Quantifying the Spectrum of Early Motor and Language Milestones in Sex Chromosome Trisomy

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abstract

BACKGROUND AND OBJECTIVES: Sex chromosome trisomy (SCT) is a common chromosomal abnormality associated with increased risks for early developmental delays and neurodevelopmental disorders later in childhood. Our objective was to quantify the spectrum of early developmental milestones in SCT. We hypothesized later milestone achievement in SCT than the general population.

METHODS: Data were collected as part of the eXtraordinarY Babies Study, a prospective natural history of developmental and health trajectories in a prenatally identified sample of infants with SCT. Parent-reported, clinician-validated, early motor and language milestones were collected at ages 2, 6, 12, 18, 24, and 36 months. Age distributions of milestone achievement were compared with normative data.

RESULTS: In all SCT conditions, compared with normative data, there was increased variability and a later median age of skill development across multiple gross motor and expressive language milestones. Results also show a significant amount of overlap with the general pediatric population, suggesting that for many children with prenatally identified SCT, early milestones present within, or close to, the expected timeline.

CONCLUSIONS: As increasing numbers of infants with prenatal SCT diagnoses present at pediatric practices, we provide an evidence-based schedule of milestone achievement in SCT as a tool for pediatricians and families. Detailed data on SCT milestones can support clinical interpretation of milestone achievement. Increased variability and later median age of milestone acquisition in SCT compared with norms support consideration of all infants with SCT as high risk.

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WHAT'S KNOWN ON THIS SUBJECT: Sex chromosome trisomy (SCT) is a common chromosomal aneuploidy associated with early developmental delays and increased risk for neurodevelopmental disorders later in childhood. Specific data on the timing of early SCT developmental milestones is missing from the literature.

WHAT THIS STUDY ADDS: This study quantifies the spectrum of motor and language milestone acquisition among children with SCT. Timing for milestone achievement is highly variable, with later median ages of achievement across SCT conditions compared with normative samples.

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BACKGROUND

Sex chromosome trisomy (SCT) (XXY/Klinefelter syndrome, XYY/Jacob syndrome, XXX/Trisomy X) is a common chromosomal aneuploidy, occurring in 1 of every 500 live births.[1] Prior SCT research, often limited by small sample sizes and/or ascertainment bias, has provided broad descriptions of early development. Early unbiased newborn screening studies documented profiles of increased risk for delays in gross motor and communication,[2,3] and a more current national survey identified high rates of EI.[4] Recent advances in noninvasive prenatal screening[5] have led to increasing rates of prenatally identified SCT and, subsequently, a growing population of infants with a confirmed SCT diagnosis early in life. As the literature lacks concrete information on the timing of typical milestone achievement in SCT, parents, and clinicians lack clear guidance on what to expect during a child's early years.

Close surveillance of key developmental milestones is a critical part of pediatric care, supporting the promotion of healthy development and the early detection of potential developmental delays.[6] However, common surveillance methods (eg, Centers for Disease Control and Prevention [CDC] milestones[7] checklists) may have less utility for children with genetic conditions and those at-risk for delays such as infants born prematurely. Research has shown that the timing of milestone acquisition differs from the general population in children with Down syndrome (DS),[8] fragile X (FXS),[9] and preterm and very low-birth-weight infants.[9–11] If this is the case for SCT as well, early developmental care should go beyond surveillance and general screening to include periodic direct developmental assessment. Further, a clear understanding of when children with SCT acquire key developmental milestones is critical for setting reasonable expectations, alerting families to potential concerns, and guiding clinicians in their referrals for EI. This is especially important with the increased frequency of prenatal SCT diagnoses, as pediatricians will be responsible for developmental care in a higher number of infants with SCT presenting to their practices. Therefore, the primary purpose of this study is to fill this gap in the SCT literature with a current, evidence-informed schedule of key early gross motor and language milestone achievement for each of the SCT conditions. These findings will support a more personalized approach to monitoring and care in SCT. Comparisons with previously published normative data to the 3 SCT conditions will provide critical context and a richer understanding of the SCT phenotypes, and guide recommendations for early developmental care.

METHODS

Data were collected as part of the institutional review board (IRB)-approved eXtraordinarY Babies Natural History Study, which leverages recent advances in genetic testing with a prospective investigation of the developmental and health trajectories in a prenatally identified sample of infants with SCT (ClinicalTrials.gov NCT03396562; COMIRB 17-0118; Nemours IRB# 1151006).[12] Participants are recruited through advocacy organizations, professional networks, and social media websites. Inclusion criteria are prenatal identification of SCT (by cell-free DNA, chorionic villi sampling, and/or amniocentesis) with diagnostic confirmatory karyotype (chorionic villi sampling, amniocentesis, or postnatal), English or Spanish speaking, and child age of 6 weeks to 12 months upon enrollment. Although the prenatal diagnosis allows for representation anywhere along the spectrum of SCT, we also required that participants enroll before 12 months of age to prevent overinclusion of individuals seeking study participation because of developmental concerns. Children are excluded from participation if there is a previous diagnosis of a different genetic or metabolic disorder with neurodevelopmental or endocrine involvement, less than 37 weeks gestational age, a complex congenital malformation not previously associated with SCT, history of significant neonatal complications (ie, intraventricular hemorrhage, meningitis, hypoxic-ischemic encephalopathy), or known central nervous system malformation identified by neuroimaging. Study visits are conducted regularly at ages 2, 6, 12, 18, and 24 months, and then yearly at 2 sites (Colorado and Delaware) with a combination of in-person and telehealth visits. Visits include comprehensive health and developmental history, current interventions, physical examination, and a battery of developmental assessments and parent questionnaires. Race and ethnicity data are collected through a standardized self-report parent survey per NIH guidelines, and a 4 Factor Hollingshead Index was calculated as previously described.[13] Tartaglia et al, (2020)[12] provide additional details on the eXtraordinarY Babies natural history study protocol.

Developmental Milestone Measurement

Data on the timing of milestones were collected at every study visit as part of a parent-completed electronic health and development questionnaire asking parents to report if their child had achieved key developmental milestones, including 8 gross motor skills (rolling front to back, rolling back to front, sitting independently, crawling, cruising, walking, running, jumping) and 4 expressive communication milestones (cooing, babbling, single words, 2-word phrases). These milestones were chosen because they can be easily observed by parents within a natural setting and delays may predict other areas of known concern in older children with SCT. Response options were "Yes," "No," "I don't know." If parents marked "Yes," parents were prompted to estimate the age in months when the child acquired this skill. For example: "Is [child's preferred name] able to babble with consonant sounds like 'baba, dada, gege' etc"?" and then, "If yes, how old was [child's preferred

name] in months when they started babbling?" During the study visit, a physician reviewed the parent questionnaire responses through a detailed health and developmental history interview to confirm ages and parent understanding of the milestone. If there were discrepancies between parent-reported skill and the milestone achieved (for example parent reported the infant was "sitting independently" at the 6-month visit, but the physician confirmed the infant was still only sitting in a propped position), the physician would adjust the data on the physician data form. Discrepancies were rare, as study visits were closely spaced (no longer than a 12-month period) allowing for frequent communication and direct observation. A comparison of the parent and clinician forms showed physicians modified approximately 3% to 5% of all parent-reported data depending on the milestone. The physician data form was used for final data analysis.

Normative Data

Each of the 12 developmental milestones collected for the study sample was compared with existing published norms. We included normative data from studies with published values for the 25th, 50th, 75th, and 90th percentiles for the milestones of interest from the Denver II Scales,[14] the World Health Organization (WHO) Motor Development Study,[15] and the Primitive Reflex Profile (PRP).[16] As normative data were not available from a single source for all 12 milestones, we used the Denver II whenever possible (sitting, walking, running, jumping, cooing, babbling, single words, 2-word phrases). For milestones that were not included in the Denver II, we used data from the WHO (crawling and cruising) and the PRP (rolling front to back, rolling back to front). As the PRP normative data set only provided means and SDs, percentiles were estimated theoretically under the assumption of a normal distribution.

Analysis

All analyses were performed in R, version 4.4.0. Descriptive summaries by SCT are presented as median [IQR] and N (%). Median [IQR] is presented throughout for consistency, as most age distributions were non-normal, as tested via Shapiro-Wilks. Frequencies are also reported on children who did not achieve milestones by the age listed on the CDC milestones checklists. CDC milestones purport to represent the specific health supervision visit age when at least 75% or more of children are expected to demonstrate the skill. Demographic differences between SCTs were tested using Kruskal-Wallis tests for continuous variables and Fisher-Exact tests for categorical variables. For each milestone, achieved ages earlier than the normative 25th percentile were removed as early outliers. Normative and SCT milestone ages are visualized from their 25th to 50th, 50th to 75th, and 75th to 90th percentiles. Differences in milestones were analyzed using simulated data based on the normative percentiles, under the assumption of a non-normal distribution, and were tested with Wilcoxon Rank-Sum tests. Levene's test, given non-normality, was used to test for homogeneity of variance for the age distributions for achieving milestones for SCTs compared with the general population. Differences in milestones were also analyzed between children who had a history of early intervention (EI) therapies and those who did not. Exploring whether there was an overall relationship between milestone achievement with receiving EI therapy was important to ensure therapies were not significantly affecting the distribution of milestone achievement. Bonferroni adjusted significance thresholds are applied for motor and language domains separately, where $P < .006$ and $P < .013$ indicate statistical significance for motor and language domains, respectively.

RESULTS

Participants include 298 young children with prenatally identified SCT, including 174 with XXY, 50 with XYY, and 74 with XXX. All included children had at least one milestone age reported. Table 1 shows sample characteristics. At the time of analysis, the median age of patients included was 4.5 years with the youngest group being XYY children, with a median age of 2.6. The majority of the cohort was white (81.9%) and non-Hispanic/Latinx (83.9%). Included children had participated in the eXtraordinarY Babies study for a median of 3 years, with XXY children having participated the longest (median: 3.5 [IQR: 2.7, 3.8] years) and XYY children having participated for the shortest period of time (median: 1.2 [IQR: 0.4, 3.1] years).

Timing of Milestone Achievement in SCT Compared With Normative Data Sets

Figure 1 depicts the age (in months) of milestone achievement for each SCT compared with reference norms. Age distributions are characterized by plotting the values for the 25th, 50th, 75th, and 90th percentiles of each milestone and comparing them with normative data. Results indicate differences from the normative data set in distributions of age of achievement across all 12 milestones. Wilcoxon rank-sum tests indicate later median milestone achievement than the general population in at least one SCT group for all 4 language milestones and 5 of the 8 motor milestones (rolling front to back, sitting, cruising, walking, running), after multiple comparisons adjustment. Levene's tests indicated variance heterogeneity between SCTs and the general population, where greater variance of milestone achievement was found in at least one SCT group compared with the normative population for all milestones except babbling, walking, crawling, and rolling front to back.

TABLE 1. Cohort Demographics					
	Overall (N = 298)	XXY (N = 174)	XYY (N = 50)	XXX (N = 74)	*P* Value
Age (years; as of 7/9/2024)					
Median [IQR]	4.5 [2.9, 5.7]	4.9 [3.8, 6.1]	2.6 [1.4, 5.3]	3.5 [2, 5.1]	<.001[c]
Years in study					
Median [IQR]	3 [1.4, 3.8]	3.5 [2.7, 3.8]	1.2 [0.4, 3.1]	2.5 [0.9, 3.5]	<.001[c]
Race[a]					
White	244 (81.9%)	138 (79.3%)	41 (82.0%)	65 (87.8%)	.119
Native Hawaiian or Other Pacific Islander	1 (0.3%)	1 (0.6%)	0 (0%)	0 (0%)	
African American or Black	17 (5.7%)	13 (7.5%)	4 (8.0%)	0 (0%)	
Asian	24 (8.1%)	14 (8.0%)	2 (4.0%)	8 (10.8%)	
Native American or Alaska Native	3 (1.0%)	2 (1.1%)	1 (2.0%)	0 (0%)	
Other	6 (2.0%)	5 (2.9%)	1 (2.0%)	0 (0%)	
Missing	3 (1.0%)	1 (0.6%)	1 (2.0%)	1 (1.4%)	
Ethnicity[a]					
Hispanic/Latinx	45 (15.1%)	28 (16.1%)	6 (12.0%)	11 (14.9%)	.859
Non-Hispanic/Latinx	250 (83.9%)	145 (83.3%)	43 (86.0%)	62 (83.8%)	
Missing	3 (1.0%)	1 (0.6%)	1 (2.0%)	1 (1.4%)	
Hollingshead Index					
Median [IQR]	54.5 [47.9, 59.5]	54 [47, 59.5]	54.5 [46.1, 59.2]	55.5 [50.5, 59.5]	.619
Missing	10 (3.4%)	1 (0.6%)	4 (8.0%)	5 (6.8%)	
Annual family income[b]					
$50 000 or less	17 (5.7%)	12 (6.9%)	3 (6.0%)	2 (2.7%)	.437
$50 000–$100 000	67 (22.5%)	38 (21.8%)	15 (30.0%)	14 (18.9%)	
$100 000–$250 000	154 (51.7%)	91 (52.3%)	20 (40.0%)	43 (58.1%)	
>$250 000	54 (18.1%)	30 (17.2%)	11 (22.0%)	13 (17.6%)	
Missing	6 (2.0%)	3 (1.7%)	1 (2.0%)	2 (2.7%)	

[a] Race and ethnicity were self-reported by parents/guardians, as required by NIH guidelines.
[b] Family income data reported were collected at the initial eXtraordinarY Babies study visit.
[c] Significance level = 0.05. Overall differences were tested using Kruskal-Wallis tests for continuous variables and Fisher's Exact/Chi-Squared Tests for categorical variables.

Group Differences

Table 2 shows statistical results for group differences in age of milestone achievement between the SCT conditions. Results show statistically significant group differences in cooing ($P = .005$); boys with XXY achieved cooing earlier than boys with XYY ($P = .006$). Overall group differences exist for crawling ($P = .050$) and cruising ($P = .012$). Boys with XXY achieved cruising ($P = .006$) at a significantly younger age than girls with XXX. All other milestone data were statistically similar across trisomy conditions.

Comparisons With CDC Milestones

Table 3 shows the percentage of children by SCT condition who did not achieve milestones by the age listed on the CDC milestones checklists.

Consideration of EI Therapies

Of the 298 children included, 187 (63.8%) had received EI therapy and started either proactively because of risk for delays or in response to developmental concerns in one or more developmental domains. There were no differences in therapy rates between the SCT conditions. Within our cohort, children with a history of EI achieved milestones significantly later than children who had not ($P < .001$ for all milestones). This is likely because those with identified delays were more likely to be referred for developmental therapies.

DISCUSSION

This study reports on developmental milestone achievement in prenatally identified SCT and provides a novel milestone chart that can help parents and professionals better quantify and visualize what "increased risk for developmental delay" means in SCT conditions. These cohorts were not referred for any concerns and thus were as close to "population based" as possible. In all SCT conditions, there was a later median age of skill development across multiple gross motor and expressive language milestones than

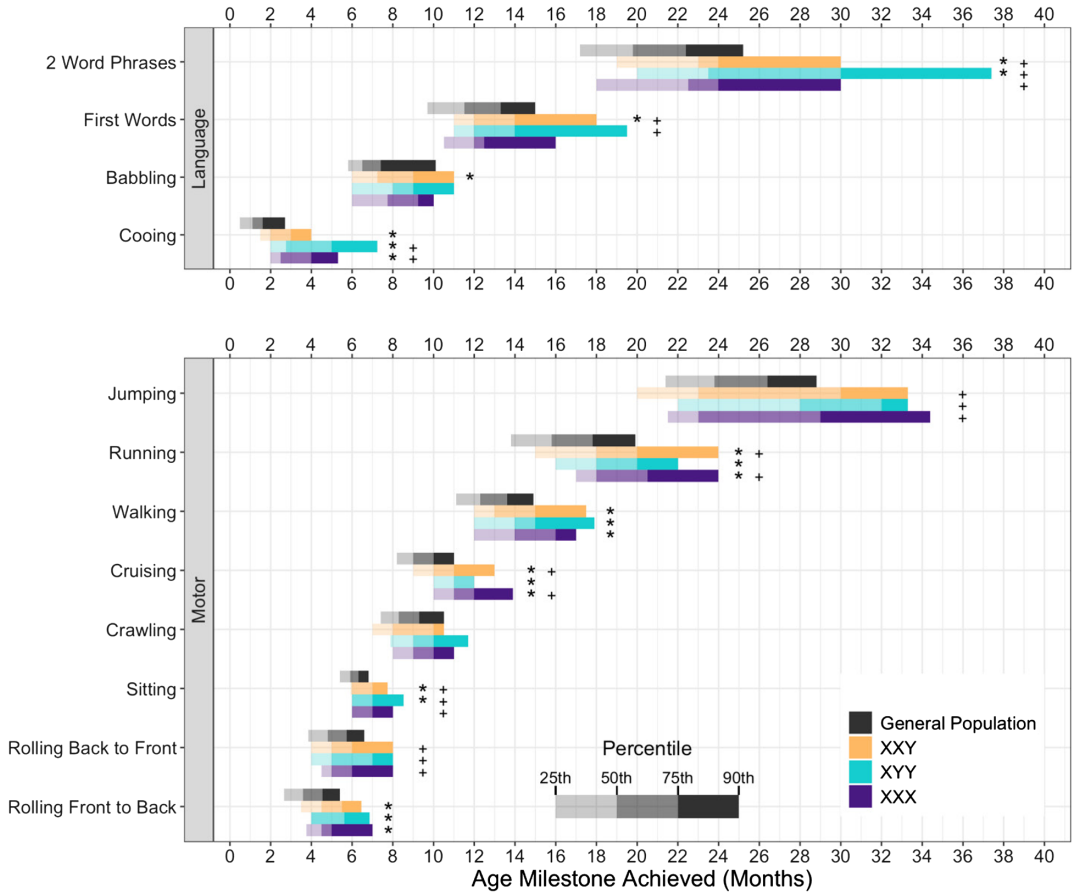

FIGURE 1.

Achievement of Language and Motor milestones in SCT compared with the general population. *Trisomy is delayed compared with simulated data based on general population percentiles, under the assumption of a non-normal distribution. Multiple comparisons significance level = 0.006 for motor milestones and 0.013 for language milestones. Differences were tested with Wilcoxon Rank-Sum Tests. +Distribution of ages of milestone achievement for the Trisomy has significantly more variance than the general population. Multiple comparisons significance level = 0.006 for motor milestones and 0.013 for language milestones. Homogeneity of variance was tested with Levene's Tests. General Population estimates are based on Denver II for Jumping, Running, Walking, Sitting, 2-Word Phrases, First Words, Babbling, and Cooing; WHO for Cruising and Crawling; and PRP for Rolling Back to Front and Rolling Front to Back.[12–14]

Abbreviations: PRP, Primitive Reflex Profile; SCT, sex chromosome trisomy; WHO, World Health Organization.

reported in normative data sets. This includes both early milestones such as cooing and rolling front to back, and later milestones including 2-word phrases, walking, and running. Furthermore, there was more variability in the age range for milestone achievement in our sample compared with reference norms, with the range of acquisition for all milestones extending later in life for children with SCT. These findings support the need to consider infants with SCT as a group at increased risk for delays and deserving of closer developmental monitoring given that the age of early motor and language milestones have been shown to predict longitudinal outcomes across all developmental domains in the general population and clinical samples.[17–28]

These results confirm prior research indicating an increased risk for developmental delays and EI services in children with SCT.[4,12,29] Further, results are consistent with findings from the early newborn screening studies that showed a slightly later onset of independent walking and two-word phrases than expected (walking: 15–22 months; 2-word phrases: >28 months).[30–32] Prior studies in other genetic disorders have shown the onset of developmental milestones is often significantly different from both population norms and milestone timing in idiopathic autism spectrum disorder (ASD).[33] However, unlike other genetic conditions such as DS and FXS,[34,35] our results show a significant amount of overlap with the general pediatric population. Figure 1 shows that, for many children with prenatally identified SCT, early milestones present within, or close to, the expected timeline. While this is reassuring, there are known later risks in SCT for many neurodevelopmental diagnoses including speech-language disorders, learning disabilities, attention-deficit/hyperactivity disorder (ADHD), executive dysfunction, motor skill deficits,

TABLE 2. Age in Months of Milestone Achievement by SCT[a]

	XXY (N = 174)	XYY (N = 50)	XXX (N = 74)	Overall Kruskal-Wallis *P* Value
Language				
Cooing	N = 165	N = 46	N = 68	
Median [25th, 75th, 90th]	2 [1.5, 3, 4]	2.8 [2, 5, 7.2]	2.5 [2, 4, 5.3]	.005[a,c]
Babbling	N = 158	N = 44	N = 61	
Median [25th, 75th, 90th]	7.2 [6, 9.2, 11]	8 [5.9, 9, 11]	7.75 [6, 9.2, 10]	.867
First Words	N = 152	N = 36	N = 55	
Median [25th, 75th, 90th]	12 [11, 14, 18]	12 [11, 14, 19.5]	12 [10.5, 12.5, 16]	.557
2 Word Phrases	N = 135	N = 23	N = 42	
Median [25th, 75th, 90th]	23 [19, 24, 30]	23.5 [20, 30, 37.4]	22.5 [18, 24, 30]	.637
Motor				
Rolling Front to Back	N = 162	N = 44	N = 64	
Median [25th, 75th, 90th]	4.5 [3.5, 5.5, 6.5]	4 [4, 5.6, 6.9]	4.5 [3.8, 5, 7]	.891
Rolling Back to Front	N = 162	N = 43	N = 64	
Median [25th, 75th, 90th]	5 [4, 6, 8]	5 [4, 7, 8]	5 [4.5, 6, 8]	.193
Sitting	N = 164	N = 45	N = 60	
Median [25th, 75th, 90th]	6 [5.9, 7, 7.8]	6 [6, 7, 8.5]	6 [6, 7, 8]	.354
Crawling	N = 162	N = 44	N = 62	
Median [25th, 75th, 90th]	8 [7, 9.9, 10.5]	9 [7.9, 10, 11.7]	9 [8, 10, 11]	.050[c]
Cruising	N = 157	N = 41	N = 62	
Median [25th, 75th, 90th]	10 [9, 11, 13]	11 [10, 12, 12]	11 [10, 12, 13.9]	.012[b,c]
Walking	N = 156	N = 32	N = 53	
Median [25th, 75th, 90th]	13 [12, 15, 17.5]	14 [12, 15, 17.9]	14 [12, 16, 17]	.239
Running	N = 145	N = 27	N = 51	
Median [25th, 75th, 90th]	18 [15, 20, 24]	18 [16, 20, 22]	18 [17, 20.5, 24]	.177
Jumping	N = 131	N = 22	N = 43	
Median [25th, 75th, 90th]	23 [20, 30, 33.3]	28 [22, 32, 33.3]	23 [21.5, 29, 34.4]	.374

[a] Pairwise test XXY ≠ XYY; Bonferroni adjusted alpha = 0.006 for motor milestones and 0.013 for language milestones.
[b] Pairwise test XXY ≠ XXX; Bonferroni adjusted alpha = 0.006 for motor milestones and 0.013 for language milestones.
[c] Significant difference in at least one trisomy; alpha = 0.05.

and autism spectrum disorders,[36–48] which all benefit from earlier diagnosis and evidence-based treatments. Thus, careful attention to development trajectories is warranted as EIs may help minimize these morbidities.

The variability of the phenotype and overlap with the general population often leads to questions of whether different developmental care pathways and extra developmental testing are needed for all infants with SCT. This is a valid concern as a relatively high proportion of individuals with SCT conditions have minimal neurodevelopmental differences with positive adult outcomes,[49–51] and many go undiagnosed from their clinical presentation. Additional recommendations for developmental monitoring and evaluation may increase family stress, negatively impact parent-child relationships, and call unnecessary attention to the genetic differences in their child, as well as increase health care use and demand on a stressed EI system. Prospective longitudinal research is needed to clarify if indeed there are specific early risk factors predictive of poorer outcomes that would warrant stratifying children with SCT into different low vs high-risk developmental care pathways, similar to extensive work done in the congenital heart disease and prematurity populations.[52,53] These pathways, however, were developed using evidence from hundreds of studies, which do not currently exist in SCT. Thus, until more prospective data are available, consideration of all infants with SCT as high risk is warranted.

Table 3 responds to our interest in whether recently published milestones from the CDC[7] are appropriate for developmental surveillance in infants with SCT. Overall, a relatively small proportion of children in our sample were delayed in milestone achievement according to the CDC milestones checklists (Table 3), even though their milestone acquisition was delayed as compared with other metrics (Denver II; WHO). This suggests that relying on the CDC milestone lists for SCT will fail to identify many infants

TABLE 3. Frequencies of Children With SCT Delayed in Milestones According to Ages Set by CDC Milestones Checklists

Milestone	Age	XXY (Total N = 174)	XYY (Total N = 50)	XXX (Total N = 74)
Language				
Cooing	4 mos	16/165 (9.7%)	13/46 (28.3%)	11/68 (16.2%)
Babbling	9 mos	35/158 (22.12%)	9/44 (20.5%)	13/61 (21.3%)
First words	15 mos	32/1582 (21.1%)	8/36 (22.2%)	10/55 (18.2%)
2-word phrases	24 mos	33/135 (24.4%)	9/33 (39.1%)	10/42 (23.8%)
Motor				
Rolling front to back	6 mos	17/162 (10.5%)	7/44 (15.9%)	9/64 (14.1%)
Sitting independently	9 mos	3/164 (1.8%)	1/45 (2.2%)	2/60 (3.3%)
Cruising	12 mos	22/157 (14%)	3/41 (7.3%)	13/62 (21%)
Walking	15 mos	33/156 (21.2%)	7/32 (21.9%)	19/53 (35.9%)
Running	24 mos	12/145 (8.3%)	1/27 (3.7%)	4/51 (7.8%)
Jumping	30 mos	22/131 (16.8%)	6/22 (27.3%)	7/43 (16.3%)

Abbreviations: CDC, Centers for Disease Control and Prevention; SCT, sex chromosome trisomy.
N (%; *P* value): Number (%) of children in each trisomy that achieved the milestone later than the ages listed on CDC milestone checklists. Total sample sizes differ for each milestone and trisomy. CDC cut points were not available for rolling back to front and crawling.

with delayed milestones and is consistent with other published concerns[54–56] about the low sensitivity of the ages presented in the CDC milestones. It is well recognized that standard developmental screening tools designed for the general population (eg, ASQ, PEDS)[57–59] have lower sensitivity in high-risk groups, which has led to guidelines for developmental follow-up of high-risk neonates with periodic direct assessment.[53,60–62] Similarly, our findings of the increased risk in SCT support that periodic direct developmental assessment should be part of SCT treatment guidelines.[63]

By offering detailed information on milestone achievement, we provide a valuable tool for clinicians and families to better interpret a child's early development within the context of their SCT condition, rather than only comparing it with general population norms. Further, any significant deviations from SCT norms may alert clinicians to potential risks for comorbid health conditions or an additional genetic difference. While pediatric clinicians can use this tool as a reference to contextualize a child's milestone achievement, it is not intended to delay referrals for developmental evaluations or EI support. Parents may appreciate the more nuanced normative data as they track their child's milestones, noting areas where their child's development aligns with children with similar genetic profiles, as well as areas of normative differences. Prior research shows parents of children with delayed milestones may have higher levels of perceived stress[64] or experience guilt that they have done something to cause their child's delays.[65] A clearly defined schedule for the timing of developmental milestones specific to each SCT, when used in conjunction with normative milestones expectations, may be more palatable in supporting early developmental care.

Results showing similarities and differences in milestone achievement by karyotype (Table 2) add to the existing literature on genetic disorders by providing more specific data regarding milestone acquisition in each trisomy condition. For most milestones, SCT groups were statistically similar. This aligns with prior research showing similar early developmental and neurocognitive profiles across the SCT conditions.[48,66–68] However, the XXY group did achieve several milestones earlier, including cooing 1 month earlier than both other groups and crawling and cruising 1 month earlier than those with XXX. While this may be an artifact of a larger and more variable sample size in XXY, it may also reflect the differential effects of the extra X chromosome in males.[69] Ongoing research with larger sample sizes for XYY and XXX will help determine if different SCT conditions have clinically relevant differences in developmental trajectories.

These study results also have practical implications for prenatal and antenatal genetic counseling and are responsive to prior research findings showing that parents receiving a prenatal SCT diagnosis desire more balanced, accurate, and current data on the range of potential neurodevelopmental outcomes specific to each SCT condition.[70–72] In the context of highly variable phenotypes associated with SCT, genetic counselors strive to provide guidance to parents with a new diagnosis and clarify parental perception of risks for developmental delays.[73] This foundation establishes how parents understand and respond to their child's development and behavior, especially as related to the genetic diagnosis. By providing a clearer picture of developmental expectations associated with the diagnosis, genetic counselors can more specifically inform parents about what to expect in their child's first few years of life, as well as promote awareness, empowerment, and a proactive approach to EI processes to facilitate early developmental care.[74]

Despite the insights gained, limitations are important to consider. First, smaller sample sizes for the XXX and XYY karyotypes limit generalizability compared with the XXY sample. There are known limitations in normative data for milestone acquisition, including unclear and inconsistent definitions of milestones,[75] ambiguity around what constitutes achievement of milestones (partial vs complete),[76] and differences in raters used to determine milestone achievement for normative data sets (parents vs clinicians).[75,77,78] Normative data sets rarely account for sociodemographic factors, which complicates their application. We used multiple data sets (Denver II, WHO, PRP), each of which has distinct sample characteristics.

Moreover, these data sets often overlook important variables such as potential sex differences,[79,80] racial and sociocultural differences,[54,81,82] and variability linked to social determinants of health.[76] This introduces additional uncertainty into our findings, as the sample characteristics for each milestone varied across the measures (eg, the WHO data set included infants from 5 countries worldwide). Our sample was disproportionately white and non-Hispanic with high socioeconomic status; future studies should aim to include more representative samples. Moreover, our primary source of normative data, the Denver II, has shown high specificity but has been criticized for its limited sensitivity.[83] As a result, our normative data set may underestimate the typical ages at which milestones are acquired, placing our sample of infants with SCT closer to the general population. Parental recall bias, another commonly recognized challenge when evaluating parent-reported milestones,[84,85] was minimized in this study with frequent visits at ages 2, 6, 12, 18, 24, and 36 months with pediatricians interviewing and verifying milestone achievements. Importantly, while there are many benefits to an ongoing natural history study, our study design is limited in that at the time of publication, not all participants in the sample had yet achieved all milestones measured and therefore sample sizes differed. Additionally, within our sample, there was an unexpectedly high proportion of children receiving EI services, which may be mitigating even more pronounced skill deficits. Future studies should directly examine the impact of EI on developmental outcomes for children with SCT, considering reasons for EI referral, quality and modality of EI services, and the exact dosage children receive. Also, while we explored the effect of EI in our analysis, the act of participating in a natural history study itself may influence developmental course. While a prenatally identified sample of nearly 300 infants with SCT provides a less biased data set than prior studies, it may still not fully represent the broad spectrum of outcomes in SCT. Future results based on direct assessments through the eXtraordinarY Babies study can address these limitations and further refine our understanding of developmental trajectories and risk groups in this population.

In conclusion, developmental milestone achievement in SCT conditions is delayed compared with the general population, however only in a subset of infants with SCT. As increasing numbers of infants with prenatal SCT diagnoses present at pediatric practices, we provide an evidence-based schedule of milestone achievement in SCT as a tool for families, pediatricians, genetic counselors, and EI teams. The use of such a tool can support shared clinical decision-making between parents and clinicians, promoting timely referrals and identifying patterns inconsistent with SCT. However, given the paucity of prospective research identifying specific risk factors for later negative outcomes, recommended care for SCT conditions should follow practices of other high-risk conditions - with more responsive attention to developmental concerns, recognition that standard surveillance and screening tools have lower sensitivities in high-risk populations, and referrals for periodic direct developmental assessments. Although more rigorous research will help identify evidence for the timing of direct assessments and highest-risk groups, general publications support assessments at ages 6 to 12 months, 18 to 24 months, and 36 months.[86–88]

ABBREVIATIONS

SCT: sex chromosome trisomy
CDC: Centers for Disease Control and Prevention
DS: Down syndrome
FXS: fragile X syndrome
WHO: World Health Organization
PRP: Primitive Reflex Profile
EI: early intervention

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