIS project study does not require referral by a neurologist and is more likely to represent prevalence in the general population of individuals with this diagnosis compared to a cohort selected for presence of seizure activity. Seizures are one of many conditions tracked as part of the project, which is aimed at gathering general health, educational, and social information over time.

4.1 | Seizure prevalence and types

Approximately 30% of individuals with trisomy 18 in our cohort experienced seizures at some point in their life. This is consistent with reports in the literature and from the authors' clinical experience (Carey, 2021). Higher estimates quoted in some studies may be due to the selection of older children and/or children with brain anomalies (Kosho et al., 2013; Kumada et al., 2013; Matricardi et al., 2016).

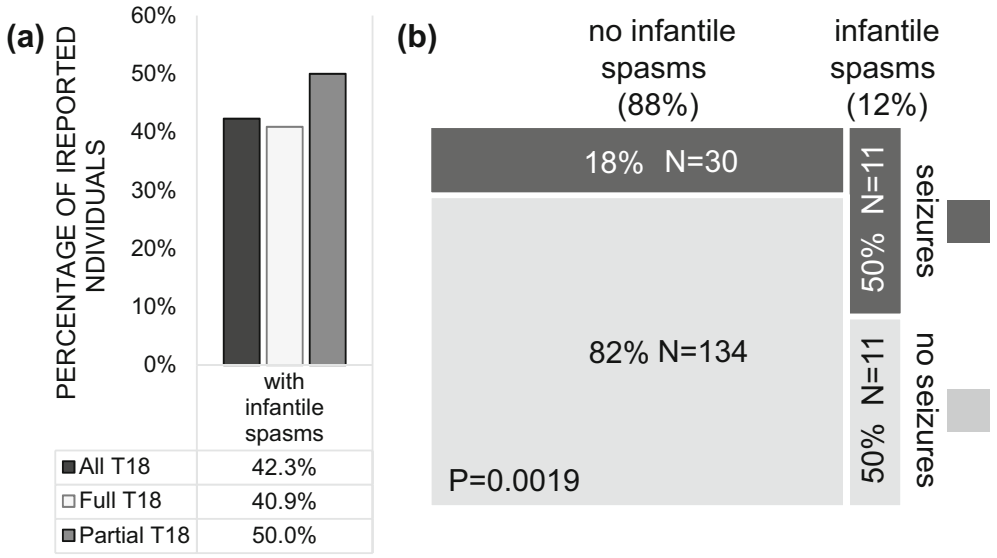

FIGURE 2 Infantile spasms are commonly reported in people with trisomy 18 and correlate with seizures. (a). Of the fifty-two individuals with seizures, the percentage that also reported infantile spasms is shown. (b). A correlation matrix shows the number of individuals with and without infantile spasms and seizures. The *p*-value from the Fisher's exact test is 0.0019.

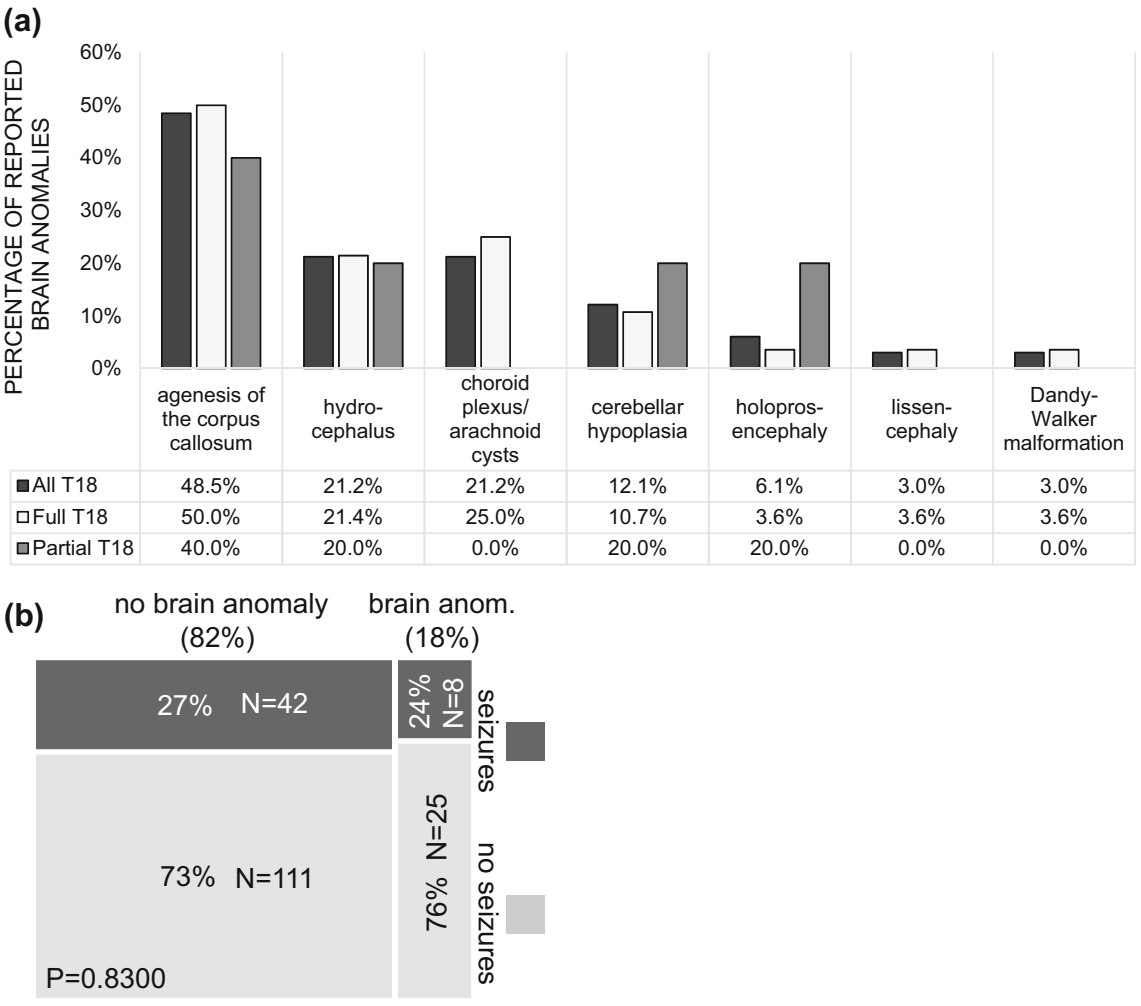

FIGURE 3 Parent-reported brain malformations in individuals with trisomy 18. (a). Thirty-eight brain malformations were reported in individuals with trisomy 18. The percentage of each anomaly listed is shown. (b). A correlation matrix showing the number of individuals with and without a structural brain anomaly and seizures. The *p*-value from the Fisher's exact test is 0.8300.

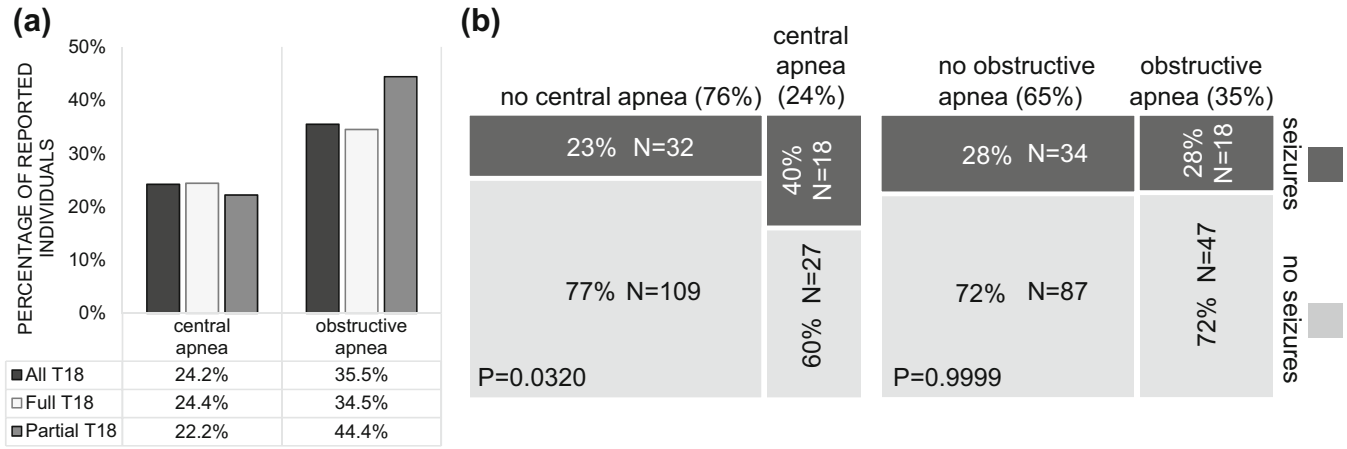

FIGURE 4 Parent-reported apnea in individuals with trisomy 18. (a). Forty-five and sixty-six individuals with trisomy 18 were reported to have central and obstructive apnea. (b). A correlation matrix shows the number of individuals with and without apnea and seizures. The *p*-value from the Fisher's exact test is 0.0320 and 0.9999 for central and obstructive apnea, respectively.

Both generalized and focal seizures were reported in individuals with trisomy 18, similar to other smaller studies that included EEG confirmation of seizure type (Kosho et al., 2013; Kumada et al., 2013; Matricardi et al., 2016). Individuals with full trisomy 18, partial trisomy 18 due to an extra copy of 18p or 18q, and mosaic forms of trisomy 18 all reported seizures, suggesting that seizure susceptibility could be related to extra material on both arms of chromosome 18. Previous analysis of seizures in individuals with partial trisomy 18 suggested that a seizure susceptibility locus was located between 18q12.2-q22.2 (Ceccarini et al., 2007; d'Orsi et al., 2013; Peron & Carey, 2014). However, (Grosso et al., 2005) also reported cases of intractable epilepsy in individuals with trisomy for 18p. Other studies involving trisomy for 18p did not observe seizures or only reported epilepsy in a small fraction of individuals (Johansson et al., 1988; Oner et al., 2000; Wolff et al., 1993). Somewhat unexpectedly, we found that a greater proportion of individuals with partial trisomy 18 than full trisomy 18 reported seizures. It is unknown if this is due to differences in the age of individuals or related to the fact that partial trisomy 18 is generally the result of an unbalanced translocation, which involves gain and loss of additional chromosomal material at the chromosome breakpoints.

4.2 | Seizure management

Seizures are common in several genetic syndromes. Some, but not all, genetic seizure disorders are associated with a characteristic pattern of seizures due to the loss or gain of genetic information (Bahi-Buisson et al., 2008; Battaglia et al., 1997; Battaglia et al., 2009; Battaglia et al., 2016; Battaglia et al., 2021; Candee et al., 2012; Conant et al., 2014; Ho et al., 2016; Samanta, 2021; Thibert et al., 2009; Uemura et al., 2005; Valente et al., 2006). For example, haploinsufficiency or pathogenic variants in genes involved in protein glycosylation are proposed to underlie the characteristic tonic–clonic seizures observed in over 90% of individuals with Wolf-Hirschhorn syndrome (Battaglia et al., 2009; Ho & Wassman, 2017; Makrythanasis et al., 2016; Worthington et al., 2008). Other genetic syndromes such as Pallister-Killian syndrome (PKS), trisomy 21, and, as shown here, trisomy 18 are associated with multiple types of generalized, focal, and mixed seizures as well as infantile spasms (Candee et al., 2012; Rahman & Fatema, 2019). As epilepsy treatment is aimed at minimizing abnormal, episodic brain activity that leads to seizures through modulation of neuronal activity by anti-seizure medications (Perucca et al., 2018), the pathophysiology of seizures in genetic syndromes can provide clues to short- and long-term medical management.

Chromosome 18 does not have obvious gene candidates critical for neurotransmission or seizure predisposition such as genes encoding subunits of ion channels, glutamate receptors, or the γ-aminobutyric acid response. Our data suggest that seizure management in trisomy 18, like that of PKS and trisomy 21, responds to broad spectrum anti-seizure medications that are also effective in the general population. No particular anti-epileptic was consistently associated with an adverse outcome such as seizure worsening. Broadly speaking, adverse events reported in individuals with trisomy 18, such as somnolence, were similar to those previously reported for anti-seizure medications in studies of individuals without a chromosome anomaly (French et al., 2004; Kanner et al., 2018a, 2018b; Sankaraneni & Lachhwani, 2015; Walia et al., 2004). One notable exception is the respiratory distress reported in one individual and increased apnea in a second person with trisomy 18 taking levetiracetam as these adverse events have not been seen in the general population. Given that individuals with trisomy 18 are at increased risk for respiratory complications (Cereda & Carey, 2012; Embleton et al., 1996; Root & Carey, 1994), the correlation may be coincidental. However, this observation and the widespread use of levetiracetam in seizure treatment of individuals with trisomy 18 warrants further consideration of its safety in the trisomy 18 patient population.

The specific long-term prognosis for seizure management in individuals with trisomy 18 has not been previously studied. Of the

13 individuals in the baseline survey age 20 years or older, 8 reported experiencing seizures in the past; of the 10 living people over age 20 years, 3 were reported to experience seizures at present while 7 were currently seizure free. These observations lead to questions for further study: do individuals with trisomy 18 outgrow seizures, are seizures effectively managed by anti-seizure therapy, and/or does treatment of comorbid conditions such as apnea decrease seizure frequency? Why do some individuals with trisomy 18 respond well to a broad-spectrum anti-seizure medications, while others require polytherapy and only achieve limited seizure mitigation?

It is largely unknown what precipitates or predisposes some individuals with trisomy 18 to experience seizures while others remain seizure free. One possibility is that seizure prevalence and/or severity is related to genetic status, specifically the fraction of cells that contain extra material from chromosome 18 and in which tissues. Because clinical management is based on cytogenetic status and not the presence or absence of mosaicism, we included individuals with mosaicism in our full and partial trisomy 18 categories. However, as 26% (36/140) of individuals with full trisomy and 29% (8/28) of people with full mosaic trisomy 18 were reported to have seizures, it is less likely that genetic differences with respect to chromosome 18 copy number underlie seizure predisposition or treatment.

4.3 | Seizures in trisomy 18: Infantile spasms, apnea, and brain malformations

The etiology of infantile spasms in individuals with trisomy 18 has not previously been studied or reported to our knowledge. Approximately 12% of children with trisomy 18 experienced infantile spasms, with half going on to exhibit some other type of seizure. Infantile spasms in individuals with trisomy 21 have been proposed to arise due to an underlying structural anomaly (Stafstrom, 1993). Previous work examining brain structure in individuals with trisomy 18 by ultrasound, CT, or MRI suggested that individuals can have a variety of structural brain malformations, including cerebellar hypoplasia, enlarged cisterna magna, choroid plexus cysts, agenesis of the corpus callosum, and microgyria (Fukasawa et al., 2015; Lin et al., 2006).

Although we found that structural brain anomalies were common (reported in approximately 18% of individuals with trisomy 18), their occurrence did not correlate with infantile spasms and/or seizures. This observation was unexpected based on previous work examining seizures in individuals with full trisomy 18 (Kumada et al., 2013; Matricardi et al., 2016) and in non-syndromic individuals (Barkovich et al., 2015; Kuzniecky, 2015). It is possible that structural brain anomalies were under-represented since brain MRI may not have been completed for all infants in the TRIS project database. However, as the structural brain anomalies seen in trisomy 18 do not involve the cortex or the temporal lobes from which most seizures typically arise, it is currently unknown how or if a brain malformation predisposes an individual with trisomy 18 to abnormal brain activity leading to infantile spasms and/or seizures. Additional factors may play a role, including apnea.

Interestingly, central, but not obstructive, apnea correlated with seizure presentation. As central apnea is relatively common condition in individuals with trisomy 18 (24%), its link to epilepsy is intriguing and worthy of future investigation. It is unknown if apnea is causative for seizures or if similar underlying genetic or neurologic differences could contribute to both conditions. A previous study of neonates diagnosed with trisomy 18 and with central apnea showed that three of seven individuals had abnormal EEG paroxysmal activity corresponding to the apnea leading (Fukasawa et al., 2015) to suggest that those phenomena were epileptic in nature.

4.4 | Limitations

The data presented here are based on a retrospective survey in which parents were asked identical questions in an online survey. The use of TRIS project data minimizes ascertainment bias, such as referral by a neurologist, but may be limited by recall bias, in particular communication and understanding of medical information given by clinicians to parents. We did not examine or review medical records for individuals presented in this study. As such, it is possible that seizures, brain anomalies, or other conditions may have been under or over reported. Participation in this project may be affected by a child's prognosis, longevity, and/or positive outcomes of medical intervention.

When the survey was developed, the language used for seizure classification was different than it is at the time of this publication, which required reconciliation of terminology in both yes/no questions and write-in responses. Some medications used to treat seizures have been introduced into clinical practice since the survey began in 2007. Parents were required to write in the names of these medications, whose use, availability, and names vary from country to country. This study was not a clinical trial. The efficacy and adverse events of anti-seizure medications were reported by parents and could be based on a single medication or a combination of therapies.

4.5 | Implications

We propose that early recognition and treatment of seizures may improve outcomes for individuals with trisomy 18. Currently, neurological monitoring is not standard-of-care for individuals with trisomy 18. A clinician might first suspect a seizure disorder based on the following criteria: infantile spasms, central apnea, a structural brain malformation, or evidence of exhibiting one or more seizure types. While none alone predict a seizure disorder with certainty, they may be clues to stratify individuals for further testing including EEG monitoring and/or neuroimaging.

The presentation of infantile spasms or seizures may differ in this patient population because of neurodevelopmental delays and hypotonia. Anticipatory guidance for parents on key indicators suggestive of infantile spasms or seizures could prompt earlier attention to changes in brain activity and successful treatment. Web-based materials exist to help parents recognize infantile spasms (Wheless

et al., 2012) (https://www.childneurologyfoundation.org/infantile-spasms-awareness/) and may be beneficial to provide to parents within the first year of life. Although our study does not explicitly address the age of seizure onset, the age range of individuals with seizures from 4 months to 32 years suggests that anticipatory information be given shortly after birth and be an ongoing component in medical care. Early detection of infantile spasms and/or seizures is essential for initiating treatment and optimizing development.

A cranial ultrasound and/or brain MRI is currently recommended at birth (Kepple et al., 2021); however, ultrasound imaging is insufficient to detect many structural brain anomalies reported here or in other work associated with seizures (Kumada et al., 2013; Matricardi et al., 2016). Our data does not show a correlation between reported brain anomalies and seizures, suggesting that the utility of brain MRI in providing prognostic information regarding seizure risk or severity may be limited. Furthermore, the risks of sedating infants in order to obtain high quality images should also be weighed when considering whether or not to perform brain imaging in surviving individuals with trisomy 18.

Our data linking infantile spasms with seizures suggests that, whenever dealing with clinical suspicion for seizures, an early polygraphic video-EEG study is warranted before age one to detect infantile spasms and/or focal or generalized seizure activity. A polygraphic video-EEG would be particularly helpful in individuals with central apnea to clarify whether apneic events are caused by seizures (Fukasawa et al., 2015).

Seizure management in individuals with trisomy 18 can involve the same broad spectrum anti-seizure medications used in the general population, including levetiracetam, lamotrigine, valproic acid, or phenobarbital. Parents should be counseled to anticipate some adverse events, particularly lethargy or sleepiness, and to report any concerns with breathing to their provider. Regular surveillance by a neurologist/epileptologist is indicated for seizure prevention and care.

5 | FUTURE DIRECTIONS

Our cross-sectional retrospective cohort study adds to our current knowledge of seizure prevalence, description, and treatment in trisomy 18, but unanswered questions deserve further investigation. Are seizures more frequent in individuals with partial trisomy 18 or is seizure prevalence related to age? What is the frequency of intractable seizures among patients with trisomy 18? Is there a specific EEG pattern in children with trisomy 18? Does screening infants with trisomy 18 in the first year of life with brain MRI and EEGs improve likelihood of future epilepsy diagnosis or outcome? Extension of the TRIS project database or creation of a new international registry of children with trisomy 18 and seizures that collects information from clinicians and allows for patient contact and recruitment into studies could facilitate larger clinical trials of seizure management in this population that would address some of these outstanding questions.

AUTHOR CONTRIBUTIONS

Concept and initial design for the project: Kristen P. Fishler, Sue L. Jaspersen, John C. Carey.
Database development and collection of data: Deborah A. Bruns.
Data analysis and figure/table preparation: Sue L. Jaspersen.
Interpretation of data: all authors.
Manuscript writing: Sue L. Jaspersen with input from all authors.
Final approval of manuscript: all authors.
Supervision: Kristen P. Fishler.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

ORCID

Sue L. Jaspersen https://orcid.org/0000-0001-8312-7063
Deborah A. Bruns https://orcid.org/0000-0002-9794-3659
Meghan S. Candee https://orcid.org/0000-0001-5587-3472
Agatino Battaglia https://orcid.org/0000-0002-7128-7606
John C. Carey https://orcid.org/0000-0002-6007-8518
Kristen P. Fishler https://orcid.org/0000-0001-6721-8598

REFERENCES

Bahi-Buisson, N., Guttierrez-Delicado, E., Soufflet, C., Rio, M., Daire, V. C., Lacombe, D., Heron, D., Verloes, A., Zuberi, S., Burglen, L., Afenjar, A., Moutard, M. L., Edery, P., Novelli, A., Bernardini, L., Dulac, O., Nabbout, R., Plouin, P., & Battaglia, A. (2008). Spectrum of epilepsy in terminal 1p36 deletion syndrome. *Epilepsia*, *49*(3), 509–515. https://doi.org/10.1111/j.1528-1167.2007.01424.x

Barkovich, A. J., Dobyns, W. B., & Guerrini, R. (2015). Malformations of cortical development and epilepsy. *Cold Spring Harbor Perspectives in Medicine*, *5*(5), a022392. https://doi.org/10.1101/cshperspect.a022392

Battaglia, A., Bernardini, L., Torrente, I., Novelli, A., & Scarselli, G. (2016). Spectrum of epilepsy and electroencephalogram patterns in idic (15) syndrome. *American Journal of Medical Genetics. Part A*, *170*(10), 2531–2539. https://doi.org/10.1002/ajmg.a.37844

Battaglia, A., Filippi, T., South, S. T., & Carey, J. C. (2009). Spectrum of epilepsy and electroencephalogram patterns in wolf-Hirschhorn syndrome: Experience with 87 patients. *Developmental Medicine and Child Neurology*, *51*(5), 373–380. https://doi.org/10.1111/j.1469-8749.2008.03233.x

Battaglia, A., Gurrieri, F., Bertini, E., Bellacosa, A., Pomponi, M. G., Paravatou-Petsotas, M., Mazza, S., & Neri, G. (1997). The inv dup(15) syndrome: A clinically recognizable syndrome with altered behavior, mental retardation, and epilepsy. *Neurology*, *48*(4), 1081–1086. https://doi.org/10.1212/wnl.48.4.1081

Battaglia, A., Lortz, A., & Carey, J. C. (2021). Natural history study of adults with wolf-Hirschhorn syndrome 1: Case series of personally observed 35 individuals. *American Journal of Medical Genetics. Part A*, *185*(6), 1794–1802. https://doi.org/10.1002/ajmg.a.62176

Baty, B. J., Jorde, L. B., Blackburn, B. L., & Carey, J. C. (1994). Natural history of trisomy 18 and trisomy 13: II. Psychomotor development.

American Journal of Medical Genetics, *49*(2), 189–194. https://doi.org/10.1002/ajmg.1320490205

Berg, A. T., Berkovic, S. F., Brodie, M. J., Buchhalter, J., Cross, J. H., van Emde Boas, W., Engel, J., French, J., Glauser, T. A., Mathern, G. W., Moshé, S. L., Nordli, D., Plouin, P., & Scheffer, I. E. (2010). Revised terminology and concepts for organization of seizures and epilepsies: Report of the ILAE commission on classification and terminology, 2005-2009. *Epilepsia*, *51*(4), 676–685. https://doi.org/10.1111/j.1528-1167.2010.02522.x

Boghosian-Sell, L., Mewar, R., Harrison, W., Shapiro, R. M., Zackai, E. H., Carey, J., Davis-Keppen, L., Hudgins, L., & Overhauser, J. (1994). Molecular mapping of the Edwards syndrome phenotype to two non-contiguous regions on chromosome 18. *American Journal of Human Genetics*, *55*(3), 476–483.

Braddock, B., McDaniel, J., Spragge, S., Loncke, F., Braddock, S. R., & Carey, J. C. (2012). Communication ability in persons with trisomy 18 and trisomy 13. *Augmentative and Alternative Communication*, *28*(4), 266–277. https://doi.org/10.3109/07434618.2012.706637

Brewer, C. M., Holloway, S. H., Stone, D. H., Carothers, A. D., & FitzPatrick, D. R. (2002). Survival in trisomy 13 and trisomy 18 cases ascertained from population based registers. *Journal of Medical Genetics*, *39*(9), e54. https://doi.org/10.1136/jmg.39.9.e54

Bruns, D. (2008). Pregnancy and birth history of newborns with trisomy 18 or 13: A pilot study. *American Journal of Medical Genetics. Part A*, *146a(3)*, 321–326. https://doi.org/10.1002/ajmg.a.32147

Bruns, D. A. (2015). Developmental status of 22 children with trisomy 18 and eight children with trisomy 13: Implications and recommendations. *American Journal of Medical Genetics. Part A*, *167a(8)*, 1807–1815. https://doi.org/10.1002/ajmg.a.37102

Bruns, D. A., & Martinez, A. (2016). An analysis of cardiac defects and surgical interventions in 84 cases with full trisomy 18. *American Journal of Medical Genetics. Part A*, *170A*(2), 337–343. https://doi.org/10.1002/ajmg.a.37427

Candee, M. S., Carey, J. C., Krantz, I. D., & Filloux, F. M. (2012). Seizure characteristics in Pallister-Killian syndrome. *American Journal of Medical Genetics. Part A*, *158a(12)*, 3026–3032. https://doi.org/10.1002/ajmg.a.35567

Carey, J. C. (2021). Trisomy 18 and trisomy 13 syndromes. In J. C. Carey, A. Battaglia, D. Viskochil, & S. B. Cassidy (Eds.), *Cassidy and Allanson's management of genetic syndromes* (4th ed., pp. 937–956). John Wiley & Sons, Inc.

Carter, P. E., Pearn, J. H., Bell, J., Martin, N., & Anderson, N. G. (1985). Survival in trisomy 18. Life tables for use in genetic counselling and clinical paediatrics. *Clinical Genetics*, *27*(1), 59–61. https://doi.org/10.1111/j.1399-0004.1985.tb00184.x

Ceccarini, C., Sinibaldi, L., Bernardini, L., de Simone, R., Mingarelli, R., Novelli, A., & Dallapiccola, B. (2007). Duplication 18q21.31-q22.2. *American Journal of Medical Genetics. Part A*, *143*(4), 343–348. https://doi.org/10.1002/ajmg.a.31588

Cereda, A., & Carey, J. C. (2012). The trisomy 18 syndrome. *Orphanet Journal of Rare Diseases*, *7*, 81. https://doi.org/10.1186/1750-1172-7-81

Conant, K. D., Finucane, B., Cleary, N., Martin, A., Muss, C., Delany, M., Murphy, E. K., Rabe, O., Luchsinger, K., Spence, S. J., Schanen, C., Devinsky, O., Cook, E. H., LaSalle, J., Reiter, L. T., & Thibert, R. L. (2014). A survey of seizures and current treatments in 15q duplication syndrome. *Epilepsia*, *55*(3), 396–402. https://doi.org/10.1111/epi.12530

Cortezzo, D. E., Tolusso, L. K., & Swarr, D. T. (2022). Perinatal outcomes of fetuses and infants diagnosed with trisomy 13 or trisomy 18. *The Journal of Pediatrics*, *247*(116–123), e115. https://doi.org/10.1016/j.jpeds.2022.04.010

Crider, K. S., Olney, R. S., & Cragan, J. D. (2008). Trisomies 13 and 18: Population prevalences, characteristics, and prenatal diagnosis, metropolitan Atlanta, 1994-2003. *American Journal of Medical Genetics. Part A*, *146a(7)*, 820–826. https://doi.org/10.1002/ajmg.a.32200

Donovan, J. H., Krigbaum, G., & Bruns, D. A. (2016). Medical interventions and survival by gender of children with trisomy 18. *American Journal of Medical Genetics. Part C, Seminars in Medical Genetics*, *172*(3), 272–278. https://doi.org/10.1002/ajmg.c.31522

d'Orsi, G., Pascarella, M. G., Pansini, A., Buonadonna, A. L., Trivisano, M., Pacillo, F., Carapelle, E., Demaio, V., Minervini, M., Gentile, M., & Specchio, L. M. (2013). Partial trisomy 18q and epileptic spasms induced by eating associated with bilateral opercular dysplasia. *American Journal of Medical Genetics. Part A*, *161a(5)*, 1194–1195. https://doi.org/10.1002/ajmg.a.35859

Embleton, N. D., Wyllie, J. P., Wright, M. J., Burn, J., & Hunter, S. (1996). Natural history of trisomy 18. *Archives of Disease in Childhood. Fetal and Neonatal Edition*, *75*(1), F38–F41. https://doi.org/10.1136/fn.75.1.f38

Fogarasi, A., Janszky, J., & Tuxhorn, I. (2006). Autonomic symptoms during childhood partial epileptic seizures. *Epilepsia*, *47*(3), 584–588. https://doi.org/10.1111/j.1528-1167.2006.00472.x

Forrester, M. B., & Merz, R. D. (1999). Trisomies 13 and 18: Prenatal diagnosis and epidemiologic studies in Hawaii, 1986-1997. *Genetic Testing*, *3*(4), 335–340. https://doi.org/10.1089/gte.1999.3.335

French, J. A., Kanner, A. M., Bautista, J., Abou-Khalil, B., Browne, T., Harden, C. L., Theodore, W. H., Bazil, C., Stern, J., Schachter, S. C., Bergen, D., Hirtz, D., Montouris, G. D., Nespeca, M., Gidal, B., Marks, W. J., Jr., Turk, W. R., Fischer, J. H., Bourgeois, B., … Glauser, T. A. (2004). Efficacy and tolerability of the new antiepileptic drugs, I: Treatment of new-onset epilepsy: Report of the TTA and QSS subcommittees of the American Academy of Neurology and the American Epilepsy Society. *Epilepsia*, *45*(5), 401–409. https://doi.org/10.1111/j.0013-9580.2004.06204.x

Fukasawa, T., Kubota, T., Tanaka, M., Asada, H., Matsusawa, K., Hattori, T., Kato, Y., & Negoro, T. (2015). Apneas observed in trisomy 18 neonates should be differentiated from epileptic apneas. *American Journal of Medical Genetics. Part A*, *167a(3)*, 602–606. https://doi.org/10.1002/ajmg.a.36929

Goel, N., Morris, J. K., Tucker, D., de Walle, H. E. K., Bakker, M. K., Kancherla, V., Marengo, L., Canfield, M. A., Kallen, K., Lelong, N., Camelo, J. L., Stallings, E. B., Jones, A. M., Nance, A., Huynh, M. P., Martínez-Fernández, M. L., Sipek, A., Pierini, A., Nembhard, W. N., … Morgan, M. (2019). Trisomy 13 and 18-prevalence and mortality-a multi-registry population based analysis. *American Journal of Medical Genetics. Part A*, *179*(12), 2382–2392. https://doi.org/10.1002/ajmg.a.61365

Goldstein, H., & Nielsen, K. G. (1988). Rates and survival of individuals with trisomy 13 and 18. Data from a 10-year period in Denmark. *Clinical Genetics*, *34*(6), 366–372. https://doi.org/10.1111/j.1399-0004.1988.tb02894.x

Grosso, S., Pucci, L., Di Bartolo, R. M., Gobbi, G., Bartalini, G., Anichini, C., Scarinci, R., Balestri, M., Farnetani, M. A., Cioni, M., Morgese, G., & Balestri, P. (2005). Chromosome 18 aberrations and epilepsy: A review. *American Journal of Medical Genetics. Part A*, *134a(1)*, 88–94. https://doi.org/10.1002/ajmg.a.30575

Ho, K. S., South, S. T., Lortz, A., Hensel, C. H., Sdano, M. R., Vanzo, R. J., Martin, M. M., Peiffer, A., Lambert, C. G., Calhoun, A., Carey, J. C., & Battaglia, A. (2016). Chromosomal microarray testing identifies a 4p terminal region associated with seizures in wolf-Hirschhorn syndrome. *Journal of Medical Genetics*, *53*(4), 256–263. https://doi.org/10.1136/jmedgenet-2015-103626

Ho, K. S., & Wassman, E. R. (2017). A case for cannabidiol in wolf-Hirschhorn syndrome seizure management. *American Journal of Medical Genetics. Part A*, *173*(2), 324–326. https://doi.org/10.1002/ajmg.a.37979

Hsiao, C. C., Tsao, L. Y., Chen, H. N., Chiu, H. Y., & Chang, W. C. (2009). Changing clinical presentations and survival pattern in trisomy 18. *Pediatrics and Neonatology*, *50*(4), 147–151. https://doi.org/10.1016/s1875-9572(09)60053-x

Irving, C., Richmond, S., Wren, C., Longster, C., & Embleton, N. D. (2011). Changes in fetal prevalence and outcome for trisomies 13 and 18: A population-based study over 23 years. *The Journal of Maternal-Fetal & Neonatal Medicine*, *24*(1), 137–141. https://doi.org/10.3109/14767051003758879

Janvier, A., Farlow, B., & Wilfond, B. S. (2012). The experience of families with children with trisomy 13 and 18 in social networks. *Pediatrics*, *130*(2), 293–298. https://doi.org/10.1542/peds.2012-0151

Johansson, B., Mertens, F., Palm, L., Englesson, I., & Kristoffersson, U. (1988). Duplication 18p with mild influence on the phenotype. *American Journal of Medical Genetics*, *29*(4), 871–874. https://doi.org/10.1002/ajmg.1320290418

Kanner, A. M., Ashman, E., Gloss, D., Harden, C., Bourgeois, B., Bautista, J. F., Abou-Khalil, B., Burakgazi-Dalkilic, E., Llanas Park, E., Stern, J., Hirtz, D., Nespeca, M., Gidal, B., Faught, E., & French, J. (2018a). Practice guideline update summary: Efficacy and tolerability of the new antiepileptic drugs I: Treatment of new-onset epilepsy: Report of the guideline development, dissemination, and implementation Subcommittee of the American Academy of neurology and the American Epilepsy Society. *Neurology*, *91*(2), 74–81. https://doi.org/10.1212/wnl.0000000000005755

Kanner, A. M., Ashman, E., Gloss, D., Harden, C., Bourgeois, B., Bautista, J. F., Abou-Khalil, B., Burakgazi-Dalkilic, E., Llanas Park, E., Stern, J., Hirtz, D., Nespeca, M., Gidal, B., Faught, E., & French, J. (2018b). Practice guideline update summary: Efficacy and tolerability of the new antiepileptic drugs II: Treatment-resistant epilepsy: Report of the guideline development, dissemination, and implementation Subcommittee of the American Academy of neurology and the American Epilepsy Society. *Neurology*, *91*(2), 82–90. https://doi.org/10.1212/wnl.0000000000005756

Kepple, J. W., Fishler, K. P., & Peeples, E. S. (2021). Surveillance guidelines for children with trisomy 18. *American Journal of Medical Genetics. Part A*, *185*(4), 1294–1303. https://doi.org/10.1002/ajmg.a.62097

Kosho, T., Kuniba, H., Tanikawa, Y., Hashimoto, Y., & Sakurai, H. (2013). Natural history and parental experience of children with trisomy 18 based on a questionnaire given to a Japanese trisomy 18 parental support group. *American Journal of Medical Genetics. Part A*, *161a(7)*, 1531–1542. https://doi.org/10.1002/ajmg.a.35990

Kumada, T., Maihara, T., Higuchi, Y., Nishida, Y., Taniguchi, Y., & Fujii, T. (2013). Epilepsy in children with trisomy 18. *American Journal of Medical Genetics. Part A*, *161a(4)*, 696–701. https://doi.org/10.1002/ajmg.a.35763

Kuzniecky, R. (2015). Epilepsy and malformations of cortical development: New developments. *Current Opinion in Neurology*, *28*(2), 151–157. https://doi.org/10.1097/wco.0000000000000175

Lin, H. Y., Lin, S. P., Chen, Y. J., Hung, H. Y., Kao, H. A., Hsu, C. H., Chen, M. R., Chang, J. H., Ho, C. S., Huang, F. Y., Shyur, S. D., Lin, D. S., & Lee, H. C. (2006). Clinical characteristics and survival of trisomy 18 in a medical center in Taipei, 1988-2004. *American Journal of Medical Genetics. Part A*, *140*(9), 945–951. https://doi.org/10.1002/ajmg.a.31173

Makrythanasis, P., Kato, M., Zaki, M. S., Saitsu, H., Nakamura, K., Santoni, F. A., Miyatake, S., Nakashima, M., Issa, M. Y., Guipponi, M., Letourneau, A., Logan, C. V., Roberts, N., Parry, D. A., Johnson, C. A., Matsumoto, N., Hamamy, H., Sheridan, E., Kinoshita, T., … Murakami, Y. (2016). Pathogenic variants in PIGG cause intellectual disability with seizures and Hypotonia. *American Journal of Human Genetics*, *98*(4), 615–626. https://doi.org/10.1016/j.ajhg.2016.02.007

Martin-McGill, K. J., Bresnahan, R., Levy, R. G., & Cooper, P. N. (2020). Ketogenic diets for drug-resistant epilepsy. *Cochrane Database of Systematic Reviews*, *6*(6), Cd001903. https://doi.org/10.1002/14651858.CD001903.pub5

Matricardi, S., Spalice, A., Salpietro, V., Di Rosa, G., Balistreri, M. C., Grosso, S., Parisi, P., Elia, M., Striano, P., Accorsi, P., Cusmai, R., Specchio, N., Coppola, G., Savasta, S., Carotenuto, M., Tozzi, E., Ferrara, P., Ruggieri, M., & Verrotti, A. (2016). Epilepsy in the setting of full trisomy 18: A multicenter study on 18 affected children with and without structural brain abnormalities. *American Journal of Medical Genetics. Part C, Seminars in Medical Genetics*, *172*(3), 288–295. https://doi.org/10.1002/ajmg.c.31513

Meyer, R. E., Liu, G., Gilboa, S. M., Ethen, M. K., Aylsworth, A. S., Powell, C. M., Flood, T. J., Mai, C. T., Wang, Y., & Canfield, M. A. (2016). Survival of children with trisomy 13 and trisomy 18: A multi-state population-based study. *American Journal of Medical Genetics. Part A*, *170a(4)*, 825–837. https://doi.org/10.1002/ajmg.a.37495

Nelson, K. E., Rosella, L. C., Mahant, S., & Guttmann, A. (2016). Survival and surgical interventions for children with trisomy 13 and 18. *JAMA*, *316*(4), 420–428. https://doi.org/10.1001/jama.2016.9819

Neubauer, K., & Boss, R. D. (2020). Ethical considerations for cardiac surgical interventions in children with trisomy 13 and trisomy 18. *American Journal of Medical Genetics. Part C, Seminars in Medical Genetics*, *184*(1), 187–191. https://doi.org/10.1002/ajmg.c.31767

Niedrist, D., Riegel, M., Achermann, J., & Schinzel, A. (2006). Survival with trisomy 18–data from Switzerland. *American Journal of Medical Genetics. Part A*, *140*(9), 952–959. https://doi.org/10.1002/ajmg.a.31172

Oner, G., Jauch, A., Eggermann, T., Hardwick, R., Kirsch, S., Schiebel, K., Rappold, G., Robson, L., & Smith, A. (2000). Mosaic rearrangement of chromosome 18: Characterization by FISH mapping and DNA studies shows trisomy 18p and monosomy 18p both of paternal origin. *American Journal of Medical Genetics*, *92*(2), 101–106.

Peron, A., & Carey, J. C. (2014). *The molecular genetics of trisomy 18: Phenotype-genotype correlations*. John Wiley & Song, Ltd. https://doi.org/10.1002/9780470015902.a0025246

Perucca, P., Scheffer, I. E., & Kiley, M. (2018). The management of epilepsy in children and adults. *The Medical Journal of Australia*, *208*(5), 226–233. https://doi.org/10.5694/mja17.00951

Rahman, M. M., & Fatema, K. (2019). Seizures in down syndrome: An update. *Mymensingh Medical Journal*, *28*(3), 712–715.

Rasmussen, S. A., Wong, L. Y., Yang, Q., May, K. M., & Friedman, J. M. (2003). Population-based analyses of mortality in trisomy 13 and trisomy 18. *Pediatrics*, *111*(4 Pt 1), 777–784. https://doi.org/10.1542/peds.111.4.777

Riikonen, R. (2020). Infantile spasms: Outcome in clinical studies. *Pediatric Neurology*, *108*, 54–64. https://doi.org/10.1016/j.pediatrneurol.2020.01.015

Root, S., & Carey, J. C. (1994). Survival in trisomy 18. *American Journal of Medical Genetics*, *49*(2), 170–174. https://doi.org/10.1002/ajmg.1320490203

Samanta, D. (2021). Epilepsy in Angelman syndrome: A scoping review. *Brain and Development*, *43*(1), 32–44. https://doi.org/10.1016/j.braindev.2020.08.014

Sankaraneni, R., & Lachhwani, D. (2015). Antiepileptic drugs–a review. *Pediatric Annals*, *44*(2), e36–e42. https://doi.org/10.3928/00904481-20150203-10

Scheffer, I. E., Berkovic, S., Capovilla, G., Connolly, M. B., French, J., Guilhoto, L., Hirsch, E., Jain, S., Mathern, G. W., Moshé, S. L., Nordli, D. R., Perucca, E., Tomson, T., Wiebe, S., Zhang, Y. H., & Zuberi, S. M. (2017). ILAE classification of the epilepsies: Position paper of the ILAE Commission for Classification and Terminology. *Epilepsia*, *58*(4), 512–521. https://doi.org/10.1111/epi.13709

Stafstrom, C. E. (1993). Epilepsy in down syndrome: Clinical aspects and possible mechanisms. *American Journal of Mental Retardation*, *98*, 12–26.

Thibert, R. L., Conant, K. D., Braun, E. K., Bruno, P., Said, R. R., Nespeca, M. P., & Thiele, E. A. (2009). Epilepsy in Angelman syndrome: A questionnaire-based assessment of the natural history and current treatment options. *Epilepsia*, *50*(11), 2369–2376. https://doi.org/10.1111/j.1528-1167.2009.02108.x

Toffa, D. H., Touma, L., el Meskine, T., Bouthillier, A., & Nguyen, D. K. (2020). Learnings from 30 years of reported efficacy and safety of

vagus nerve stimulation (VNS) for epilepsy treatment: A critical review. *Seizure*, *83*, 104–123. https://doi.org/10.1016/j.seizure.2020.09.027

Tucker, M. E., Garringer, H. J., & Weaver, D. D. (2007). Phenotypic spectrum of mosaic trisomy 18: Two new patients, a literature review, and counseling issues. *American Journal of Medical Genetics. Part A*, *143a (5)*, 505–517. https://doi.org/10.1002/ajmg.a.31535

Uemura, N., Matsumoto, A., Nakamura, M., Watanabe, K., Negoro, T., Kumagai, T., Miura, K., Ohki, T., Mizuno, S., Okumura, A., Aso, K., Hayakawa, F., & Kondo, Y. (2005). Evolution of seizures and electroencephalographical findings in 23 cases of deletion type Angelman syndrome. *Brain Dev*, *27*(5), 383–388. https://doi.org/10.1016/j.braindev.2004.01.009

Valente, K. D., Koiffmann, C. P., Fridman, C., Varella, M., Kok, F., Andrade, J. Q., Grossmann, R. M., & Marques-Dias, M. J. (2006). Epilepsy in patients with angelman syndrome caused by deletion of the chromosome 15q11-13. *Archives of Neurology*, *63*(1), 122–128. https://doi.org/10.1001/archneur.63.1.122

Walia, K. S., Khan, E. A., Ko, D. H., Raza, S. S., & Khan, Y. N. (2004). Side effects of antiepileptics–a review. *Pain Practice*, *4*(3), 194–203. https://doi.org/10.1111/j.1533-2500.2004.04304.x

Weber, W. W. (1967). Survival and the sex ratio in trisomy 17-18. *American Journal of Human Genetics*, *19*(3 Pt 2), 369–377.

Wheless, J. W., Gibson, P. A., Rosbeck, K. L., Hardin, M., O'Dell, C., Whittemore, V., & Pellock, J. M. (2012). Infantile spasms (west syndrome): Update and resources for pediatricians and providers to share with parents. *BMC Pediatrics*, *12*, 108. https://doi.org/10.1186/1471-2431-12-108

Wilson, G. N. (1993). Karyotype/phenotype correlation: Prospects and problems illustrated by trisomy 18. *Progress in Clinical and Biological Research*, *384*, 157–173.

Wolff, D. J., Schwartz, M. F., Cohen, M. M., & Schwartz, S. (1993). Precise mapping of a de novo duplication 18(q21–>q22) utilizing cytogenetic, biochemical, and molecular techniques. *American Journal of Medical Genetics*, *46*(5), 520–523. https://doi.org/10.1002/ajmg.1320460512

Worthington, J. C., Rigby, A. S., & Quarrell, O. W. (2008). Seizure frequency in adults with wolf-Hirschhorn syndrome. *American Journal of Medical Genetics. Part A*, *146A*(19), 2528–2531. https://doi.org/10.1002/ajmg.a.32483

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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