

# Novel Features of 3q29 Deletion Syndrome: Results From the 3q29 Registry

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3q29 deletion syndrome is caused by a recurrent, typically *de novo* heterozygous 1.6 Mb deletion, but because incidence of the deletion is rare (1 in 30,000 births) the phenotype is not well described. To characterize the range of phenotypic manifestations associated with 3q29 deletion syndrome, we have developed an online registry (3q29deletion.org) for ascertainment of study subjects and phenotypic data collection via Internet-based survey instruments. We report here on data collected during the first 18 months of registry operation, from 44 patients. This is the largest cohort of 3q29 deletion carriers ever assembled and surveyed in a systematic way. Our data reveal that 28% of registry participants report neuropsychiatric phenotypes, including anxiety disorder, panic attacks, depression, bipolar disorder, and schizophrenia. Other novel findings include a high prevalence (64%) of feeding problems in infancy and reduced weight at birth for 3q29 deletion carriers (average reduction 13.9 oz (394 g), adjusted for gestational age and sex,  $P=6.5e-07$ ). We further report on the frequency of heart defects, autism, recurrent ear infections, gastrointestinal phenotypes, and dental phenotypes, among others. We also report on the expected timing of delayed developmental milestones. This is the most comprehensive description of the 3q29 deletion phenotype to date. These results are clinically actionable toward improving patient care for 3q29 deletion carriers, and can guide the expectations of physicians and parents. These data also demonstrate the value of patient-reported outcomes to reveal the full phenotypic spectrum of rare genomic disorders. © 2016 The Authors. *American Journal of Medical Genetics Part A* Published by Wiley Periodicals, Inc.

**Key words:** 3q29 deletion; 3q29 microdeletion; autism spectrum disorder; schizophrenia; copy number variation; developmental delay; genomic disorders; patient-reported outcomes

## INTRODUCTION

The incidence for 3q29 deletion is estimated to be one in 30–40,000 births [Stefansson et al., 2014] and is frequently *de novo*, though

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there are rare reports of inheritance [Digilio et al., 2009]. The typical recurrent, interstitial deletion is 1.6 Mb in size and contains 22 protein-coding genes and three antisense transcripts. In addition to intellectual disability [Willatt et al., 2005; Ballif et al., 2008], the deletion is associated with bipolar disorder [Quintero-Rivera et al., 2010; Green et al., 2016] and schizophrenia [Mulle et al., 2010; Mulle, 2015]. The syndrome was first described in 2005 in six patients with a recurrent deletion [Willatt et al., 2005], presenting with mild to moderate intellectual disability that was not apparent until after the first year of life [Willatt et al., 2005]. Facial dysmorphology was subtle and included a long and narrow face, short philtrum, and high nasal bridge [Willatt et al., 2005]. Additional features observed in some

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but not all of these patients included chest-wall deformity, long and tapering fingers, microcephaly, cleft lip and palate, horseshoe kidney and hypospadias, ligamentous laxity, recurrent middle ear infections, and abnormal pigmentation. Notably, two of these six patients had a diagnosis of autism and a third was described as having autistic features [Willatt et al., 2005]. The phenotypic description was expanded in 2008; 15 patients were characterized [Ballif et al., 2008]. Phenotypes included large, posteriorly rotated ears, speech and developmental delay, high-arched palate, widely-spaced teeth, macrocephaly, patent ductus arteriosus, clinodactyly, and camptodactyly [Ballif et al., 2008]. Four of the 15 patients (27%) had autism (ASD) or autistic features.

Case reports have provided additional insights into the heterogeneity of 3q29 deletion syndrome. Cobb et al. described a seven-year-old boy with a 1.3Mb 3q29 deletion with low average to average IQ, some dysmorphic features of 3q29 deletion syndrome, and a diagnosis of ASD [Cobb et al., 2010]. A case report on four individuals found “withdrawal, anxiety/depression, thought problems,” problems interacting in social environments, and aggressiveness to be a commonality for all four patients [Citta et al., 2013]. One of the four patients was described as having a history of psychotic outbursts and another patient exhibited symptoms consistent with a diagnosis of pervasive developmental disorder, not otherwise specified (PDD-NOS). Another case report described two cases: a 10-year-old female and a 15-year-old male [Quintero-Rivera et al., 2010]. The female patient became completely nonverbal between five and seven years of age and was diagnosed with ASD at the age of five. She experienced auditory hallucinations, exhibited intense episodes of anger and violence towards others, and was diagnosed with bipolar disorder with psychotic features by the age of 10. The male patient was diagnosed with ASD at the age of six, and was later diagnosed with attention deficit hyperactivity disorder and demonstrated severe anxiety, aggression, and violence. Sagar et al. described a more severe case of psychotic symptoms co-occurring with a 3q29 deletion and an ASD diagnosis [Sagar et al., 2013]. At the age of four, this patient was diagnosed with PDD-NOS and displayed signs consistent with obsessive compulsive disorder [Sagar et al., 2013]. At the age of five, he started exhibiting psychotic symptoms, including severe auditory and visual hallucinations that significantly impacted his daily life. Two other case reports found clinical depression in adults with 3q29 deletions [Digilio et al., 2009; Clayton-Smith et al., 2010].

These case reports indicate there is an astonishing range of neuropsychiatric features that can be present with variable severity in 3q29 deletion carriers. The deletion is detected by clinical microarray in young patients. With longitudinal follow-up, the symptoms, course and outcome of 3q29 deletion syndrome could be fully described, including the neuropsychiatric features that emerge over the lifespan. To facilitate this goal, we have created an internet-based registry and research study to determine the medical, behavioral, and biological consequences of the deletion, consistent with the “genetics first” approach utilized in other CNV studies [Simons Vip, 2012]. Here we describe results from the first 18 months of data collection for the registry, and report on 44 patients, the largest sample of 3q29 deletion patients ever studied in a systematic way.

## MATERIALS AND METHODS

An internet-based registry was created (Patient Crossroads, La Jolla, CA) to ascertain individuals with 3q29 deletion syndrome. Recruitment of study subjects, informed consent, assent, HIPAA authorization, and data collection are all enabled by the website. Emory University’s Institutional Review Board (IRB00064133) approved this study. Emails bearing information about the registry were sent to health care providers, medical geneticists, genetic counselors, and support organizations. The registry is also advertised via an internet campaign (Google AdWords) wherein a series of specific keywords were chosen to target the website. Individuals who register and complete informed consent have a personal profile page, where they can complete data collection instruments. Answers may be submitted by an individual with 3q29 deletion syndrome or a family member (usually a parent or guardian) if the 3q29 deletion patient is underage or not capable of submitting answers. At registration, information is collected about the participant (the person with the condition), including gender, birthdate, race, and ethnicity. Contact information is obtained for the participant and the informant. A medical questionnaire was developed by selecting questions from a larger “question library” containing all questions from existing registries that are managed by Patient Crossroads. Seven health-related domains were intentionally prioritized for data collection based on medical issues previously noted in 3q29 individuals [Ballif et al., 2008; Cox and Butler, 2015]. All domains could be assessed with existing questions; no new or custom questions were developed. The website and questionnaire were beta-tested for functionality by research staff. No pilot study was conducted. Data presented here are based on 20 questions from the medical questionnaire related to 7 domains: Birth History, Development, Ear/Nose/Throat, Gastrointestinal, Renal, Oral/Dental, and Seizures/Psychiatric (full questionnaire in supplemental Table S1). To ease participant burden, most questions are answered by radio buttons, checkboxes, or pull-down menus. Data for birth weight are collected via a drop-down menu where selections are in 1-lb increments (1–2, 2–3, 3–4 lbs, etc). Similarly, data for developmental milestones is collected with a drop-down menu with a choice of intervals (selections were: 0–3, 4–7, 8–11 months, etc). Documents can be uploaded to the registry website, and it is requested but not required that participants upload their clinical genetics report indicating a diagnosis of 3q29 deletion syndrome. Of 11 clinical genetics reported that have been submitted, all 11 were identified by array CGH, all were tested in 2010 or later, and all have the typical, recurrent 1.6 Mb deletion.

The registry was launched in November 2013. In June 2015, data for the medical questionnaire, along with demographic information collected at registration, were extracted for analysis. Of 57 individuals registered, 44 (77%) had completed the medical questionnaire. One participant, who registered but did not fill out the questionnaire despite communicating a very enthusiastic response about the registry and research into 3q29 deletion syndrome, reports “research fatigue” as the reason the data were not entered. It is not known why other registrants failed to complete questionnaires. Efforts are underway to encourage more complete participation. Recruitment of additional patients is ongoing.

Data were coded and responses tallied manually or in the R software package [R\_Core\_Team, 2015]. For birth weight analysis, comparison data was obtained from the Centers for Disease Control and Prevention's National Center for Health Statistics (NCHS) 2012 Natality Public Use data [Martin et al., 2013], containing birth data for 3,960,796 births in the United States for the year 2012. From this file, data were extracted for birth weight, sex, gestational age, and maternal race, which was used as a proxy for infant race. Birth weight in the NHCS file was converted from grams to pounds and then "binned" into 1-lb categories to be consistent with data collection from the registry. Multiple linear regression was conducted in R with the glm package [R\_Core\_Team, 2015]. Time-to-event (Kaplan-Meier) analysis for developmental milestones was accomplished in R with the survival package [Therneau, 2015]. For analysis purposes, when a given "bin" of time was chosen as the interval during which a developmental milestone was reached, it was assumed that the milestone was reached at the midpoint of that interval. For children who had not yet reached a developmental milestone, their data were treated as censored observations, where time in the study is recorded consistent with age at the time of entry into the registry.

## RESULTS

### Demographic Information

Characteristics of study participants can be found in Tables I and II. Of 44 individuals included in the present analysis, 75% (33/44) reside in the United States. Sixty-six percent (29/44) are male. Forty-one participants were parents (40) or a legal guardian (1) submitting information about a minor with 3q29 deletion; three participants were the 3q29 deletion carriers themselves. Ninety-five percent (42/44) of participants describe themselves as white; no 3q29 deletion carriers of African descent participate in the registry at this time. Nine percent of responders (4/44) are Hispanic or Latino; 86% are not Hispanic or Latino. The average age of registry participants is 11.1 years (median age 7.8 years, range less than 1 year to 76 years). The average age at diagnosis for registry participant is 7.95 years (median 4.5 years, range less than 1 year to 75 years).

### Birth Weight

Figure 1 shows the distribution of weight at birth for registry participants compared to the 2012 US general population (our survey collected data in units of lbs; for clarity we have retained these units in Fig. 1). The average birth weight for 44 deletion carriers is 6.09 lbs (2762 g), compared to an average weight at birth in the 2012 US general population of 7.2 lbs (3266 g) (NCHS,  $n = 3,960,796$ ). However, gestational age is also reduced in 3q29 deletion carriers compared to the US general population (average 37.95 w in 3q29 deletion carriers versus 38.71 w in the 2012 US general population, Fig. 1). We performed multiple linear regression to assess the effect size of the deletion on birth weight, adjusting for gestational age and sex. The beta coefficient for the 3q29 deletion is estimated to be  $-0.86$  ( $P$ -value  $6.5e-07$ ), suggesting even after adjusting for gestational age and sex, carriers of the 3q29 deletion weigh 0.86 pounds (13.9 oz or 394 g), less at birth

TABLE I. Demographic Characteristics of Registry Participants

|                               | Number (%) |
|-------------------------------|------------|
| Sex                           |            |
| Male                          | 29 (66)    |
| Female                        | 15 (34)    |
| Race                          |            |
| White                         | 42 (96)    |
| Asian                         | 1 (2)      |
| American Indian/Alaska Native | 1 (2)      |
| Ethnicity                     |            |
| Not Hispanic or Latino        | 38 (86)    |
| Hispanic or Latino            | 4 (9)      |
| Unknown                       | 1 (2)      |
| Left blank                    | 1 (2)      |
| Country                       |            |
| USA                           | 33 (75)    |
| Australia                     | 3 (7)      |
| UK                            | 3 (7)      |
| Germany                       | 1 (2)      |
| Spain                         | 1 (2)      |
| Netherlands                   | 1 (2)      |
| Canada                        | 1 (2)      |
| Macedonia                     | 1 (2)      |

than babies born in the US general population. Because registry participants are largely white we repeated this analysis restricting both the registry participants ( $n = 42$ ) and the NCHS population ( $n = 3,007,229$ ) to individuals who self-identify as white. In this analysis the deletion remains significant, and the effect size slightly increases (beta coefficient =  $-0.93$ , or 14.94 oz (423 g) less birth weight for deletion carriers;  $p$ -value  $1.44e-07$ ). Goodness-of-fit analysis reveals that a model with deletion status, gestation age, and sex fits the data significantly better than a model with gestational age and sex alone ( $P$ -value  $6.501e-07$ ). (Table SII)

### Heart Defects

Forty-two participants responded to the question "Was the participant born with a heart defect?" Of these, 11 (26%) responded affirmatively. The most frequently reported condition is patent ductus arteriosus (PDA,  $n = 5$ , 12%), which has previously been reported in 3q29 deletion syndrome. [Cox and Butler, 2015] Other reported heart defects include pulmonary valvar stenosis (2), ventricular septal defect (2), aortic valvar stenosis (1), atrial septal defect (1), and pulmonary atresia (1). One patient reports both pulmonary atresia and atrial septal defect; a second patient reports both ventricular septal defect and pulmonary valvar stenosis. One person reported yes but responded "Unsure" to the type of heart defect. Full results are in Table SIII.

### Problems in the First Year of Life

This question sought to elicit whether significant health problems existed in infancy among 3q29 deletion carriers. Eighty-nine percent of respondents ( $n = 39$ ) report at least one problem in

**TABLE II. Ages of Study Participants at Diagnosis of 3q29 Deletion Syndrome and at Study Registration**

| Age         | Age at diagnosis<br>(n) | Age at registration<br>(n) |
|-------------|-------------------------|----------------------------|
| Less than 1 | 4                       | 2                          |
| 1           | 2                       | 0                          |
| 2           | 7                       | 3                          |
| 3           | 4                       | 4                          |
| 4           | 4                       | 0                          |
| 5           | 3                       | 6                          |
| 6           | 0                       | 5                          |
| 7           | 3                       | 2                          |
| 8           | 0                       | 4                          |
| 9           | 4                       | 0                          |
| 10          | 5                       | 2                          |
| 11          | 0                       | 0                          |
| 12          | 1                       | 4                          |
| 13          | 1                       | 2                          |
| 14          | 0                       | 2                          |
| 15          | 1                       | 1                          |
| 16          | 1                       | 2                          |
| 17          | 0                       | 0                          |
| 18–25       | 0                       | 2                          |
| 25–35       | 1                       | 1                          |
| 35–40       | 0                       | 1                          |
| Over 40     | 1                       | 1                          |

the first year of life (Fig. 2, Table SIV). Feeding problems are experienced by 64% of this population ( $n=28$ ), and in 39% ( $n=17$ ) there is a failure to gain weight. Hypotonia is reported in 34% ( $n=15$ ), jaundice in 34% ( $n=15$ ), respiratory distress in 25% ( $n=11$ ), and infection in 22% ( $n=10$ ).

### Autism and Learning Disabilities

There are 18 possible responses to the question, “Has a doctor ever diagnosed the patient with any of the following?” Participants are directed to “Select all that apply.” There was a single response of “Unsure.” All other participants reported at least one learning problem. The mean number of reported learning problems was 3.8. Fifty-nine percent of respondents ( $n=25$ ) report speech delay, and 40% ( $n=17$ ) report global developmental delay. Twenty-six percent ( $n=11$ ) report a diagnosis of autism, which is consistent with previous reports [Ballif et al., 2008; Cox and Butler, 2015], and suggests autism is associated with 3q29 deletion syndrome. Also reported are learning disability in math (43%,  $n=18$ ) learning disability in reading (38%,  $n=16$ ), receptive language delay (33%,  $n=14$ ), and writing disability (32%,  $n=14$ ) (Table SV).

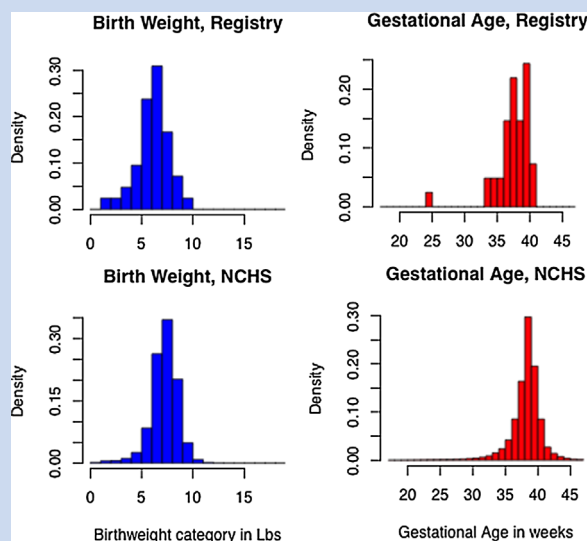
### Delay of Developmental Milestones

In the registry, data are collected on the ages when 32 distinct developmental milestones are achieved. These are relevant to social-emotional development ( $n=6$  milestones), communication ( $n=7$  milestones), gross motor skills ( $n=9$  milestones), and fine

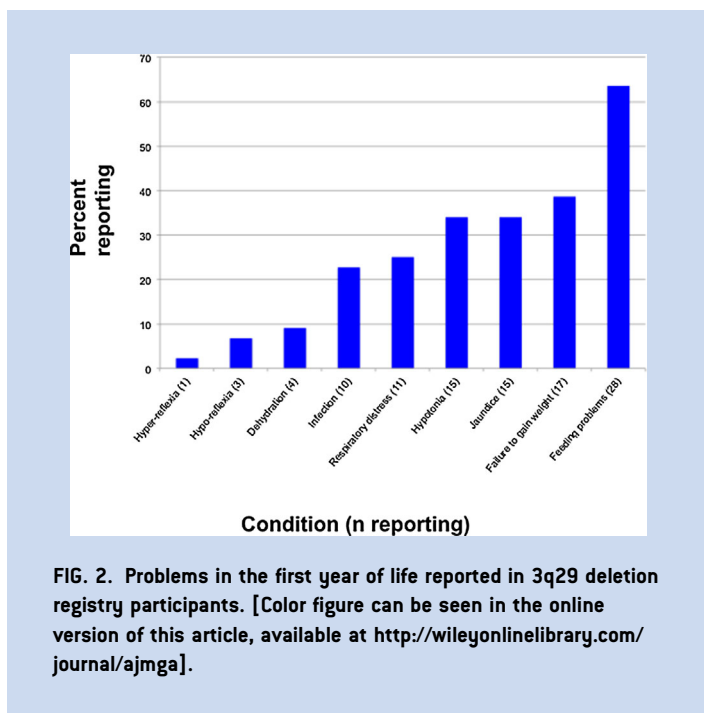
motor skills ( $n=10$  milestones). Our survey did not include questions related to cognitive developmental milestones. Using survival analysis, we have estimated the average time-to-event for developmental milestones for 3q29 deletion carriers. Although we had 44 respondents to the medical and demographic survey, we have between 23 and 38 responses for each of the developmental milestones, with the remaining responses recorded as “Unsure” or left blank. Four exemplar milestones are shown in Figure 3; remaining developmental milestones can be found in Table SVI and Figure S1. These data can be compared to the times at which typically developing children achieve the same developmental milestones [Dosman et al., 2012] (indicated by a dashed green line in Fig. 3). There are two important results revealed by this analysis. First, while some 3q29 deletion carriers achieve developmental milestones at a time consistent with typically developing children, there is a wide variance; the average time to developmental milestones is delayed by 1–13 months as compared to typically developing children. Second, even though the developmental milestones we report here are substantially delayed, the overwhelming majority of 3q29 carriers eventually achieve them.

### Recurrent Ear Infections

This question was motivated by prior reports of recurrent ear infections in 3q29 deletion carriers [Ballif et al., 2008; Cox and



**FIG. 1.** The distribution of birth weight (blue) and gestational age (red) in the 3q29 deletion registry population (top) and US natality data for 2012 (bottom). There are differences in birth weight [3q29 deletion registry participants, mean = 6.09 lbs; 2012 US general population, mean = 7.2 lbs] and gestational age [3q29 deletion registry participants, mean = 37.95 w; 2012 US general population, mean = 38.71 w]. After adjusting for sex and gestational age, 3q29 deletion carriers are predicted to weigh 0.86 lbs less at birth than babies in the general population. [Color figure can be seen in the online version of this article, available at <http://wileyonlinelibrary.com/journal/ajmga>].



**FIG. 2.** Problems in the first year of life reported in 3q29 deletion registry participants. [Color figure can be seen in the online version of this article, available at <http://wileyonlinelibrary.com/journal/ajmga>].

Butler, 2015]. Indeed, we find that 32% ( $n = 13$ ) of 3q29 deletion carriers experience recurrent ear infections (Table SVII). This is noteworthy in light of the considerable speech and receptive language delay experienced by this population. In a 3q29 deletion carrier exhibiting a behavioral disturbance of sudden onset, ear pain due to recurrent ear infection may be the cause.

### Gastrointestinal Disorders

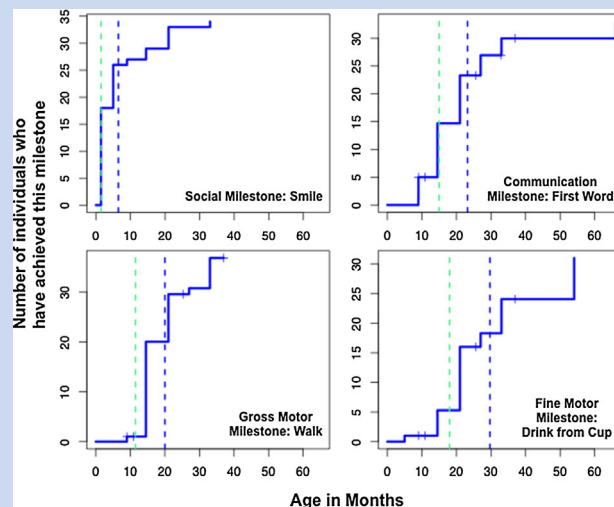
Of the 41 people who responded to this question, 68% ( $n = 28$ ) report at least one gastrointestinal disorder. Feeding problems (41%,  $n = 17$ ), gastroesophageal reflux (39%,  $n = 16$ ) and chronic constipation (22%,  $n = 9$ ) are the most commonly reported gastrointestinal symptoms. Twelve percent of respondents ( $n = 5$ ) also report dysphagia (Table SVIII).

### Dental Phenotypes

Previous reports had indicated crowded teeth were found among 3q29 deletion patients [Ballif et al., 2008], which motivated an expanded question about dental phenotypes. Of 42 responders to this question, 66% ( $n = 28$ ) report one or more dental conditions. Twenty-four percent ( $n = 10$ ) report crowded teeth, 24% ( $n = 10$ ) report a high number of cavities, 19% ( $n = 8$ ) report weak or soft tooth enamel, and 17% ( $n = 7$ ) report widely spaced teeth (Table SIX). As was noted above with recurrent ear infections, in a child with 3q29 deletion syndrome who has speech delay, a sudden behavioral disturbance may be a response to tooth pain due to a dental abnormality.

### Psychiatric Phenotypes

Of 42 participants responding to this question, 12 (28%) indicate the presence of a psychiatric disorder. This is surprising given that



**FIG. 3.** Time-to-event curves for four exemplar developmental milestones. The dashed green line indicates the time at which 50% of typically developing children achieve the milestone [Dosman et al., 2012]; the dashed blue line indicates when 50% of 3q29 deletion registry participants are reported to achieve the same milestone. [Color figure can be seen in the online version of this article, available at <http://wileyonlinelibrary.com/journal/ajmga>].

the average age of registry participants is 11.1 years (median age 7.8 years). The most commonly reported condition is anxiety disorder (19%,  $n = 8$ ), followed by panic attacks (9%,  $n = 4$ , all individuals also reporting anxiety disorder), bipolar disorder (5%,  $n = 2$ ), depression (5%,  $n = 2$ ), schizophrenia (5%,  $n = 2$ ), and oppositional defiant disorder (2%,  $n = 1$ ). Six respondents reported more than one psychiatric condition (four with comorbid anxiety disorder and panic attacks) (Fig. 4 and Table SX).

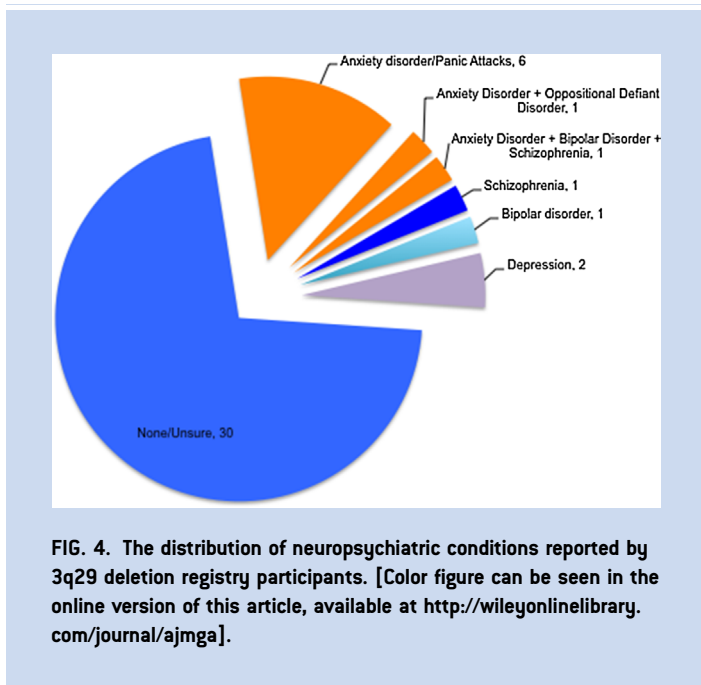
### Other Phenotypes

Individual phenotypes involving the genitourinary (Table SXI) and renal (Table SXII) systems were reported by three and two participants, respectively; one participant reported cleft palate (Table SXIII), and two participants reported seizures (Table SXIV).

## DISCUSSION

The study reported here is the first of its kind: we have systematically solicited data about phenotypic manifestations in a standardized way from the largest sample of 3q29 deletion patients in existence. Novel findings from our study include the quantitative effect of the 3q29 deletion on weight at birth (estimated to be a 13.9 oz reduction); the high prevalence of feeding disorders in the first year of life and beyond (68% in infancy); and the high burden of anxiety disorders in this population (19%). Symptoms reported by at least 25% of study participants are listed in Table III.

We also report on timelines of developmental milestones in 3q29 deletion syndrome and show that, on average, there is delay in all



domains of development. The most comprehensive prior study has aggregated multiple case reports (reporting on between 8 and 38 cases, depending on the phenotype), and our estimates are remarkably similar [Cox and Butler, 2015]. Confirmatory findings include the prevalence of autism (27%), speech delay (60%), gastrointestinal reflux (40%), and recurrent ear infections (32%) [Cox and Butler, 2015]. For other phenotypes, our study has provided additional crucial detail, for example, the range and type of learning disorders, dental abnormalities, and problems in the first year of life.

The high prevalence of feeding problems in the first year of life has not been previously reported in the 3q29 deletion population. The term “feeding problem” is vague, but descriptions from parents indicate that this encompasses refusal to eat, disinterest in eating, failure to gain weight, and failure to thrive (although we note that failure to thrive can be due to many contributing factors, and may not solely be due to the 3q29 deletion). At least one 3q29 deletion carrier has a feeding tube. Anecdotal reports from families suggest that feeding problems in infancy and childhood, and failure to gain weight in infancy, are among the most stressful and disruptive symptoms experienced and have the greatest impact on quality of life. This is partly because many of these symptoms are experienced prior to diagnosis of 3q29 deletion syndrome. Future studies to resolve the specific types of feeding problems experienced by 3q29 deletion carriers are currently underway. However, the finding of reduced birth weight in 3q29 deletion carriers, combined with feeding problems in infancy, suggests a possible metabolic imbalance and reduced capacity for energy harvest, a phenotype that may exist prenatally. This hypothesis could be explored through metabolomic data from 3q29 deletion carriers, which might identify disrupted metabolic pathways. Imbalances in energy harvest have been reported in other genomic disorders. [Zufferey et al., 2012]

There has been recent interest in the risk for neuropsychiatric phenotypes associated with 3q29 deletion syndrome, with an

estimated 40-fold increase in risk for schizophrenia [Mulle, 2015] and recent reports linking the deletion to bipolar disorder [Green et al., 2016]. The registry population we report here has 28 people aged 10 years or less. Many individuals in the registry have therefore not approached the age of risk for phenotypes such as bipolar disorder or schizophrenia, where typical age at onset is in late adolescence or early adulthood. Thus, the prevalence of neuropsychiatric phenotypes reported here may be an underestimate and is likely to climb as the registry population ages. The high burden of anxiety disorders is surprising and suggests the hypothesis that anxiety may be a possible prodromal symptom. Longitudinal follow-up of registry participants will allow for a more precise estimate of the prevalence and types of neuropsychiatric phenotypes in 3q29 deletion syndrome, and would also resolve whether anxiety disorder is a predecessor to schizophrenia or bipolar disorder. If this is true, it is clinically actionable, as individuals with 3q29 deletion syndrome also exhibiting an anxiety disorder could be closely monitored and treated for early symptoms of psychosis. Such longitudinal follow-up could entail yearly updates with registry participants, to record whether new neuropsychiatric (or any other) phenotypes have emerged, and whether existing phenotypes have abated or become exacerbated.

Some phenotypes are equally noteworthy for their absence in 3q29 deletion carriers. It is now hypothesized that there is a continuum of neuropsychiatric phenotypes, bolstered by the observation of cross-disorder effects for many genetic variants. These include intellectual disability, autism, schizophrenia, and epilepsy/seizures. An identical SNV or CNV can contribute to risk for each of these phenotypes. It is therefore noteworthy that while the 3q29 deletion is associated with intellectual disability, autism, and

**TABLE III. Symptoms Reported in at Least 25% of 3q29 Deletion Carriers**

| Medical condition or developmental delay | Percent of 3q29 deletion carriers (%) |
|--|---------------------------------------|
| Learning problems                        | 98                                    |
| Speech delay                             | 60                                    |
| Learning disability in math              | 43                                    |
| Global developmental delay               | 41                                    |
| Learning disability in reading           | 38                                    |
| Receptive language delay                 | 33                                    |
| Writing disability                       | 33                                    |
| Autism                                   | 26                                    |
| Problems in the first year of life       | 89                                    |
| Feeding problems                         | 64                                    |
| Failure to gain weight                   | 39                                    |
| Hypotonia                                | 34                                    |
| Jaundice                                 | 34                                    |
| Respiratory problems                     | 25                                    |
| GI disorders                             | 68                                    |
| Gastrointestinal reflux                  | 39                                    |
| Dental phenotypes                        | 66                                    |
| Recurrent ear infections                 | 32                                    |
| Psychiatric phenotypes                   | 28                                    |
| Heart defects                            | 26                                    |

schizophrenia, seizures are not a significant part of the 3q29 deletion phenotype, with only two people (4.8%) reporting a seizure. This is lower than the seizure frequency reported in other CNV disorders [Zufferey et al., 2012; Vanlerberghe et al., 2015]. While these results need replication and careful scrutiny, one possible interpretation is that the neurodevelopmental pathway affected by 3q29 deletion is relevant to the underlying biology of intellectual disability, autism, and schizophrenia, but not epilepsy or seizure.

There are several limitations of this study. The population we have recruited is likely biased in at least two ways. First, the registry is indexed on the internet by several highly specific keywords. We have also contacted many clinical labs, but outreach efforts to publicize the registry are not systematic nor comprehensive. We are therefore reaching only a subset of the population, one with access to technology such as a computer. It is highly likely that we are not reaching 3q29 deletion individuals in the lower socioeconomic strata, and our sample is therefore not representative of the general population with 3q29 deletion syndrome. While the website has a mobile version that is accessed by tablet or smartphone, it is also possible that for some individuals trying to answer questions on these devices, their answers (particularly to open-ended questions) may be compromised, diminishing the completeness of our data collection efforts. A second bias is also probable: families with severely affected children may be more likely to participate in the registry, and more motivated to fill out questionnaires, than are families with moderately or mildly affected children. If we have ascertained the most severely affected, we may be overestimating the consequences of 3q29 deletion syndrome.

We also note the limitations of self-report data. The symptoms reported in this study have not been independently confirmed by review of medical records, and may therefore contain errors of under- or over-reporting. Additionally, because we are relying on patient-reported outcomes, we do not have detailed clinical information such as dysmorphology data, and as noted previously, we did not collect data on cognitive developmental milestones. Furthermore, our estimates, particularly for average time to developmental milestones, are necessarily inexact: the data suffer from biases due to missing data, recall, and an unavoidable lack of precision in our data collection methods. However, these estimates nevertheless can serve as a basis for health professionals to communicate expectations to patients and their families.

We note that our registry population is homogeneous with respect to race and ethnicity, and is devoid of any participants of African ancestry. Two possible explanations exist: either information about the registry is not reaching this segment of the population, or the genetic architecture that gives rise to the 3q29 deletion is restricted to individuals of European descent. The latter scenario is plausible: other structural variants have exhibited similar patterns [Stefansson et al., 2005]. For several regions, it has been noted that copy number neutral inversions can predispose to pathogenic rearrangements [Antonacci et al., 2010]. Inversions of the 3q29 region have been reported, and in one small study, the 3q29 inversion was detected in 12.5% of CEPH Caucasian chromosomes and 9.5% of Yoruba Nigerian chromosomes [Antonacci et al., 2009]. Future investigations of the 3q29 registry population could resolve whether the parent in which the deletion arose is an inversion carrier. Population-based studies with larger sample

sizes than previously reported could also verify inversion frequencies in individuals of European and African descent.

The data reported in this study serve to refine and expand the phenotypic description of 3q29 deletion syndrome. The initial success of this work highlights the utility of internet-based registries and patient-reported outcomes for the study of rare variants. Future directions will include direct assessment of cognitive function and adaptive behavior in registry participants using a battery of standardized instruments. We will also obtain photographs of registry participants, and have dysmorphology rated by medical geneticists. In addition, specific feeding problems seen in this population will be defined. We will continue longitudinal characterization of this population to describe phenotypes and outcomes in older children, including neuropsychiatric phenotypes. We look forward to future studies where we can address these additional aspects of the 3q29 deletion phenotype. The current results are clinically actionable toward improving patient care for 3q29 deletion carriers, and emphasize the importance of the 3q29 deletion as a potential molecular handle on neurodevelopmental pathways relevant to neuropsychiatric phenotypes.

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