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Age-Related Differences in Prevalence of Autism Spectrum Disorder Symptoms in Children and Adolescents with Costello Syndrome

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Abstract

Dysregulation of the mitogen activated protein kinase (MAPK) pathway in Costello syndrome (CS) may contribute to increased risk for autism-spectrum disorder (ASD). We examined prevalence of ASD symptoms in 14 individuals (6 females) age 1–18 years with molecularly confirmed CS. Caregivers completed the Modified Checklist for Autism in Toddlers (M-CHAT) for ages 0–4 years (n=7), and the Social Communication Questionnaire (SCQ) for ages 4 and older (n=7). Age was associated with meeting ASD criteria: 5/7 (71.4%) younger children met the ASD cut-off on the MCHAT, compared to 0/7 older children on the SCQ. The following medical and developmental factors were strongly associated with ASD criteria on the M-CHAT: having a gastrostomy tube at time of assessment, not eating solid food, not walking, and not being toilet trained. Two children who met stricter ASD criteria had significantly lower adaptive functioning and were physically much more impaired. Among older participants, SCQ subscale scores in communication, socialization, and repetitive behavior domains were comparable to the typically-developing normative sample.

ASD symptoms were highly elevated in younger CS individuals. Older children did not differ from typically-developing samples in prevalence of ASD symptoms. CS individuals may appear to fall on the autism spectrum in early childhood due to severe feeding and orthopedic problems that improve by age four, suggesting many of these children may eventually emerge out of an ASD presentation.

Keywords

Autism Spectrum Disorder; Costello Syndrome; genetics

INTRODUCTION

Costello Syndrome (CS) belongs to the neuro-cardio-facial-cutaneous syndromes or rasopathies that include neurofibromatosis type 1 (NF1), Noonan syndrome (NS), Noonan syndrome with multiple lentigines, and cardio-facial-cutaneous syndrome (CFCS), all of which are caused by germline mutations in RAS pathway proteins. Different gain-of-function variations in the proto-oncogene *HRAS* cause CS, most often affecting the glycine in position 12 or 13 of the protein product [Gripp and Lin, 2012]. CS is characterized by severe feeding difficulties and failure to thrive in infancy, growth delay, orthopedic impairment, and global developmental delays, as well as distinctive facial features, cardiac problems, and neurological abnormalities [Gripp et al., 2010; Gripp and Lin, 2012]. Cognitive impairment is also characteristic, with studies documenting intellectual and adaptive functioning in the mild to moderate range of disability [see Axelrad et al., 2011 for review]. Relative strengths have been noted in receptive vocabulary, recognition memory, facial processing, and affect recognition, whereas relative weaknesses were noted in expressive language, speech, and motor skills [Axelrad et al., 2007; Axelrad et al 2009; Schwartz et al., 2013].

There has been speculation that dysregulation of the RAS/mitogen activated protein (MAPK) pathway in the RASopathies may contribute to increased risk for autism-spectrum disorder (ASD) [Packer, 2012]. Autism spectrum disorders are developmental disorders characterized by persistent deficits in social interaction and communication, and restricted, repetitive, or stereotypical patterns of behavior or interest [American Psychiatric Association, 2013]. Numerous genes have been correlated with symptoms of autism, with over 100 genetic and genomic disorders implicated [Betancur, 2011]. For example, *ADORA2A* on 22q11.23 (Velocardiofacial syndrome) has been associated with ASD symptomology, as well as with increased anxiety within the ASD spectrum [Freitag et al., 2010]. Similarly, dosage abnormalities of 16p11.2 have been correlated with ASD [Crepel et al., 2011], as has expression of the fragile X protein FMRP [Iossifov, et al., 2012]. Importantly, all these loci have links to RAS/MAPK-pathway signaling [Crepel et al., 2011; Hu et al., 2008; Kim et al., 2006; Loesch et al., 2007]. These findings and others have led to the hypothesis that RAS pathway over-activation may be an overarching risk factor for ASD [Packer, 2012].

Recent studies support the presence of elevated ASD symptomology in the RASopathies. Adviento and colleagues [2014] found a high prevalence of ASD traits in four major RASopathies, including CS. In the CS group, 26% of subjects age 2–32 years met screening criteria for a possible ASD on the Social Communication Questionnaire (SCQ), significantly higher than the estimated 1.5% prevalence in the general population [CDC, 2014]. In another recent study [Alfieri et al., 2015], 44% of CS subjects age 2–28 years met criteria for a possible ASD on the SCQ or the Modified Checklist for Autism in Toddlers (M-CHAT)[Robins et al., 2001].

Contrasting with these findings are common reports of “the friendly, sociable personality associated with Costello syndrome” [Gripp and Lin, 2012; Kawame et al., 2003], which has

been described as “consistent enough to be proposed as a diagnostic criterion” for CS [Philip and Sigaudy, 1998]. In our own research with a well-defined cohort of individuals with CS whom we have followed for over ten years, we have found a relative strength in social interest and social functioning [Axelrad et al., 2004, 2009], especially among girls [Axelrad et al., 2011], compared to overall intellectual and adaptive abilities.

The reasons for this discrepancy between findings of heightened ASD symptomology on one hand, and qualitative descriptions of the sociability of individuals with CS on the other, are unclear. One possibility is that children with CS may screen positive on ASD screeners due to their significant medical, physical, and speech/motor problems, which can result in high false positive rates in children with complex neurodevelopmental presentations [Johnson and Marlow, 2009]. In particular, failure to thrive and speech delays characterize the youngest children with CS, but tend to resolve to some degree by age 4 years. In the present study we therefore examined the hypothesis that younger children with CS (< 4 years) would show elevated rates of ASD symptoms, but that significant symptoms of ASD would not be evident in older children.

MATERIALS AND METHODS

Participants were 14 children (6 females) with CS who were recruited with their parents at the 8th International Costello Syndrome Family Forum conference in Orlando, FL (2013). All children had CS confirmed by identification of an *HRAS* mutation via molecular analysis [Gripp et al, 2006]. Seven participants had the common p.G12S mutation, four had p.G13C, two had p.G12C, and one had p.G12A (Table I). Ages ranged from 22 months to 18 years (mean = 7.0 years, median = 4.2 years, SD = 5.6 years). Nonverbal IQ was only available for children who were six years and older; the test battery could not be successfully completed by any younger children, given their level of impairment. IQ scores for the older children fell in the Very Low range (Leiter-R Brief IQ Mean = 64.8, Median = 62.0, SD = 14.1, Range = 44–87), consistent with prior studies.

Informed consent was obtained from parents prior to testing, and whenever possible, child assent was also obtained. The study was approved by the appropriate institutional research ethics boards. Assessments occurred individually in a private location during the Costello Syndrome Family Forum Conference. Caregivers/guardians were interviewed by a licensed psychologist (JMK) and each child was tested individually by JMK or a board-certified psychometrist.

Symptoms of ASD were assessed using either the Modified Checklist for Autism in Toddlers (M-CHAT) [Robins et al., 2001] or the Social Communication Questionnaire (SCQ) [Rutter et al., 2003] based on the child’s age. The M-CHAT is validated for use with children age 16–30 months, whereas the SCQ has been validated with children age 48 months and older (provided they have a mental age greater than 24 months). Given the neurodevelopmental delays that characterize our sample of children with CS, we felt that the M-CHAT would be the more valid measure for the children younger than 48 months in our study. Parents of children younger than four years (n=7) therefore completed the M-CHAT, a 23-item yes/no questionnaire that has been widely used to screen for ASD symptoms in

toddlers (due to administrative error, one child who was slightly above the age group cutoff also received the M-CHAT instead of the SCQ). A total score of 3 has been recommended as the cutoff for further evaluation, in order to maximize sensitivity [Robins et al., 2001]. However, in a large study of 18,989 toddlers screened for ASD at pediatric well-child visits, a cutoff score of 3 had a positive predictive value (PPV) of only .06, whereas a cutoff of 7 had a PPV of .82 [Chlebowski et al., 2013]. We therefore examined both cutoff scores in the present study. Parents of children four years and older ($n=7$) completed the Lifetime version of the SCQ, a 40-item yes/no questionnaire originally designed as a companion screening measure of the Autism Diagnostic Interview – Revised (ADI-R). The recommended cutoff score of 15 has a sensitivity of 0.85 and specificity of 0.75 for detecting the presence of a possible ASD [Berument et al, 1999; Snow and LeCavalier, 2008]. Domain scores can be calculated in three areas: Reciprocal Social Interaction; Communication; and Restricted, Repetitive, and Stereotyped Patterns of Behavior. The SCQ has strong reliability and validity [Chandler et al, 2007; Charman et al., 2007].

Adaptive functioning was assessed using the Vineland-II Adaptive Behavior Scales Survey Interview Form (VABS-II) [Sparrow et al., 2005], a semi-structured interview administered to caregivers by a licensed psychologist (JMK). The VABS-II was used to assess participants' daily adaptive skills in the domains of Communication (receptive, expressive, and written language skills), Daily Living Skills (personal, domestic, and community skills), and Socialization (interpersonal relations, play, and coping skills). In addition, *Motor Skills* are assessed in children younger than 7 years. The VABS-II has good internal reliability (Cronbach's $\alpha = .84-.86$) and test-retest reliability (.74 –.93), and has demonstrated validity based on factor analysis and correlation with other measures of adaptive functioning.

All measures were scored by a licensed psychologist, and scoring was verified by a trained technician before entry into the database. VABS-II standard scores were derived using normative data based upon the participants' chronological age. The VABS-II was completed by all but one participant, who declined due to time constraint. A second participant did not complete all items, so the Daily Living Skills index and Adaptive Behavior Composite could not be derived. These subjects were omitted from the relevant analyses. Data were analyzed using SPSS 23 (IBM Corp., 2015). Descriptive statistics and bivariate correlations were generated for all variables. Group differences were analyzed with Fisher's exact test, univariate analyses of variance, and independent samples t-test.

RESULTS

Descriptive statistics are presented in Table I. The younger and older groups had equal numbers of males and females, and did not differ significantly in terms of different mutations. Scores on the M-CHAT and SCQ did not correlate significantly with any Vineland scales. As shown in the table, the older group had somewhat higher Vineland scores, but no difference approached statistical significance.

Age group was significantly associated with meeting ASD criteria on the respective screening measures. Five of seven (71.4%) of the younger children met the recommended ASD cutoff of 3 on the MCHAT, compared to 0/7 of the older children who received the

SCQ ($\Phi = .745$, $p = .021$, Fisher's exact test). In fact, no SCQ score even approached the cutoff of 15 (see Table II). In addition, 2/7 (28.6%) of the younger children met the stricter cutoff of 7 on the MCHAT.

Table II shows medical and developmental information for all 14 subjects. 86% of the younger children had a gastrostomy tube at the time of our assessment, compared to 29% of the older children; however, this difference was not significant ($p = .103$). Having a gastrostomy tube, however, was strongly associated with meeting the recommended ASD criterion on the M-CHAT; 33% of children who did not meet ASD criteria had a gastrostomy tube versus 100% of children who did meet ASD criteria ($\Phi = .645$, $p = .031$, Fisher's exact test). Not yet eating solid food was also associated with meeting ASD criteria ($\Phi = .701$, $p = .027$, Fisher's exact test). The younger and older groups did not differ on other medical variables. As would be expected, the older group had met many more developmental milestones than the younger group. Developmental factors associated with meeting the ASD cutoff were: not yet walking ($\Phi = 1.0$, $p = .000$ Fisher's exact test) and not being toilet trained ($\Phi = .861$, $p = .003$, Fisher's exact test). There was no association between other medical problems or surgeries and ASD criteria in our sample.

Two children who had the p.G12S mutation met conservative ASD criteria on the M-CHAT. One (subject #6) was quite impaired. She was the only subject who had seizures, was not yet crawling, and had not yet begun to produce any words. To further examine whether functional impairment might be associated with meeting ASD criteria, we compared adaptive behavior in children who did and did not meet ASD criteria. The two children who met conservative ASD criteria together had a significantly lower Vineland Adaptive Behavior Composite than those who did not ($M=58$ versus 73), $t(10)=2.603$, $p = .026$, effect size $r = .733$. Children who met liberal ASD criteria did not differ on any Vineland scale from children not meeting ASD criteria. It is also worth noting that social functioning was the highest rated adaptive behavior domain for both age groups, with the older group falling in the low-average range relative to same-age peers.

Finally, we compared our cohort's scores on SCQ subdomains with the SCQ normative samples [Rutter et al., 2003]. As shown in Figure 1, children with CS scored below the mean (i.e., had fewer symptoms) compared to all three normative groups, including typically-developing children (the non-ASD group). In fact, no child with CS scored above the mean for typically-developing children in any subdomain.

DISCUSSION

In our sample of individuals with CS, symptoms of ASD were elevated only in younger children. Among those assessed with the M-CHAT, 71% (5/7) met the liberal screening cutoff, and 29% (2/7) met the more conservative cutoff for possible ASD. In contrast, no older child or youth assessed with the SCQ in our study exceeded the screening cutoff score. In fact, SCQ domain scores were equal to or lower than domain scores in the typically-developing normative sample [Rutter et al., 2003], and this was true not only of the overall sample but of each individual child. We are therefore confident that, at least in our small sample, the older children were not presenting with notable ASD symptoms.

Screening questionnaires for ASD are designed to maximize sensitivity, as it is preferable to over-identify children in need of further evaluation than to miss true cases of ASD, which can have significant consequences for a child's ability to receive early intervention. However, a downside is that these tools may overestimate the prevalence of ASD symptoms in medically-complex children [Johnson and Marlow, 2009]. As noted above, the first four or five years of life for a child with CS are characterized by severe feeding problems and failure to thrive. Most infants with CS require gastrostomy feeding, and many experience severe gastroesophageal reflux disease. Language development is delayed, and many children with CS do not begin to talk until they start tolerating oral feeds between the ages of two and four [Gripp and Lin, 2012]. In our sample, all five children who met ASD criteria were still being fed via gastrostomy tube, and two could not yet tolerate any solid food. It should be noted that all 14 children in our study had a gastrostomy tube at some time, but only those children who still had one at the time of our assessment met ASD criteria. These data suggest that feeding and nutritional problems early in life might contribute to an elevated rate of positive findings of ASD symptoms in very young children with CS.

Other authors have described ASD-like presentations in very young children with CS that resolve as feeding problems improve. Kawame et al. [2003] reported irritability, hypersensitivity to touch, and excessive shyness in infants with CS that resolved with improved feeding between ages two and four. At four to five years of age, the same children "showed social and happy characteristics ... [that were] typically appreciated at the clinic visits." Galera et al. [2006] reported significant anxiety and somatic complaints in children with CS under age four but not in older children, which they also attributed to the feeding problems and hospitalizations that characterized the younger children's lives. An association between feeding/nutritional problems and behavior has also been reported in children with other neurodevelopmental disabilities. Reflux esophagitis has been noted as a potentially important contributor to irritability in children with autism [Horvath et al., 1999], and chronic under-nutrition has been identified as contributing to irritability, increased fatigue, and lack of motivation in children with cerebral palsy [Stallings et al., 1993]. There is also evidence that treatments for feeding problems such as fundoplication improve social functioning in children with neurological impairment [Srivastava et al., 2007].

Children with CS also have orthopedic complications and musculoskeletal abnormalities [Detweiler et al., 2011] that limit mobility and activity [Johnson et al. 2014], which may impede their social functioning and contribute to an elevated false-positive rate for ASD on the M-CHAT. Research by Kuban and colleagues [2009] has shown that children born at extremely low gestational age (i.e., before 28 weeks gestation) have significantly elevated rates of ASD symptoms on the M-CHAT that are strongly associated with severity of neuro-motor impairment. In another study, positive responses on multiple M-CHAT items appeared directly attributable to motor impairment [Luyster et al., 2011]. In our sample, a majority of parents endorsed motor-related items on the M-CHAT such as *Does not like climbing* (n=6), *Does not walk* (n=5), and *Does not bring objects to you* (n=4), and not yet walking was perfectly correlated with meeting ASD criteria. These findings suggest caution when using screening tools for ASD in children with CS and other genetic and neurodevelopmental disorders with involvement of the motor system. In particular, clinicians may consider

examining specific test items to see whether physical delays (e.g., in motor development) may be elevating scores.

Our findings are consistent with Alfieri et al. [2014], who found elevated ASD rates primarily in subjects aged four years or younger. Two of four of their CS subjects who exceeded the ASD cutoff on the SCQ were assessed in infancy, and a third was four years old. They likewise suggested age as a partial explanation of increased ASD symptoms in their cohort. Our findings are similar to those of Adviento et al. [2014] regarding prevalence of positive screens, especially when using the more conservative M-CHAT cutoff, but they differ in that Adviento et al. [2014] found an elevated rate of ASD symptoms on the SCQ, whereas we only saw elevation on the M-CHAT. As they did not report findings by age, it is unclear whether this effect may have been due to subject age. In any case, given their larger sample (n = 43), our finding of no positive SCQ screens must be interpreted with caution. Adviento et al. [2014] found elevated scores on the Social Responsiveness Scale (SRS) consistent with ASD in a portion of their sample, though the overall score for the CS group was only somewhat elevated (T-score=61), below the reported ASD mean (T=86) and the cutoff for possible autism (T=76). Moreover, it has been argued that the SRS is influenced by internalizing and externalizing behaviors and developmental level, to the degree that its specificity for ASD is questionable [Hus et al., 2013]. Thus, Adviento et al.'s [2014] findings do not unequivocally support a significantly elevated rate of ASD in individuals with CS.

Two case reports have been published of children with CS and ASD confirmed by more comprehensive evaluation. Adviento et al. [2014] completed the ADI-R and ADOS for one participant who was found to have atypical autism, meaning the child exhibited some but not all symptoms of an ASD, while Alfieri and colleagues [2015] reported a case of confirmed ASD in a child with a rare mutation in HRAS (p.E37dup). Thus, these two cases differ either from more typical ASD or the more common variants of CS, making it difficult to generalize from them to the broader CS population.

Limitations and Future Directions

Our study has a number of limitations. First, we had a relatively small sample size, which limits the generalizability of our findings, though given the rarity of CS, our sample size is not atypical. Second, only the older children were able to complete IQ testing. Third, given time limitations and the geographic distribution of the individuals, we were unable to follow-up with more comprehensive evaluations for ASD in children who screened positive. Completing the gold-standard evaluations for ASD is time-consuming and did not prove feasible for this study. Use of gold standard measures to verify all positive screens within a sample is needed to estimate the true prevalence of ASD in CS. Finally, our study was cross-sectional in nature. It is possible that our group difference was due not to age but to the use of different screening measures for different ages. Future research using longitudinal designs will help more definitively answer the question of whether children with CS show stable ASD symptoms or emerge out of an ASD presentation as they get older.

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References

- Adviento B, Corbin I, Widjaja F, Desachy G, Enrique N, Rosser T, Risi S, Marco EJ, Hendren RL, Bearden CE, Rauen KA, Weiss LA. Autism traits in the RASopathies. *J Med Genet*. 2014; 51(1): 10–20. [PubMed: 24101678]
- Alfieri P, Caciolo C, Piccini G, D'Elia L, Valeri G, Menghini D, Tartaglia M, Digilio MC, Dallapiccola B, Vicari S. Behavioral Phenotype in Costello Syndrome with Atypical Mutation: A Case Report. *Am J Med Genet Part B*. 2015; 168B:66–71. [PubMed: 25367099]
- Alfieri P, Piccini G, Caciolo C, Perrino F, Gambardella ML, Mallardi M, Cesarini L, Leoni C, Leone D, Fossati C, Selicorni A, Digilio MC, Tartaglia M, Mercuri E, Zampino G, Vicari S. Behavioral profile in RASopathies. *Am J Med Genet Part A*. 2014; 9999:1–9.
- American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 5. Arlington, VA: American Psychiatric Publishing; 2013.
- Axelrad ME, Glidden R, Nicholson L, Gripp KW. Adaptive skills, cognitive, and behavioral characteristics of Costello syndrome. *Am J Med Genet Part A*. 2004; 128A:396–400. [PubMed: 15264285]
- Axelrad ME, Nicholson L, Stabley DL, Sol-Church K, Gripp KW. Longitudinal assessment of cognitive characteristics in Costello syndrome. *Am J Med Genet Part A*. 2007; 143A:3185–3193. [PubMed: 17963256]
- Axelrad ME, Schwartz DD, Fehlis JE, Hopkins E, Stabley DL, Sol-Church K, Gripp KW. Longitudinal course of cognitive, adaptive, and behavioral characteristics in Costello syndrome. *Am J Med Genet Part A*. 2009; 149A:2666–2672. [PubMed: 19919001]
- Axelrad ME, Schwartz DD, Katzenstein JM, Hopkins E, Gripp KW. Neurocognitive, adaptive, and behavioral functioning of individuals with Costello syndrome: A review. *Am J Med Genet*. 2011; 157:115–122.
- Berument SB, Rutter M, Lord C, Pickles A, Bailey A. Autism screening questionnaire: Diagnostic validity. *Br J Psychiatry*. 1999; 175:444–451. [PubMed: 10789276]
- Betancur C. Etiological heterogeneity in autism spectrum disorders: More than 100 genetic and genomic disorders and still counting. *Brain Res*. 2011; 1380:42–77. [PubMed: 21129364]
- Birmaher B, Brent D, Chiappetta L, Bridge L, Monga S, Baugher M. Psychometric properties of the Screen for Child Anxiety Related Emotional Disorders (SCARED): A replication study. *J Am Acad Child Adolesc Psychiatry*. 1999; 38(10):1230–1236. [PubMed: 10517055]
- Brooks WT, Benson BA. The validity of the Social Communication Questionnaire in adults with intellectual disability. *Res Autism Spectr Disord*. 2013; 7:247–255.
- Chandler S, Charman T, Baird G, Simonoff E, Loucas T, Meldrum D, Scott M, Pickles A. Validation of the Social Communication Questionnaire in a population cohort of children with Autism Spectrum Disorders. *J Am Acad Child Adolesc Psychiatry*. 2007; 46(10):1324–1332. [PubMed: 17885574]
- Charman T, Baird G, Simonoff E, Loucas T, Chandler S, Meldrum D, Pickles A. Efficacy of three screening instruments in the identification of autistic-spectrum disorders. *Br J Psychiatry*. 2007; 191(6):554–559. [PubMed: 18055961]

- Chlebowski C, Robins DL, Barton ML, Fein D. Large-scale use of the modified checklist for autism in low-risk toddlers. *Pediatrics*. 2013; 131(4)
- Crepel A, Steyaert J, De la Marche W, De Wolf V, Fryns JP, Noens I, Devriendt K, Peeters H. Narrowing the critical deletion region for autism spectrum disorders on 16p11.2. *Am J Med Genet B: Neuropsychiatr Genet*. 2011; 156:243–245. [PubMed: 21302354]
- Dekker M, Koot HM. DSM-IV Disorders in children with borderline to moderate intellectual disability. I: Prevalence and impact. *J Am Acad Child Adolesc Psychiatry*. 2003; 42:915–922. [PubMed: 12874493]
- Detweiler S, Thacker MM, Hopkins E, Conway L, Gripp KW. Orthopedic manifestations and implications for individuals with Costello syndrome. *Am J Med Genet Part A*. 2013; 161A:1940–1949. [PubMed: 23813656]
- Freitag CM, Agelopoulos K, Huy E, Rothermundt M, Krakowitzky P, Meyer J, Deckert J, von Gontard A, Hohoff C. Adenosine A2a- receptor gene (ADORA2A) variants may increase autistic symptoms and anxiety in autism spectrum disorder. *Eur Child Adolesc Psychiatry*. 2010; 19:67–74. [PubMed: 19565319]
- Galera C, Delrue M, Goizet C, Etchegoyhen K, Taupiac E, Sigaudy S, Arveiler B, Philip N, Bouvard M, Lacombe D. Behavioral and temperamental features of children with Costello syndrome. *Am J Med Genet*. 2006; 140A:968–974.
- Ghazuiuddin M, Bolyhard B, Alessi N. Autistic disorder in Noonan syndrome. *J Intellect Disabil Res*. 1994; 38:67–72. [PubMed: 8173225]
- Gripp K, Lin A. Costello syndrome: A Ras/mitogen activated protein kinase pathway syndrome (rasopathy) resulting from HRAS germline mutations. *Genet Med*. 2012; 14:285–292. [PubMed: 22261753]
- Gripp KW, Hopkins E, Doyle D, Dobyns WB. High incidence of progressive postnatal cerebellar enlargement in Costello syndrome: Brain overgrowth associated with HRAS mutations as the likely cause of structural brain and spinal cord abnormalities. *Am J Med Genet Part A*. 2010; 152A:1161–1168. [PubMed: 20425820]
- Gripp KW, Hopkins E, Sol-Church K, Stabley DL, Axelrad ME, Doyle D, Dobyns WB, Hudson C, Johnson J, Tenconi R, Graham GE, Sousa AB, Heller R, Piccione M, Corsello G, Herman GE, Tartaglia M, Lin AE. Phenotypic analysis of individuals with Costello syndrome due to HRAS p.G13C. *Am J Med Genet Part A*. 2011; 155:706–716.
- Gripp KW, Innes AM, Axelrad ME, Gillan TL, Parboosingh JS, Davies C, Leonard NJ, Lapointe M, Doyle D, Catalano S, Nicholson L, Stabley DL, Sol-Church K. Costello syndrome associated with novel germline HRAS mutations: An attenuated phenotype? *Am J Med Genet Part A*. 2008; 146A:683–690. [PubMed: 18247425]
- Horvath K, Papadimitriou JC, Rabsztyan A, Drachenberg C, Tildon JT. Gastrointestinal abnormalities in children with autistic disorder. *J Pediatr*. 1999; 135(5):559–563. [PubMed: 10547242]
- Hu H, Qin Y, Bochorishvili G, Zhu Y, van Aelst L, Zhu JJ. Ras signaling mechanisms underlying impaired GluR1-dependent plasticity associated with fragile X syndrome. *J Neurosci*. 2008; 28:7847–62. [PubMed: 18667617]
- Hus V, Bishop S, Gotham K, Huerta M, Lord C. Factors influencing scores on the social responsiveness scale. *J Child Psychol Psychiatry*. 2013; 54(2):216–224. [PubMed: 22823182]
- IBM Corp. IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp; Released 2015
- Iossifov I, Ronemus M, Levy D, Wang Z, Hakker I, Rosenbaum J, Yamrom B, Lee YH, Narzisi G, Leotta A, Kendall J, Grabowska E, Ma B, Marks S, Rodgers L, Stepansky A, Troge J, Andrews P, Bekritsky M, Pradhan K, Ghiban E, Kramer M, Parla J, Demeter R, Fulton LL, Fulton RS, Magrini VJ, Ye K, Darnell JC, Darnell RB, Mardis ER, Wilson RK, Schatz MC, McCombie WR, Wigler M. De novo gene disruptions in children on the autism spectrum. *Neuron*. 2012; 74:285–299. [PubMed: 22542183]
- Johnson B, Goldberg-Strassler D, Gripp K, Thacker M, Leoni C, Stevenson D. Function and disability in children with Costello syndrome and Cardiofaciocutaneous syndrome. *Am J Med Genet Part A*. 2015; 167A:40–44. [PubMed: 25346259]
- Johnson S, Marlow N. Positive screening results on the modified checklist for autism in toddlers: implications for very preterm populations. *J Pediatr*. 2009; 154(4):478–80. [PubMed: 19185316]

- Kawame H, Matsui M, Kurosawa K, Matsuo M, Masuno M, Ohashi H, Fueki N, Aoyama K, Miyatsuka Y, Suzuki K, Akatsuka A, Ochiai Y, Fukushima Y. Further delineation of the behavioral and neurologic features in Costello Syndrome. *Am J Med Genet Part A*. 2003; 118A:8–14. [PubMed: 12605434]
- Kerns C, Kendall P. The presentation and classification of anxiety in autism spectrum disorder. *Clinical Psychology Science and Practice*. 2012; 19(4):323–347.
- Kim E, Lee S, Mian MF, Yun SU, Song M, Yi KS, Ryu SH, Suh PG. Crosstalk between Src and major vault protein in epidermal growth factor-dependent cell signalling. *FEBS J*. 2006; 273:793–804. [PubMed: 16441665]
- Kuban KCK, O'Shea TM, Allred EN, Tager-Flusberg H, Goldstein DJ, Leviton A. Positive screening on the Modified Checklist for Autism in Toddlers (M-CHAT) in extremely low gestational age newborns. *J Pediatr*. 2009; 154:535–540. [PubMed: 19185317]
- Levitt P, Campbell DB. The genetic and neurobiologic compass points toward common signaling dysfunction in autism spectrum disorders. *J Clin Invest*. 2009; 119:747–754. [PubMed: 19339766]
- Loesch DZ, Bui QM, Dissanayake C, Clifford S, Gould E, Bulhak-Paterson D, Tassone F, Taylor AK, Hessler D, Hagerman R, Huggins RM. Molecular and cognitive predictors of the continuum of autistic behaviours in fragile X. *Neurosci Biobehav Rev*. 2007; 31(3):315–326. [PubMed: 17097142]
- Luyster RJ, Kuban KCK, O'Shea TM, Paneth N, Allred EN, Leviton A. The Modified Checklist for Autism in Toddlers in extremely low gestational age newborns: individual items associated with motor, cognitive, vision and hearing limitations. *Paediatr Perinat Epidemiol*. 2011; 25:366–76. [PubMed: 21649679]
- Mbarek O, Marouillat S, Martineau J, Barthelemy C, Muh JP, Andres C. Association study of the NF1 gene and autistic disorder. *Am J Med Genet Part A*. 1999; 88:729–732.
- Packer, A. [Accessed 6/7/2016] RAS Pathway, a potentially unifying theory of autism. 2012. <http://sfari.org/news-and-opinion/directors-columns/2012/ras-pathway-a-potentially-unifying-theory-of-autism>
- Philip N, Sigaudy S. Costello syndrome. *J Med Genet*. 1998; 35:238–40. [PubMed: 9541110]
- Pine D, Guyer A, Goldwin M, Towbin K, Leibenluft E. Autism Spectrum Disorder scale scores in pediatric mood and anxiety disorders. *J Am Acad Child Adolesc Psychiatry*. 2008; 47(6):652–661. [PubMed: 18434923]
- Robins DL, Fein D, Barton ML, Green JA. The Modified Checklist for Autism in Toddlers: An initial study investigating the early detection of autism and pervasive developmental disorders. *J Autism Dev Disord*. 2001; 31:133–144.
- Roid, GM., Miller, LJ. *Leiter International Performance Scale-Revised: Examiners Manual*. Wood Dale, IL: Stoelting Company; 1997.
- Rutter, M., Bailey, A., Lord, C. *The Social Communication Questionnaire Manual*. Los Angeles: Western Psychological Services; 2003.
- Sappok T, Diefenbacher A, Gaul I, Bolte S. Validity of the Social Communication Questionnaire in adults with intellectual disabilities and suspected autism spectrum disorder. *Am J Intellect Dev Disabil*. 2015; 120:203–214. [PubMed: 25928433]
- Schwartz DD, Katzenstein JM, Hopkins E, Stabley DL, Sol-Church K, Gripp KW, Axelrad ME. Verbal memory functioning in adolescents and young adults with Costello syndrome: Evidence for relative preservation of recognition memory. *Am J Med Genet Part A*. 2013; 161A:2258–2265. [PubMed: 23918324]
- Snow AV, LeCavalier L. Sensitivity and specificity of the Modified Checklist for Autism in Toddlers and the Social Communication Questionnaire in preschoolers suspected of having pervasive developmental disorders. *Autism*. 2008; 12(6):627–644. [PubMed: 19005032]
- Sparrow, SS., Cicchetti, DV., Balla, DA. *Vineland Adaptive Behavior Scales*. 2. American Guidance Service; Circle Pines, MN, USA: 2005.
- Srivastava R, Downey EC, Feola P, Samore M, Coburn L, Holubkov R, Mundorff M, Nkoy F, Desrochers D, James BC, Rosenbaum P, Young PC, Dean JM, O'Gorman M. Quality of life of children with neurological impairment who receive a fundoplication for gastroesophageal reflux disease. *J Hosp Med*. 2007; 2(3):165–173. [PubMed: 17549766]

- Stallings VA, Charney EB, Davies JC, Cronk CE. Nutrition-related growth failure of children with quadriplegic cerebral palsy. *Dev Med Child Neurol*. 1993; 35:126–138. [PubMed: 8444326]
- Towbin K, Pradella A, Gorrindo T, Pine D, Leibenluft E. Autism spectrum traits in children with mood and anxiety disorders. *J Child Adolesc Psychopharmacol*. 2005; 15:452–464. [PubMed: 16092910]

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Figure 1.

SCQ subdomain scores for individuals with Costello syndrome ($n=7$) compared to normative data from Rutter, Bailey, and Lord (2003) for children without an autism spectrum disorder or intellectual disability (non-ASD; $n=25$), intellectual disability ($n=15$), and autism spectrum disorder (ASD; $n=160$). Higher scores indicate greater impairment.

Table I

Patient characteristics and group differences between younger and older participants

	Younger (n=7)	Older (n=7)	p-value
Age, months (M, SD)	35.4 (9.1)	131.6 (66.3)	0.003
Sex (n, %)			1.000
Female	4 (57%)	4 (57%)	
Male	3 (43%)	3 (43%)	
HRAS mutation (n, %)			0.767
p.G12A	1 (14%)	0 (0%)	
p.G12C	1 (14%)	1 (14%)	
p.G12S	3 (43%)	4 (57%)	
p.G13C	2 (29%)	2 (29%)	
Vineland-2 (M, SD)			
Adaptive Behavior Composite	67.8 (11.1)	73.3 (6.9)	0.326
Communication	75.0 (13.3)	77.1 (7.7)	0.724
Daily Living Skills	68.2 (15.3)	76.8 (9.7)	0.268
Social	75.3 (18.3)	83.1 (10.0)	0.350
ASD cutoff			
Liberal (n, %)	5 (71%)	0 (0%)	0.002
Conservative (n, %)	2 (29%)	N/A	0.147

Note. Vineland-2 scores are standard scores with M = 100 and SD = 15. The liberal (recommended) ASD cutoff score for further screening on the M-CHAT = 3 and on the SCQ = 15. The conservative cutoff on the M-CHAT = 7.

Table II

ASD screening data by patient

Subject ID	Group 1							Group 2						
	1	2	3	4	5	6	7	8	9	10	11	12	13	14
HRAS Change	p.G13C	p.G12S	p.G12S	p.G13C	p.G12A	p.G12S	p.G12C	p.G13C	p.G13C	p.G12S	p.G12S	p.G12S	p.G12S	p.G12C
Sex	F	M	F	M	M	F	F	M	M	F	M	F	F	F
Age (months)	22	30	33	37	37	37	52	48	72	101	121	145	214	220
Medical														
Gastrostomy tube	+	+	+		+	+	+	+						+
Seizures						+								
Cardiac	+		+				+		+					
Neurosurgery	+	+			+	+			+		+	+	+	
Orthopedic surgery					+		+				+	+	+	+
Developmental														
Solid food	+	+		+			+	+	+	+	+	+	+	+
Crawling	+	+	+	+	+		+	+	+	+	+	+	+	+
Walking				+			+	+	+	+	+	+	+	+
Toilet trained							+	+	+	+	+	+	+	+
First word	+	+	+	+	+		+	+	+	+	+	+	+	+
Names 10 objects			+		+		+	+	+	+	+	+	+	+
M-CHAT score	6	8	3	2	5	15	1	6	3	6	1	8	8	0
SCQ score														
ASD Cutoff?	YES	YES	YES	NO	YES	YES	NO	NO	NO	NO	NO	NO	NO	NO
Strict ASD cutoff?	NO	YES	NO	NO	NO	YES	NO	n/a	n/a	n/a	n/a	n/a	n/a	n/a

Note. Gastrostomy tube refers to have a g-tube at the time of assessment. M-CHAT and SCQ data are presented as raw scores. Higher scores indicate greater impairment. ASD cutoffs: M-CHAT raw score 3, SCQ raw score 15. Strict cutoff (M-CHAT only): raw score 7.