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Patterns of delay in early gross motor and expressive language milestone attainment in probands with genetic conditions versus idiopathic ASD from SFARI registries

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Abstract

Background: Recent large-scale initiatives have led to systematically collected phenotypic data for several rare genetic conditions implicated in autism spectrum disorder (ASD). The onset of developmentally expected skills (e.g. walking, talking) serve as readily quantifiable aspects of the behavioral phenotype. This study's aims were: (a) describe the distribution of ages of attainment of gross motor and expressive language milestones in several rare genetic conditions, and (b) characterize the likelihood of delays in these conditions compared with idiopathic ASD.

Methods: Participants aged 3 years and older were drawn from two Simons Foundation Autism Research Initiative registries that employed consistent phenotyping protocols. Inclusion criteria were a confirmed genetic diagnosis of one of 16 genetic conditions (Simons Searchlight) or absence of known pathogenic genetic findings in individuals with ASD (SPARK). Parent-reported age of acquisition of three gross motor and two expressive language milestones was described and categorized as on-time or delayed, relative to normative expectations.

Results: Developmental milestone profiles of probands with genetic conditions were marked by extensive delays (including nonattainment), with highest severity in single gene conditions and more delays than idiopathic ASD in motor skills. Compared with idiopathic ASD, the median odds of delay among the genetic groups were higher by 8.3 times (IQR 5.8–16.3) for sitting,

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Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article:

Conflict of interest statement: See Acknowledgements for full disclosures.

12.4 times (IQR 5.3–19.5) for crawling, 26.8 times (IQR 7.7–41.1) for walking, 2.7 times (IQR 1.7–5.5) for single words, and 5.7 times (IQR 2.7–18.3) for combined words.

Conclusions: Delays in developmental milestones, particularly in gross motor skills, are frequent and may be among the earliest indicators of differentially affected developmental processes in specific genetically defined conditions associated with ASD, as compared with those with clinical diagnoses of idiopathic ASD. The possibility of different developmental pathways leading to ASD-associated phenotypes should be considered when deciding how to employ specific genetic conditions as models for ASD.

Keywords

copy number variant; intellectual disability; developmental phenotype

Introduction

Large-scale collaborations (e.g. Simons Simplex Collection; Fischbach & Lord, 2010; Simons VIP Consortium, 2012) have made available larger cohorts of individuals with specific genetic diagnoses associated with neurodevelopmental disorders, allowing for an approach to examining phenotypes as they relate to specific genotypes (Chawner et al., 2021). Defining the phenotypic landscape of these genetic conditions, particularly in early childhood, is important for improving identification and clinical management. Additionally, given their established association with autism spectrum disorder (ASD), characterizing the extent of similarity between the early developmental profiles of these genetic conditions with those from idiopathic ASD may help promote understanding of how, and at what points in development, their phenotypic profiles overlap.

Information regarding attainment of developmental milestones, such as walking and talking, is one way to quantify very early aspects of the phenotype. Extensive data on such developmental milestones are available for the general population (Carruth & Skinner, 2002; Sheldrick et al., 2019; Størvold, Aarethun, & Bratberg, 2013; Taanila, Murray, Jokelainen, Isohanni, & Rantakallio, 2005; World Health Organization, 2006). Information about developmental milestone attainment is lacking in rare genetic conditions, but has been a focal point in ASD research. Among children with ASD, early motor milestones are generally achieved within normal age limits (Bishop, Thurm, Farmer, & Lord, 2016; Havdahl et al., 2020; Matson, Mahan, Kozlowski, & Shoemaker, 2010), while the onset of language milestones is more variable (Eigsti, de Marchena, Schuh, & Kelley, 2011; Mayo, Chlebowski, Fein, & Eigsti, 2013; Mitchell et al., 2006). Further, among individuals with ASD, those with identifiable rare genetic conditions walk later than those without known genetic conditions (Bishop et al., 2017). However, data regarding early development (‘developmental phenotypes’) from genetics-first investigations that include recently identified rare genetic conditions associated with ASD are only beginning to emerge (Arnett et al., 2020; Bernier et al., 2017; Chawner et al., 2019; Hinton et al., 2013; Winders, Wolter-Warmerdam, & Hickey, 2019).

The first aim of this study was to extend the limited literature by describing developmental phenotypes in multiple genetic conditions (1q21.1 deletion, 1q21.1 duplication, 16p11.2

deletion, 16p11.2 duplication, *ADNP*, *ASXL3*, *CSNK2A1*, *DYRK1A*, *GRIN2B*, *MED13L*, *PACS1*, *PPP2R5D*, *SCN2A*, *SLC6A1*, *STXBP1*, *SYNGAP1*) using contemporaneously and systematically collected data regarding gross motor and expressive language milestone acquisition (Simons VIP Consortium, 2012). Because of their putative association with ASD, the second aim was to compare the developmental phenotypes of each genetic condition to those of children with ASD without known genetic conditions (SPARK Consortium, 2018) to elucidate the extent to which each condition reflects phenotypes characteristic of idiopathic ASD. Based on limited reports of milestone attainment in these genetic conditions in the literature, we expected (a) extensive delays across genetic conditions, and (b) that relative to idiopathic ASD, genetic conditions would exhibit greater rates of delays and nonattainment in language and motor skills, with delays most pronounced in motor skills.

Methods

Cohorts

Simons Searchlight.—Simons Searchlight, an effort launched by the Simons Foundation Autism Research Initiative (SFARI; previously known as Simons Variation in Individuals Project; Simons VIP Consortium, 2012), is comprised of groups of people with rare genetic variants implicated in ASD. This study was approved by the Columbia University Irving Medical Center Institutional Review Board (IRB) as well as the Geisinger IRB. Parents or legal guardians signed consent forms while verbal assent was given by children over age 10. While nearly all participants have developmental disabilities of varying severity, not all participants have ASD. Individuals with a genetic diagnosis on the Simons Searchlight Gene List (https://www.simonssearchlight.org/research/what-we-study/), which contains 152 gene changes and 23 copy number variants (CNVs), enrolled in the registry from 2014 to September 2020. Participants were recruited worldwide by the Simons Searchlight community website (https://www.simonssearchlight.org) as well as with social media outreach, clinical referrals, and other means of web recruitment (e.g. clinicaltrials.gov) targeting individuals with a diagnosis of one of the genetic conditions in Simons Searchlight. The protocol consists of developmental and behavioral surveys in an online study portal, a telephone interview to obtain medical history and administer the Vineland Adaptive Behavior Scales (Sparrow, Cicchetti, & Balla, 2005; Sparrow, Cicchetti, & Saulnier, 2016), and the collection of biospecimens. Files from Version 7, the latest version available at the time, were downloaded on September 29, 2020 from SFARI.org, and included the 1q21.1, 16p11.2, and single gene mutation datasets. Releases on SFARI Base are biannual for Searchlight.

SPARK.—The SPARK registry is the largest existing genetic study of ASD (SPARK Consortium, 2018). Individuals from the United States with a reported professional ASD diagnosis and their family members are eligible for enrollment in SPARK, regardless of age or genetic status. This study was approved under a centralized IRB protocol, Western IRB, and parents or legal guardians signed consent forms, while verbal assent was given by children over age 10. Families were recruited by 31 sites across the United States using an extensive web recruitment strategy. Similar to Simons Searchlight, medical and

developmental history, current behavioral data, and biospecimens were collected remotely through an online portal beginning in late 2015. Version 4, the latest version available at the time, was downloaded on April 30, 2020 from SFARI.org. SPARK data releases at least quarterly on SFARI Base.

Sample selection

A detailed description of how data were combined (Appendix S1), as well as a flow diagram of sample selection (Figure S1, pg. 3), are provided. From both cohorts (i.e. Simons Searchlight and SPARK), participants for this study were initially identified probands at least 3 years of age with verified genetic results, and at least one valid response for any of the five developmental milestones of interest. The minimum age was selected because normative acquisition of the milestones considered in these analyses occurs before the age of 3 years (Centers for Disease Control, 2020; Sheldrick et al., 2019; World Health Organization, 2006). This allowed for the interpretation of milestones which were reportedly 'not yet achieved' as 'delayed'.

Cohort-specific inclusion criteria were as follows. Simons Searchlight groups containing at least 15 cases with available walking milestone data were included in the genetic conditions sample. The threshold of 15 was selected to allow for more stable parameter estimates, and the walking milestone was selected because it has been studied previously in some of these specific genetic conditions (Bishop et al., 2017; Satterstrom et al., 2020). The resulting sample included 479 participants across 16 conditions: four CNVs (1q21.1 deletion, 1q21.1 duplication, 16p11.2 deletion, 16p11.2 duplication) and twelve single genes (*ADNP*, *ASXL3*, *CSNK2A1*, *DYRK1A*, *GRIN2B*, *MED13L*, *PACS1*, *PPP2R5D*, *SCN2A*, *SLC6A1*, *STXBP1*, *SYNGAP1*). Refer to Table S1 for a brief description of the single-gene mutations. Simons Searchlight participants, both with and without reported ASD diagnoses, were included. Probands from the SPARK sample were included in the idiopathic ASD group (n = 3,506) if they underwent genetic analyses and were found to have no known pathogenic single gene or CNV events strongly associated with ASD based on SNP genotyping array, whole-exome sequencing, and review by the SPARK medical genetics committee (Feliciano et al., 2019). Adults who independently enrolled in Simons Searchlight and SPARK were not included in this study because reports of milestone attainment are only provided by caregivers of dependent children or adults.

Measures

Upon enrolling in either registry, participants were invited to complete a standard set of questionnaires. All questionnaires for participants in this study were completed by parents or caregivers. For a list of exact variables and datasets used for each registry, please refer to Figure S2. Whereas specific measures used for medical history and other data collection varied by registry (see subsections below), the developmental milestone and demographic data were collected via a Background History form in both registries.

The primary developmental phenotypes of interest included ages of milestone attainment for sitting, crawling, walking, using single words, and using combined words. For each milestone, respondents chose one of the following from a drop-down menu: attainment

age in months (1–84 months), achieved after age 7 years, or not yet achieved (for exact wording and answer options, see Appendix S2 for Simons Searchlight and Appendix S3 for SPARK). The response options for the milestone questions changed slightly during the data collection period: minimum age floors for certain milestones as well as the option of 'not yet [achieved]' were introduced for quality control and quality assurance reasons. Prior to these changes, parents of children who did not acquire a skill may have left the age of milestone attainment blank. To the extent that this is true, the observed data are biased toward children who had acquired a milestone. For this reason, we explored options for partially imputing missing data on milestone acquisition using scores from the Vineland-II Adaptive Behavior Scales Survey Interview Form (Sparrow et al., 2005).

The Vineland-II is a semistructured interview that can be used across the life span. It measures adaptive functioning in four domains (with corresponding subdomains): Communication (Expressive, Receptive, Written), Daily Living (Personal, Domestic, Community), Socialization (Interpersonal Relationships, Play and Leisure Time, Coping Skills), and, in children under age 7, Motor Skills (Gross, Fine). When available, scores from the Vineland-II were used to estimate whether a participant with missing milestone acquisition data had acquired walking and single words (see Appendix S4 for a detailed explanation). Item-level data were not available, so estimated minimum raw scores compatible with the ability to walk (Gross Motor = 27) and use single words (Expressive Language = 19) were used to determine whether or not a participant had attained the milestone. Based on these designated thresholds, attainment scores were imputed for 4% of the sample for walking and 14% of the sample for single words. Raw scores less than the threshold were used to code the milestone as 'not yet achieved'. If the raw scores exceeded the threshold, the milestone was coded as 'achieved, age unknown'. We validated this clinically-driven decision by calculating the sensitivity, specificity, and overall accuracy of the cutoffs (Figure S3). The overall accuracy of our selected cutoffs was very good (99% for walking and 91% for single words). For both walking and single words, all participants who did not acquire the milestone were correctly classified as such by our Vineland cutoff (2/2 nonwalkers and 11/11 nontalkers; specificity values of 100%). A very small proportion of participants who had acquired the skill were incorrectly classified by our Vineland cutoff (2/178 walkers and 23/250 talkers; sensitivity of 99% and 91%).

Finally, 'delay' in the acquisition of milestones was operationalized using normative data. Gross motor milestones were considered to be delayed if they occurred after 8 months for sitting, 12 months for crawling, and 16 months for walking, based on the 97th percentiles (8.4, 12.0, and 16.0, respectively) reported for normative data (World Health Organization, 2006). Expressive language milestones were categorized as delayed after 12 months for single words and 24 months for combined words based on the Act Early CDC Recommendations (Centers for Disease Control, 2020). Milestones which were not yet attained were considered delayed because all participants were 3 years of age or older. For descriptive purposes, the degree of delay was further categorized as attainment occurring within 6 months or beyond 6 months (including those who never attained) of the expected age of acquisition.

Simons Searchlight.—Parent-reported diagnoses of ASD, Intellectual Disability (ID), Seizure Disorder/Epilepsy, and gestational age were drawn from the medical history interview. Parents or caregivers also participated in the Vineland-II with licensed genetic counselors over the phone at the time of the medical history interview. Raw scores on the Expressive Communication and Gross Motor subdomains at first administration of the Vineland-II were used to guide the imputation of some missing milestone data, as described above.

SPARK.—Parent-reported diagnosis of ID, Seizure Disorder/Epilepsy, gestational age, and additional demographics (i.e. ancestry) were drawn from registration, a background history form, and a medical screening survey.

Statistical analysis

The goals of this study were primarily descriptive. However, it was necessary to quantify the degree of difference in milestone acquisition between the genetic conditions and the idiopathic ASD sample. For the sake of clinical interpretability, we operationalized the outcome as on-time versus delayed (including nonattainment) acquisition of a given milestone as described above. Given the uniform delay among some of the genetic conditions, we used the penalized likelihood-based method Firth logistic regression, using the logistf package for R version 4.0.2 (Heinze, Ploner, & Jiricka, 2020). Absolute (rate) and relative (odds ratios; OR) probabilities of delay, based on genetic condition, are provided alongside 95% confidence intervals. To further describe the patterns of onset, age of acquisition for those who achieved a milestone prior to age 7 years is summarized for each group using the median and interquartile range. This was possible only for those who acquired the milestone prior to age 7 years due to the response options on the form (see Appendices S2 and S3). Proportions of the sample are also presented for those who acquired the skill after age 7 years or at an unknown age, did not acquire the skill, or had missing data regarding acquisition of that skill.

Missing data.—Nonresponse occurred for a total of 355 participants (Simons Searchlight $n = 133$, 28%; SPARK $n = 222$, 6%), with missing responses for 179 participants on one milestone (Simons Searchlight $n = 46$, 10%; SPARK $n = 133$, 4%), 102 participants on two milestones (Simons Searchlight $n = 52$, 11%; SPARK $n = 50$, 1%), and 74 participants on three or four milestones (Simons Searchlight $n = 35$, 7%; SPARK $n = 39$, 1%). We also imposed one logical constraint on the data that created missing data: where the age of using combined words was younger than the age of using single words, we treated both as missing (Simons Searchlight $n = 5$; SPARK $n = 15$). To the extent possible, missing data were imputed as acquired/not acquired, as described above. Vineland-II data were available only for Simons Searchlight, and were not available for all participants with missing milestone data. Data were imputed for Simons Searchlight participants for $n = 19$ of 28 missing information about walking and $n = 69$ of 80 missing information about single words. No other imputation of missing data was performed.

Results

Demographics for the genetic conditions sample (Simons Searchlight) and idiopathic ASD sample (SPARK) are provided in Table 1; inheritance status and parent report of specific diagnoses for each of the 17 groups are provided in Table S2. Overall, the genetic conditions sample had a lower proportion of males (53%) compared with the idiopathic ASD sample (82%). Annual household income was $81,000 or above for 54% of the genetic conditions sample and 51% of the idiopathic ASD sample. Among the 16 genetic conditions, the parent-reported prevalence ranged from 8% to 39% for ASD-only (no ID), 0% to 41% for ID-only (no ASD), 0% to 39% for comorbid ASD and ID, 4% to 79% for seizure disorder/epilepsy, and 0% to 18% for premature birth, whereas for idiopathic ASD, prevalence was 87%, 0%, 13%, 4%, and 10%, respectively.

The rates of on-time attainment across the 16 genetic conditions were more variable for gross motor milestones than for expressive language milestones (Figure 1). Rates of delay in gross motor milestones ranged from 6% to 84% in sitting, 6% to 87% in crawling, and 29% to 100% in walking. Rates met or exceeded 50% for 10 (63%) conditions on sitting, eight (50%) conditions on crawling, and 12 (75%) conditions on walking. The rates of delay in expressive language milestones were also very high among the genetic conditions, ranging from 71% to 100% for single words and 61% to 100% for combined words, and exceeded 50% for all 16 (100%) conditions for each language milestone. Rates of delay were also higher in single gene conditions compared with CNVs, especially for sitting (44%–84% vs. 6%–47%, respectively), crawling (29%–87% vs. 6%–20%, respectively), and walking (47%–100% vs. 29%–58%, respectively), and to a lesser extent for single words (72%–100% vs. 71%–75%, respectively) and combined words (84%–100% vs. 61%–76%, respectively).

The delays observed in these genetic conditions were frequently extreme. Severe delays of greater than 6 months beyond expected norms were common (≥50% of the sample) for both single words (11 of 12 single gene disorders, no CNVs) and combined words (12 of 12 single gene disorders, three of four CNVs). Commonly, participants in the genetic groups exhibited delays in both expressive language and gross motor domains; this occurred for at least 50% of the sample in 13 (81%) conditions (12 of 12 single gene disorders; one of four CNVs; see Figure S4). The rate of delays for all five milestones was at least 50% for eight (50%) conditions (8 of 12 single gene disorders; no CNVs): *ADNP*, *ASXL3*, *GRIN2B*, *MED13L*, *PACS1*, *PPP2R5D*, *STXBP1*, and *SYNGAP1*.

To characterize the likelihood of delays in these rare genetic conditions compared with that of children with idiopathic ASD, descriptive statistics (quartiles and proportions) for age of milestone acquisition, and odds ratios for delay are provided in Table 2 (see also Table S3). Overall, probands with genetic conditions were more likely to exhibit both delayed attainment and nonattainment of milestones than the idiopathic ASD comparison group. Delays were most pronounced for gross motor milestones. Compared with the idiopathic ASD group, the median odds of delay for the genetic condition groups were higher by 8.3 times (IQR 5.8–16.3) for sitting, 12.4 times (IQR 5.3–19.5) for crawling, and 26.8 times (IQR 7.7–41.1) for walking. For the expressive language milestones, the median odds of

delay for the genetic condition groups were higher than the idiopathic ASD group by 2.7 times (IQR 1.7–5.5) for single words and 5.7 times (IQR 2.7–18.3) for combined words.

Rates of nonattainment in the genetic conditions and idiopathic ASD group were also reported for all milestones. For the gross motor milestones, the nonattainment rates across all genetic conditions compared with the rates in idiopathic ASD were 0% [0%–3%] versus 1% for crawling and 0% [0%–8%] versus <1% for walking, respectively. For the expressive language milestones, nonattainment rates for the genetic conditions compared with idiopathic ASD were 18% [3%–29%] versus 3% for single words and 28% [8%–41%] versus 11% for combined words, respectively.

Discussion

This study examined developmental phenotypes across multiple rare genetic conditions, several of which were recently identified, and about which there is very limited systematically collected phenotypic information. Patterns of attainment of early gross motor and expressive language milestones in these conditions were compared with those of individuals who had received clinical diagnoses of ASD and who were confirmed to not have a genetic condition, as yet recognized by the field. This study extends previous work from the Simons Simplex Collection (Bishop et al., 2017; Buja et al., 2018) by examining multiple early developmental milestones (sitting, crawling, walking, single-word talking, combined-word talking) in selected rare genetic conditions associated with ASD. As anticipated, the early developmental milestone profiles of probands with genetic conditions were marked by extensive delays, including nonattainment. Delays were more common and more severe among the single gene conditions than for the CNVs, and for the expressive language milestones than for gross motor skills. Overall, however, delays in all milestones were more common and more pronounced among the genetic conditions than in those with idiopathic ASD. These findings add to a growing literature about the diverse patterns of early gross motor and expressive language skill acquisition among probands with genetic conditions associated with ASD, and extend the literature by documenting the difference in these patterns from those observed in idiopathic ASD.

While phenotypic data are just now becoming available from some of the genetic conditions reported here (Arnett et al., 2020; Berg, Palac, Wilkening, Zelko, & Schust Meyer, 2020; Hanly, Shah, Au, & Murias, 2020), the availability of systematically collected developmental and other behavioral phenotypic data from both the Simons Searchlight and SPARK registries allowed for cross-registry comparisons. Our focus on developmental milestones augments the available literature on cross-sectional cognitive and psychiatric profiles by documenting the earliest manifestations of phenotypes, which may cascade into lifelong neurodevelopmental conditions. Examination of key gross motor and expressive language milestones indicates that most children with the 16 genetic conditions reported here exhibit delays in both of these domains. In particular, varying patterns of delays in gross motor milestones were found across groups, with greater delays on average found in the single gene conditions compared with the CNVs included in this study. Of note, compared with single gene conditions, microarray testing for CNVs has been available longer, costs less, is more widely available, and is more established as a primary genetic

test, all of which may have contributed over time to ascertainment of milder phenotypes in the population. Language delays on the other hand, tended to be consistently delayed across all genetic conditions. The genetic groups with the largest proportion of expressive language delays also had the largest proportion of gross motor delays, which is consistent with previous literature, suggesting that these systems are strongly related (Ghassabian et al., 2016; Libertus & Hauf, 2017).

The difference between idiopathic ASD and the genetic conditions was most obvious for the gross motor milestones. While this study is not the first to note early motor impairments associated with rare genetic mutations (Buja et al., 2018), or generally intact motor milestones of children diagnosed with idiopathic ASD (Bishop et al., 2016; Havdahl et al., 2020; Matson et al., 2010; Ozonoff et al., 2008), it extends the findings of others by documenting this pattern across multiple genetic condition groups. These results reveal the great extent and variability of delays, and support the idea that severe motor delays may be indicative of specific genetic etiologies, as well as predictive of ID (Bishop et al., 2017; Satterstrom et al., 2020). Our description of delays using established norms and demarcation of delay exceeding 6 months (including nonattainment) illustrates the magnitude of delay in the selected genetic conditions, and suggests that exacerbated gross motor delays are a likely predictor of identification of these types of genetic abnormalities. By contrast, delays in expressive language milestones were pervasive across all 16 genetic conditions, as well as the idiopathic ASD group, confirming previous research in ASD that suggests delays in early language are not specific to probands with an identifiable genetic condition (Harris, Sideridis, Barbaresi, & Harstad, 2020).

Given the small samples of these genetic conditions, the fact that many participants never acquired fundamental gross motor milestones such as walking cannot be overemphasized: this suggests an extreme degree of motor impairment that occurs very rarely in the general population (99% of the population walks by 18 months; World Health Organization, 2006), and in this study, it generally did not occur for the idiopathic ASD or CNV groups. This discrepancy illustrates that at least some of these genes have mechanisms that lead to severe motor problems, which raises further questions regarding why some individuals also end up with ASD diagnoses. It is also important to note that a child may achieve a skill ‘on time’ but still have an atypical developmental trajectory. For example, there might be differences in the quality of the behavior (e.g. floppy sitting, asymmetrical walking) that would signal obvious impairment without the presence of delays, which is missed when only collecting age of acquisition information.

Single gene conditions, such as those included in this study, may be induced in animal and cell culture model systems, providing a mechanism to investigate pathogenesis of ASD-related phenotypes. Questions regarding whether these models can actually provide insight into *all* cases of idiopathic ASD, which models might be best-suited to this objective, and whether ASD neurobiology can be distinguished from broader developmental disabilities, have yet to be addressed. Answering these questions will require a more detailed understanding of the relationships between developmental delays and ASD; however, thus far both gene discovery and genotype-phenotype analyses support a model in which single gene mutations seem to vary in their contributions to developmental delay versus ASD

(Satterstrom et al., 2020). Our results are consistent with this model. Single gene disorders with high rates of significant delays or nonattainment in early milestones (e.g. *PPP2R5D ASXL3*) may be observed more frequently in developmental delay/ID cohorts than in ASD cohorts, while those with relatively lower (but still clinically significant) rates of delayed milestones (e.g. *SLC6A1, SCN2A*) may be observed at similar rates in both developmental delay/ID cohorts and ASD cohorts (Satterstrom et al., 2020). Of note, none of the genes observed at a higher rate in ASD than developmental delay (e.g. *PTEN, NRXN1*) from Satterstrom et al. (2020) were included in this study due to insufficient numbers of cases. With larger sample sizes and consistent ascertainment, developmental phenotype results across gene groups are likely to provide critical benchmarks to orient the results of model system analyses (Sanders et al., 2019).

Limitations

A main limitation of this study is that the samples were drawn from registries based on self-referral, and small sample sizes precluded the inclusion of some groups (only 16 of the 29 genetic conditions with data currently available in Simons Searchlight are represented here). Further, participants in the Simons Searchlight registry were enrolled based on genetic testing, which could have been precipitated by delays in early milestones, as developmental delay is one of the main indications for genetic testing. These results may therefore reflect an ascertainment bias in the genetic conditions. These registries are not population-based, so it is possible that individuals with a more or less severe phenotype are not represented. In this way, the extent to which ascertainment strategies may affect these results likely varies by the different conditions and diagnoses. At present, we do not consider a multitude of factors that may be affecting variability within genetic subgroups, including inheritance and variant effect (e.g. missense vs. protein-truncating variant). In addition, the individuals in the idiopathic ASD group included here may go on to receive a genetic diagnosis as new genetic discoveries are made. Still, a major strength of this study is that the idiopathic group was defined not by the lack of any ‘known genetic syndrome’, as is common in ASD research, but rather confirmed to not have significant genetic findings based on the current state of the field.

Given the high socioeconomic status and the distribution and missing data on race of the participants in the registries, these results may not be generalizable to the larger population of probands with these conditions. In addition, the age of milestone acquisition was not collected past the age of 7 years, age floors were introduced at one point for age selection, and missing data were common, so the summary statistics for acquisition may be biased. Caregiver report of milestone data could not be directly verified from these online data registries, so we cannot exclude the possibility that inaccurate parental report impacted the descriptive statistics in this paper. Although telescoping (a type of recall bias which may result in later estimates for older probands) is always possible with retrospective reporting, the standardized data collection strategy across both registries should provide for similar levels of such bias across groups. It is also possible that milestone wording/descriptions in the SFARI registries may have led to different responses than those used in the normative data we reference. Finally, the current analyses provide descriptions of between-group differences in milestone delays, but do not directly consider the multiple factors that may

have contributed to these delays. Various exposures, such as medications taken for seizures, or participation in certain interventions, may contribute to rates or magnitude of delays in attainment of certain milestones for some of these conditions.

Future directions

Future studies could explore the specificity of the phenotypes among these genetic conditions, and whether known factors (e.g. pathological mechanisms) may explain such patterns. Due to the variability in both absolute levels of skills acquisition and timing of that acquisition, this would be facilitated through the accumulation of larger samples within each condition. In addition, larger samples may also be explored with direct testing, to assess differences within groups over time, beyond the time of these early developmental milestones. However, given the challenges of assessment in the context of genetically defined conditions (Soorya, Leon, Trelles, & Thurm, 2018), the delineation of differences in phenotypes would best be done for cases in which in-depth phenotyping is performed (e.g. Bishop et al., 2017). Also, examining the quality of early milestones, rather than just the age of acquisition, could yield important answers to whether probands with genetic conditions in the absence of delay differ in the *way* they perform the skills.

Conclusions

For children with genetic conditions associated with ASD, findings here provide evidence that delays in gross motor and expressive language milestone attainment are among the early indicators of a diverging developmental trajectory. Motor delays, and especially nonattainment, may distinguish children with specific identifiable genetic etiologies from those with idiopathic ASD and should prompt early referral for genetic testing. Further, given its different profile, currently defined ‘idiopathic’ ASD may reflect differing etiologies and mechanisms from rare genetic variants. Broader and deeper data are needed to investigate the possibility of distinguishing among genetic conditions on the basis of phenotypic profiles.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Key points

- There is an increasing number of genes and genetic conditions being identified that impart risk for autism spectrum disorder and other neurodevelopmental disorders.
- Charting early developmental milestones in genetic conditions, based on norms acquired from typically developing children, provides valuable information regarding developmental phenotypes that characterize these conditions.
- Compared to children with idiopathic autism spectrum disorder and typically developing children, children with the 16 rare genetic conditions reported here are more likely to display pronounced delays in early motor and expressive language milestones.
- Description of early developmental phenotypes in genetic conditions associated with autism spectrum disorder may be helpful for referral and identification, as well as for the search for mechanisms for potential interventions.

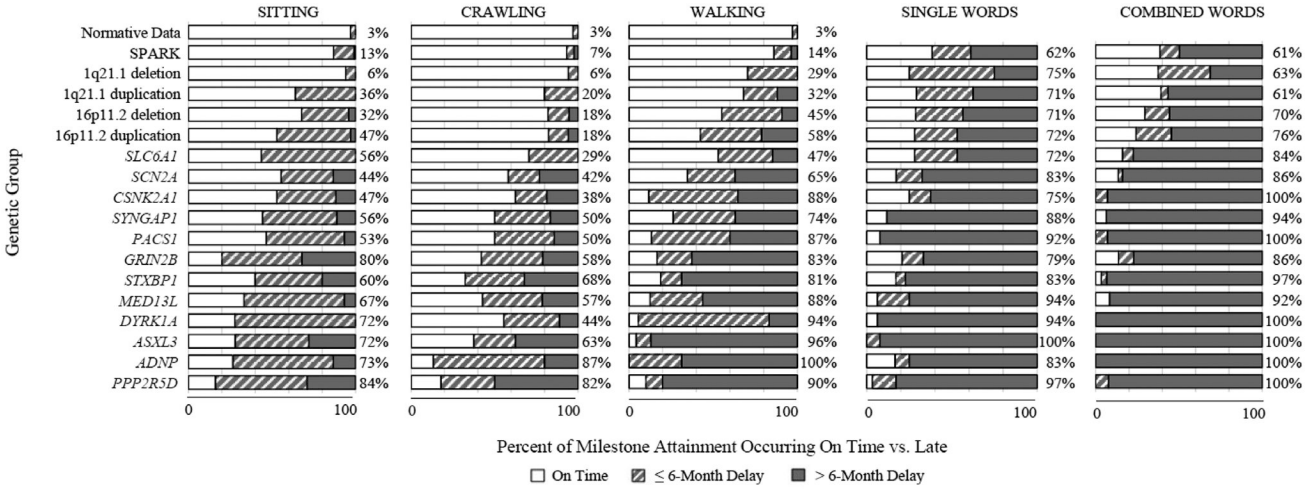

Figure 1.

For each genetic group, the percent of milestone attainment is provided for sitting, crawling, walking, and single and combined words. This figure indicates the percentage of on-time versus late attainment, with late attainment divided by delays of up to 6 months versus beyond 6 months (including those who never attained the skill). Delays were defined as >8 months for sitting (WHO), >12 months for crawling (WHO), >16 months for walking (WHO), >12 months for single words (CDC), and >24 months for combined words (CDC). Total percentages for late attainment are provided in the right margin of each bar graph.

Table 1

Sample demographics are provided for all genetic conditions in Simons Searchlight combined and the idiopathic ASD group from SPARK

	Overall genetic sample (Searchlight)	Overall control sample (SPARK)
Sample information		
Total sample	479 (100%)	3,506 (100%)
16p11.2 Deletion	100 (21%)	–
16p11.2 Duplication	35 (7%)	–
1q21.1 Deletion	17 (4%)	–
1q21.1 Duplication	26 (5%)	–
ADNP	16 (3%)	–
ASXL3	26 (5%)	–
CSNK2A1	17 (4%)	–
DYRK1A	18 (4%)	–
GRIN2B	25 (5%)	–
MED13L	16 (3%)	–
PACS1	16 (3%)	–
PPP2R5D	31 (7%)	–
SCN2A	47 (10%)	–
SLC6A1	34 (7%)	–
STXBP1	36 (8%)	–
SYNGAP1	19 (4%)	–
Age		
Mean ± *SD*	9.1 ± 5.6	9.5 ± 5.3
[Min, Max]	[3.0, 39.1]	[3.0, 46.8]
Sex		
Female	223 (47%)	645 (18%)
Male	256 (53%)	2,861 (82%)
Annual household income		
50,000 or below	112 (23%)	834 (24%)
51,000–80,000	94 (20%)	787 (22%)
81,000–130,000	124 (26%)	1,006 (29%)
131,000 or above	134 (28%)	797 (23%)
Unknown (Missing)	15 (3%)	82 (2%)
Race		
Asian	6 (1%)	91 (3%)
Black	4 (<1%)	85 (2%)
Native American	0 (0%)	6 (<1%)
Pacific Islander	1 (<1%)	1 (<1%)
White	265 (55%)	2,465 (70%)
Other	0 (0%)	31 (<1%)
Mixed	38 (8%)	818 (23%)

	Overall genetic sample (Searchlight)	Overall control sample (SPARK)
Unknown (Missing)	165 (34%)	9 (<1%)

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Table 2

Quartiles for milestone acquisition, as well as proportion of the sample, are provided for those who achieved a milestone prior to age 7

Genetic status, sample size (*n*), proportion > age 18 (%), age in months (Mean ± *SD*)	Milestone	Milestone acquisition						Milestone delay			
		Yes < Age 7				Yes > Age 7	Yes, age unknown (Vineland)	No	Not reported	Total delay	Odds of delay for genetic conditions vs. ASD Odds ratios [95% CI]
		Q1	Q2	Q3	%	%	%	%	%	%	
16p11.2 Deletion	Sat	6.00	7.00	9.00	99	0	0	0	1	32	3.19 [2.05, 4.86]
n = 100 (4%)	Crawled	8.00	10.00	12.00	95	0	0	0	5	18	3.06 [1.74, 5.10]
Age = 9.2 ± 4.5	Walked	13.00	15.00	18.00	98	0	1	0	1	45	5.08 [3.36, 7.62]
	Single words	12.00	18.00	25.00	91	2	4	1	2	71	1.53 [0.99, 2.43]
	Combined words	24.00	36.00	43.50	82	4	0	2	12	70	1.49 [0.95, 2.39]
16p11.2 Duplication	Sat	6.00	8.00	10.00	97	0	0	0	3	47	5.90 [2.99, 11.57]
n = 35 (6%)	Crawled	9.00	10.00	12.00	94	3	0	0	3	18	3.13 [1.21, 6.97]
Age = 9.1 ± 4.5	Walked	13.00	17.00	21.50	94	0	3	0	3	58	8.36 [4.23, 16.9]
	Single words	12.00	15.50	24.00	86	3	0	3	9	72	1.54 [0.75, 3.45]
	Combined words	24.00	30.00	42.00	83	6	0	6	6	76	1.89 [0.9, 4.38]
1q21.1 Deletion	Sat	5.00	6.00	7.00	100	0	0	0	0	6	0.60 [0.07, 2.40]
n = 17 (0%)	Crawled	8.00	9.00	10.50	100	0	0	0	0	6	1.25 [0.14, 5.00]
Age = 5.9 ± 2.9	Walked	12.00	14.00	17.00	100	0	0	0	0	29	2.73 [0.91, 7.17]
	Single words	12.50	17.00	20.25	94	0	6	0	0	75	1.73 [0.63, 5.75]
	Combined words	24.00	26.50	36.00	94	0	0	0	6	63	1.02 [0.39, 2.87]
1q21.1 Duplication	Sat	6.00	7.00	9.00	96	0	0	0	4	36	3.81 [1.64, 8.37]
n = 26 (4%)	Crawled	9.50	11.00	12.00	96	0	0	0	4	20	3.68 [1.28, 8.91]
Age = 7.3 ± 4.1	Walked	13.00	14.00	18.00	96	0	4	0	0	32	3.02 [1.26, 6.71]
	Single words	12.00	16.00	24.00	92	0	0	0	8	71	1.45 [0.64, 3.65]
	Combined words	24.00	36.00	42.00	85	4	0	0	12	61	0.96 [0.43, 2.26]
ADNP	Sat	8.00	9.00	11.00	94	0	0	0	6	73	16.91 [6.01, 56.79]
n = 16 (13%)	Crawled	13.00	15.00	18.00	94	0	0	0	6	87	74.03 [22.29, 378.35]
Age = 10.5 ± 5.9	Walked	22.00	29.00	40.50	100	0	0	0	0	100	205.12 [27.74, 26,175.00]
	Single words	13.50	20.00	27.00	56	6	13	13	13	83	2.62 [0.76, 13.58]
	Combined words	39.00	48.00	57.00	56	6	0	13	25	100	15.75 [2.07, 2,018.14]
ASXL3	Sat	8.00	11.00	15.00	96	0	0	0	4	72	16.32 [7.21, 40.90]

Genetic status, sample size (*n*), proportion > age 18 (%), age in months (Mean ± *SD*)	Milestone	Milestone acquisition						Milestone delay			
		Yes < Age 7				Yes > Age 7	Yes, age unknown (Vineland)	No	Not reported	Total delay	Odds of delay for genetic conditions vs. ASD Odds ratios [95% CI]
		Q1	Q2	Q3	%	%	%	%	%	%	
n = 26 (19%)	Crawled	12.00	15.00	22.50	85	4	0	4	8	63	22.37 [10.02, 52.61]
Age = 12.2 ± 8.2	Walked	24.00	33.00	51.00	81	0	0	8	12	96	93.24 [24.06, 838.35]
	Single words	21.00	33.00	49.50	31	15	0	54	0	100	33.03 [4.63, 4,190.11]
	Combined words	37.50	48.00	67.50	15	19	0	58	8	100	30.86 [4.3, 3,918.04]
CSNK2A1	Sat	6.00	8.00	11.00	100	0	0	0	0	47	5.92 [2.28, 15.14]
n = 17 (0%)	Crawled	9.25	11.00	14.75	94	0	0	0	6	38	8.49 [2.99, 22.37]
Age = 8.2 ± 4.2	Walked	17.50	22.00	32.00	100	0	0	0	0	88	38.54 [11.89, 194.86]
	Single words	12.00	24.00	27.50	82	6	6	6	0	75	1.73 [0.63, 5.75]
	Combined words	35.25	36.00	48.00	59	12	0	12	18	100	18.26 [2.44, 2,334.79]
DYRK1A	Sat	7.75	10.00	11.25	100	0	0	0	0	72	16.24 [6.3, 48.21]
n = 18 (6%)	Crawled	10.00	12.00	15.25	100	0	0	0	0	44	11.10 [4.32, 27.71]
Age = 8.3 ± 5.4	Walked	18.00	18.50	20.50	100	0	0	0	0	94	72.52 [18.27, 657.31]
	Single words	22.50	36.00	63.00	72	0	11	17	0	94	6.44 [1.60, 58.60]
	Combined words	37.50	60.00	72.00	44	11	0	22	22	100	18.26 [2.44, 2,334.79]
GRIN2B	Sat	9.00	11.00	17.00	100	0	0	0	0	80	24.67 [10.24, 70.61]
n = 25 (0%)	Crawled	11.00	14.00	18.00	76	0	0	0	24	58	18.55 [7.61, 47.03]
Age = 8.2 ± 3.9	Walked	19.00	24.00	42.00	92	0	4	4	0	83	28.32 [11.09, 90.58]
	Single words	12.00	20.00	30.00	76	0	4	20	0	79	2.21 [0.91, 6.33]
	Combined words	27.75	42.00	60.00	56	8	0	24	12	86	3.51 [1.26, 13.27]
MED13L	Sat	8.00	10.00	12.00	94	0	0	0	6	67	12.63 [4.63, 38.58]
n = 16 (19%)	Crawled	10.50	13.50	17.75	88	0	0	0	13	57	17.93 [6.41, 52.54]
Age = 9.4 ± 8.5	Walked	18.00	23.00	26.00	94	0	0	6	0	88	36.05 [11.02, 183.01]
	Single words	17.00	24.00	42.00	81	0	0	19	0	94	6.44 [1.60, 58.60]
	Combined words	24.00	42.00		19	25	0	31	25	92	4.83 [1.15, 44.55]
PACS1	Sat	7.00	9.00	11.00	94	0	0	0	6	53	7.50 [2.77, 20.73]
n = 16 (0%)	Crawled	10.75	12.50	14.75	88	0	0	0	13	50	13.71 [4.84, 38.87]
Age = 6.8 ± 4.4	Walked	19.50	21.00	24.50	81	6	6	6	0	87	33.56 [10.15, 171.17]
	Single words	24.00	34.50	45.00	50	6	6	25	13	92	5.19 [1.26, 47.71]
	Combined words	39.00	42.00	69.00	56	6	0	25	13	100	18.26 [2.44, 2,334.79]

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Genetic status, sample size (*n*), proportion > age 18 (%), age in months (Mean ± *SD*)	Milestone	Milestone acquisition						Milestone delay			
		Yes < Age 7				Yes > Age 7	Yes, age unknown (Vineland)	No	Not reported	Total delay	Odds of delay for genetic conditions vs. ASD Odds ratios [95% CI]
		Q1	Q2	Q3	%	%	%	%	%	%	
PPP2R5D	Sat	9.00	11.00	18.00	100	0	0	0	0	84	31.89 [13.64, 89.78]
n = 31 (10%)	Crawled	13.75	18.00	26.25	84	0	0	6	10	82	58.58 [24.61, 166.71]
Age = 8.9 ± 5.2	Walked	23.00	27.50	45.00	84	0	3	6	6	90	48.84 [18.18, 181.75]
	Single words	18.00	25.00	42.00	61	3	6	29	0	97	11.84 [3.12, 105.75]
	Combined words	36.00	54.00	72.00	48	3	0	32	16	100	33.38 [4.67, 4,234.69]
SCN2A	Sat	6.00	8.00	12.00	94	0	0	2	4	44	5.32 [2.92, 9.58]
n = 47 (9%)	Crawled	10.00	11.00	17.75	85	0	0	6	9	42	9.95 [5.32, 18.28]
Age = 8.8 ± 5.3	Walked	14.00	18.00	22.50	81	0	2	17	0	65	11.49 [6.35, 21.54]
	Single words	12.00	18.00	36.00	57	9	0	32	2	83	2.82 [1.41, 6.37]
	Combined words	24.00	31.00	58.50	26	13	0	40	21	86	3.72 [1.63, 10.35]
SLC6A1	Sat	6.00	9.00	11.00	94	0	0	0	6	56	8.44 [4.23, 17.18]
n = 34 (9%)	Crawled	8.75	10.50	13.00	100	0	0	0	0	29	5.88 [2.70, 11.94]
Age = 9.0 ± 5.5	Walked	12.75	16.00	19.50	100	0	0	0	0	47	5.54 [2.81, 10.86]
	Single words	12.00	18.00	24.00	91	0	0	3	6	72	1.54 [0.75, 3.45]
	Combined words	25.00	36.00	48.00	68	6	0	18	9	84	3.03 [1.30, 8.53]
STXBP1	Sat	7.00	9.50	13.00	94	3	0	0	3	60	9.81 [5.05, 19.63]
n = 36 (17%)	Crawled	10.75	14.50	18.00	72	6	0	8	14	68	28.07 [13.56, 61.79]
Age = 11.1 ± 8.4	Walked	16.50	25.00	36.00	72	6	0	11	11	81	25.34 [11.35, 65.70]
	Single words	9.75	12.00	20.00	28	14	0	56	3	83	2.83 [1.28, 7.27]
	Combined words	23.00	36.00	54.00	14	14	0	56	17	97	12.39 [3.27, 110.54]
SYNGAP1	Sat	7.00	9.00	12.00	89	5	0	0	5	56	8.17 [3.29, 20.92]
n = 19 (11%)	Crawled	9.50	12.00	16.50	89	5	0	0	5	50	13.71 [5.44, 34.54]
Age = 9.2 ± 5.1	Walked	15.50	21.50	24.00	95	5	0	0	0	74	16.39 [6.44, 48.28]
	Single words	21.75	36.00	48.00	63	5	5	21	5	88	3.86 [1.20, 19.51]
	Combined words	42.00	60.00	60.00	37	21	0	26	16	94	6.51 [1.62, 59.22]
Idiopathic ASD	Sat	5.00	6.00	7.00	98	0	NA	0	2	13	NA
n = 3,506 (6%)	Crawled	7.00	8.00	10.00	97	0	NA	1	2	7	NA
Age = 9.5 ± 5.3	Walked	11.00	13.00	15.00	100	0	NA	0	0	14	NA
	Single words	11.00	15.00	24.00	93	0	NA	3	3	62	NA

Genetic status, sample size (*n*), proportion > age 18 (%), age in months (Mean ± *SD*)	Milestone	Milestone acquisition								Milestone delay	
		Yes < Age 7				Yes > Age 7	Yes, age unknown (Vineland)	No	Not reported	Total delay	Odds of delay for genetic conditions vs. ASD Odds ratios [95% CI]
		Q1	Q2	Q3	%	%	%	%	%	%	
	Combined words	18.00	30.00	42.00	84	1	NA	10	4	61	NA

Proportions of the sample are also presented for those who acquired the skill after age 7 or at an unknown age (age is unknown because Vineland scores were used to replace missing data where possible for walking and single words), did not acquire the skill, or had no reported data. Proportions of the sample that exhibited delays for each milestone are provided, as well as the odds ratios and confidence intervals for the odds of delay, for each respective genetic condition in comparison to the idiopathic ASD (SPARK) group.