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ORIGINAL RESEARCH

Adults with Chromosome 18 Abnormalities

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Abstract The identification of an underlying chromosome abnormality frequently marks the endpoint of a diagnostic odyssey. However, families are frequently left with more questions than answers as they consider their child's future. In the case of rare chromosome conditions, a lack of longitudinal data often makes it difficult to provide anticipatory guidance to these families. The objective of this study is to describe the lifespan, educational attainment, living situation, and behavioral phenotype of adults with chromosome 18 abnormalities. The Chromosome 18 Clinical Research Center has enrolled 483 individuals with one of the following conditions: 18q-, 18p-, Tetrasomy 18p, and Ring 18. As a part of the ongoing longitudinal study, we collect data on living arrangements, educational level attained, and employment status as well as data on executive functioning and behavioral skills on an annual basis. Within our cohort, 28 of the 483 participants have died, the majority of whom have deletions encompassing the *TCF4* gene or who have unbalanced rearrangement involving other chromosomes. Data regarding the cause of and age at death are presented. We also report on the living situation, educational attainment, and behavioral phenotype of the 151 participants over the age of 18. In general, educational level is higher for people with all these conditions than implied by the early literature, including some that received post-high school education. In addition, some individuals are able to live independently, though at this point they represent a minority of patients. Data on executive function and behavioral phenotype are also presented. Taken together, these data provide insight into the long-term outcome for individuals with a chromosome 18 condition. This information is critical in counseling families on the range of potential outcomes for their child.

Keywords 18p- · 18q- · Tetrasomy 18p · Ring 18 · Chromosome 18 · De grouchy syndrome · Genetic counceling

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Introduction

Conditions involving chromosome 18 were first described in the 1960's (de Grouchy et al. 1964). Since their initial description, these conditions have primarily been characterized by case reports and series, usually involving young children. Longitudinal data describing the course of these conditions over a lifespan have been lacking. Thus, it has been difficult for providers to offer anticipatory guidance regarding some of the primary concerns of families, namely, lifespan and the overall developmental outcome of adults with a chromosome 18 condition. The specific behavioral profile in these conditions has also not been well-established, making it impossible for parents to know what types of challenges they may encounter as the child ages.

That being said, a review of the literature is instructive in determining what has previously been reported, though the limitations of the early reports must be kept in mind. For example, the state of medical science as well as the available developmental therapies has improved greatly since these

conditions were first described. It can be anticipated that individuals born now would have an improved lifespan and quality of life with the help of these interventions.

Tetrasomy 18p The literature on adults with Tetrasomy 18p includes ten individuals reported with non-mosaic Tetrasomy 18p: five males and five females, the oldest being 51 years old. All of these individuals are reported as having severe to profound intellectual disability and 4 of whom have seizures (Batista et al. 1983; Bugge et al. 1996; Callen et al. 1990; Kleczkowska et al. 1986; Kotzot et al. 1996; Swingle et al. 2006). There is one report of a woman with 3 % Tetrasomy 18p mosaicism who had a non-mosaic child with Tetrasomy18p (Abeliovich et al. 1993).

The literature on the cause of death for individuals with Tetrasomy 18p includes only 3 individuals. They died at the age of 2.6 years after thrombosis of the inferior vena cava (Nielsen et al. 1978); at the age of 10 months after severe pneumonia (Blennow and Nielsen 1991); and suddenly at the age of 1 year old (Singer et al. 1990).

Ring 18 The five adults with Ring 18 that have been reported in the literature were identified because of a pregnancy with a child with Ring 18 (Bagherizadeh et al. 2011; Christensen et al. 1970; Fryns and Kleczkowska 1992; Fryns et al. 1992; Yardin et al. 2001). Therefore, there is little information about the life and health of these mothers. There are five reports in the literature of infants with Ring 18 who died within the first few months of life from major cardiac malformations or holoprosencephaly (Cohen et al. 1972; Fryns et al. 1992; Watanabe et al. 1971; Yanoff et al. 1970; Yardin et al. 2001). The one interesting case is a mother with Ring 18 who was not reported as having mosaicism (Christensen et al. 1970). She was reported to have an IQ of 55–60 and suffered from psychosis and delusions. She died at age 48 from metastatic cancer with tumors adherent to the left of the ovaries, uterus and rectum (reticulosarcoma and lymphosarcoma).

18p- The literature on 18p- includes 19 adults: 8 males and 11 females, the oldest being 62 years old (Babovic-Vuksanovic et al. 2004; de Ravel et al. 2005; Harris et al. 1983; Jacobsen and Mikkelsen 1968; Maranda et al. 2006; Mikelsaar et al. 2002; Moedjono et al. 1979; Portnoi et al. 2007; Postma et al. 2009; Rigola et al. 2001; Ruvalcaba 1970; Tezzon et al. 1998; Tsukahara et al. 2001; Velagaleti et al. 1996; Wester et al. 2006;). The only deaths reported have been newborns with holoprosencephaly (Faust et al. 1976; Nitowsky et al. 1966; Tonk and Krishna 1997; Uchida et al. 1965). There are several reports of women with 18p- who had children, most of whom also had 18p-; however there is likely an ascertainment bias. A parent with intellectual disability with a child with a normal intellect would likely not be worked up much less reported. Therefore the only conclusion that can be drawn is that women with 18p- are fertile and there does not appear to be any maternal 18p- effect; meaning that the children are not more severely affected than their mothers due to a potentially sub-optimal intrauterine environment. Living situations are rarely documented in the literature. However, one person was noted to live in a group home (Babovic-Vuksanovic et al. 2004) and two lived independently (Maranda et al. 2006; Wester et al. 2006). Two of these individuals held down jobs; one in a factory and the other as a janitor. The man who was employed as a janitor also drove a car.

18q- There are 28 adults (21 females and 7 males) reported in the literature with 18q- (Adab and Larner 2006; Gordon et al. 1995; Faed et al. 1972; Fryns et al. 1979; Kato et al. 2010; Keppler-Noreuil et al. 1998; Linnankivi et al. 2006; Maaswinkel-Mooij et al. 1993; Mahr et al. 1996; Margarit et al. 2012; Miller et al. 1990; Netzer et al. 2006; Subrt and Pokorny 1970; Tinkle et al. 2003; Warburg et al. 1991; Weiss et al. 1991; Wilson et al. 1979). The oldest were 49 (Fryns et al. 1979) with a distal 18q deletion and 67 (Tinkle et al. 2003) with a proximal interstitial deletion. Living situations when specified are institutions for adults with disabilities, however most often there is no mention of their housing or social living conditions. There are numerous reports of women with 18q- who have had children (Fryns et al. 1979; Keppler-Noreuil et al. 1998; Margarit et al. 2012; Subrt and Pokorny 1970) and only one report of a male with 18q- fathering children (Linnankivi et al. 2006). Many of the reports of women with children are reported because they had children, which may account for the over representation of women in the literature. Interestingly, the only father with 18q- had an interstitial distal deletion of 18q that did not include genes from *FBXO15* to the q telomere implying that there is a gene in this region influencing male fertility.

There are reports of several individuals with 18q- who have died (Felding et al. 1987; Law and Masterson 1969; Vogel et al. 1990; Wilson et al. 1979). Those who died in the first couple of years of life were described as severely impaired and died from chronic aspiration pneumonia. There is also one report involving three adult relatives who have died with proximal 18q-. Two died at 47 and 52 years old from cancer, and one died at 54 from bronchopneumonia (Chudley et al. 1992).

As previously discussed, the literature, though extensive, provides limited insight into the long-term outcomes for individuals with chromosome 18 conditions. The Chromosome 18 Clinical Research Center has been enrolling individuals with chromosome 18 abnormalities in our longitudinal study since 1993. In addition to performing high resolution molecular analysis to aid genotype-phenotype correlation, we have also been regularly collecting data regarding developmental progress and living situation for all study participants (Cody et al. 2009; Heard et al. 2009). Here, we report on the educational attainment, living situation, and employment status of

adults with Tetrasomy 18p, Ring 18, 18p-, and 18q-. In an attempt to clarify the behavioral issues present in these populations as they age, we also report the results of a series of developmental and behavioral surveys that assess executive function, behavioral regulation, and maladaptive behaviors. Additionally, we report the current age of all study participants in comparison to the age at death for those who are deceased.

Methods

Participants were enrolled as a part of the Chromosome 18 Clinical Research Center longitudinal study of individuals with chromosome 18 abnormalities. This study was approved by the University of Texas Health Science Center at San Antonio Institutional Review Board and all subjects have participated in a documented informed consent process.

Upon enrollment in the study, medical records, including the original karyotype or microarray analysis, were collected to confirm the diagnosis of a chromosome 18 condition. In addition, genotyping was performed on DNA from peripheral blood samples by microarray comparative genomic hybridization (aCGH) using the Agilent system as previously described (Heard et al. 2009). We use the Agilent system and custom designed arrays with 32,000 features across chromosome 18 and 12,000 features across the remainder of the genome. This allows for high resolution determination of each participant's chromosome 18 copy number changes as well as any additional copy number changes that had been previously undetected.

Participants were asked to complete several annual surveys. To assess planning, organization, problem solving, attentional and behavioral regulation abilities, the Behavior Rating Inventory of Executive Function – Adult Version, Informant Report (BRIEF-A) was administered (Roth et al. 2005). To assess the prevalence of maladaptive behavior, parents completed the Behavioral Assessment System for Children, Second Edition – BASC-2 (Reynolds and Kamphaus 2004). Both of these tools are well-normed instruments with demonstrated reliability and validity information provided by the test publishers and by post-publication validation studies. The specific domains assessed by each of these scales are shown in Figs. 1 and 2. Each behavior is categorized as being within normal limits, as "at-risk for developing problems", or as an area of significant concern. In addition, participants were asked about educational progress, living/social situation, and employment/volunteer work history. Data from individuals over 18 years of age are reported here.

Data regarding deaths within our entire study population were also analyzed. Records from all participants that have died were requested and reviewed.

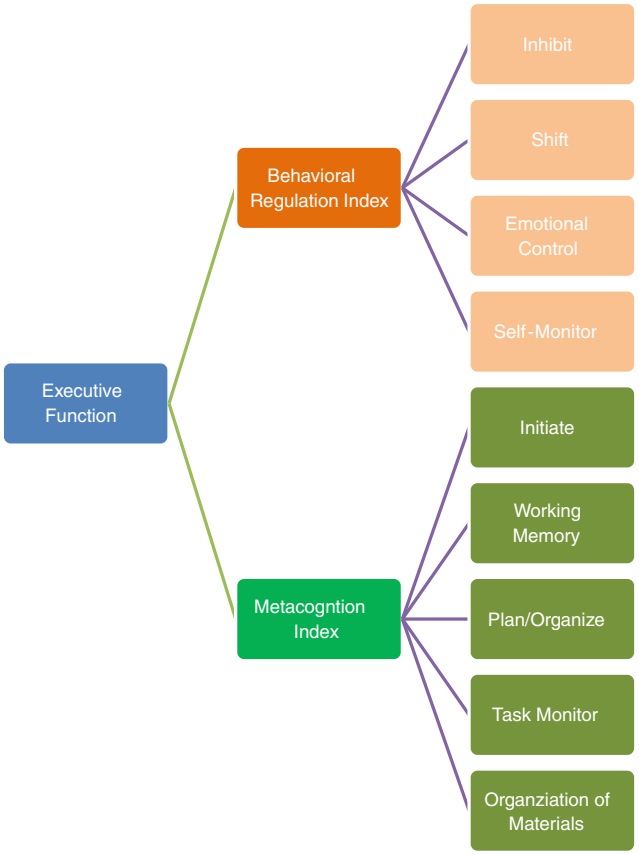

Fig. 1 Domains assessed by the BRIEF-A

Results

Tetrasomy 18p

There are 56 individuals with Tetrasomy 18p enrolled in the study, twelve of which are over 18 years of age. For the most part, all of these individuals were genotypically identical, having an isochromosome 18p with a breakpoint in the centromeric region. However, two individuals in our study were trisomic for small regions of proximal 18q as well.

Lifespan

The mean age of the 56 participants with Tetrasomy 18p was 14.0 years. In this group, only one individual had died, the cause presumed to be sudden cardiac arrest (Table 4 and Fig. 3). This case has been described previously (Sebold et al. 2010).

Educational Attainment and Living Situation

The majority of adults with Tetrasomy 18p still live with their parents (Table 3). None are married or have had children, though one individual is engaged. With regard to education,

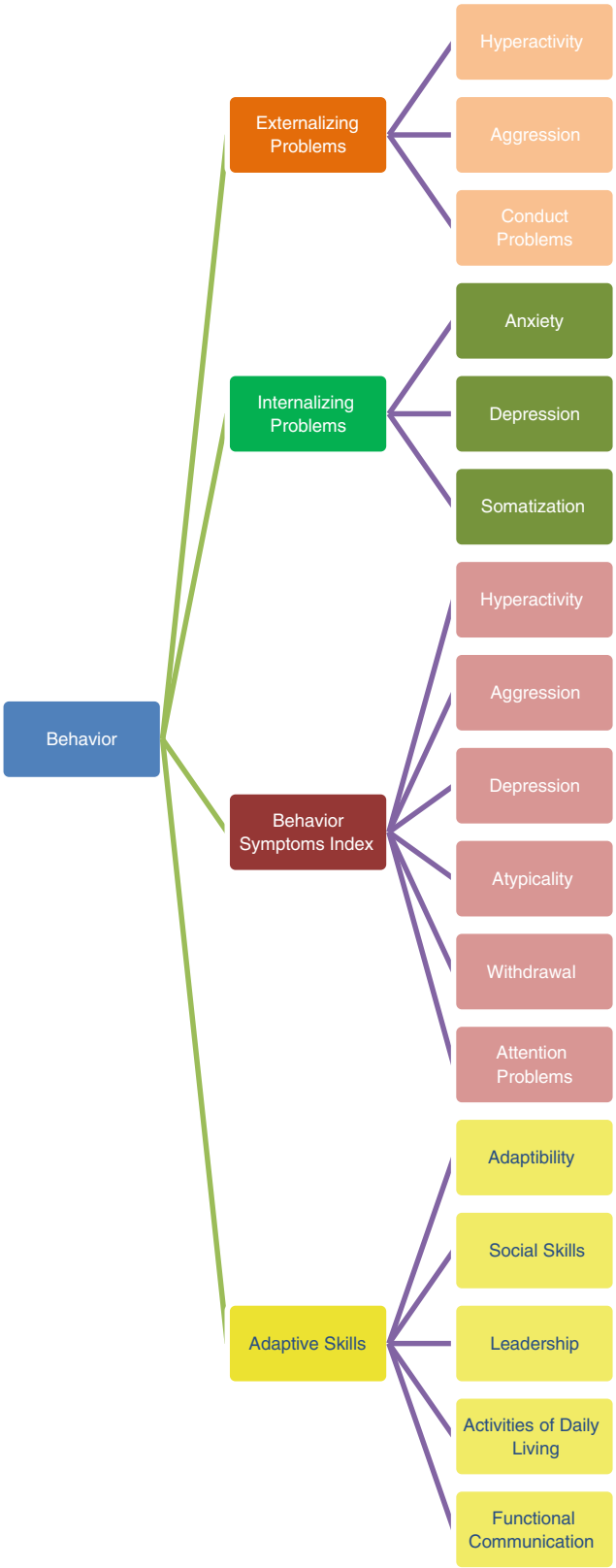

Fig. 2 Domains assessed by the BASC-2

there is more diversity in the outcome. Everyone was either in or had completed high school with the help of adapted or special education classes. One individual had a vocational degree and one was attending college. Interestingly, the majority of individuals on whom we have data are engaged in some form of work, be it voluntary or for pay. A few adults volunteer their time doing work such as: cleaning houses; light yard work; assisting the elderly; and delivering packages around campus. One does work part-time as a hostess and also does janitorial work at three different car and automotive locations.

Behavioral Outcome

Data collected from the BRIEF-A and BASC-2 parent informant reports suggest that difficulties with executive functioning are common in this population (Table 1). More than half have moderate to severe problems with behavior regulation which involves inhibiting emotions, shifting easily from one thing to another without emotional upset, and awareness of how one's behavior impacts others. Surprisingly, none of the Tetrasomy 18p adults were rated by their parents/caregivers as having many problems with controlling their emotions when stressed or upset. Tetrasomy 18p adults were also rated by their parents/caregivers as having moderate to severe difficulties with metacognitive tasks. These tasks include independently initiating, planning and organizing activities, and monitoring progress over time. Problems with working memory were also noted.

Parents and caregivers did not report significant concerns with externalizing behaviors such as aggression or conduct problems, though their ratings did indicate concerns with hyperactivity or over activity. They also report concerns with inattention (Table 2). No concerns with internalizing behaviors such as depression, anxiety, or somatization were reported. In contrast, social concerns were fairly common and included withdrawal from social and peer interactions. According to their parents/caregivers, adults with Tetrasomy 18p frequently have deficits in daily living, social interaction, and pragmatic communication skills. These concerns occurred in about half of the participants.

Ring 18

The Ring 18 group is very small, making it difficult to come to any solid conclusions about the group. It should also be noted that this is a particularly heterogeneous group with individual variability in the content of the ring chromosome in the extent of the chromosome loss for both the p and q arms. Additionally some individuals also have mosaicism for the presence of the ring chromosomes and/or have significant duplicated material within the ring chromosome (Cody et al. 2009). The Ring 18 group included 32 individuals, two of whom are over 18 years old.

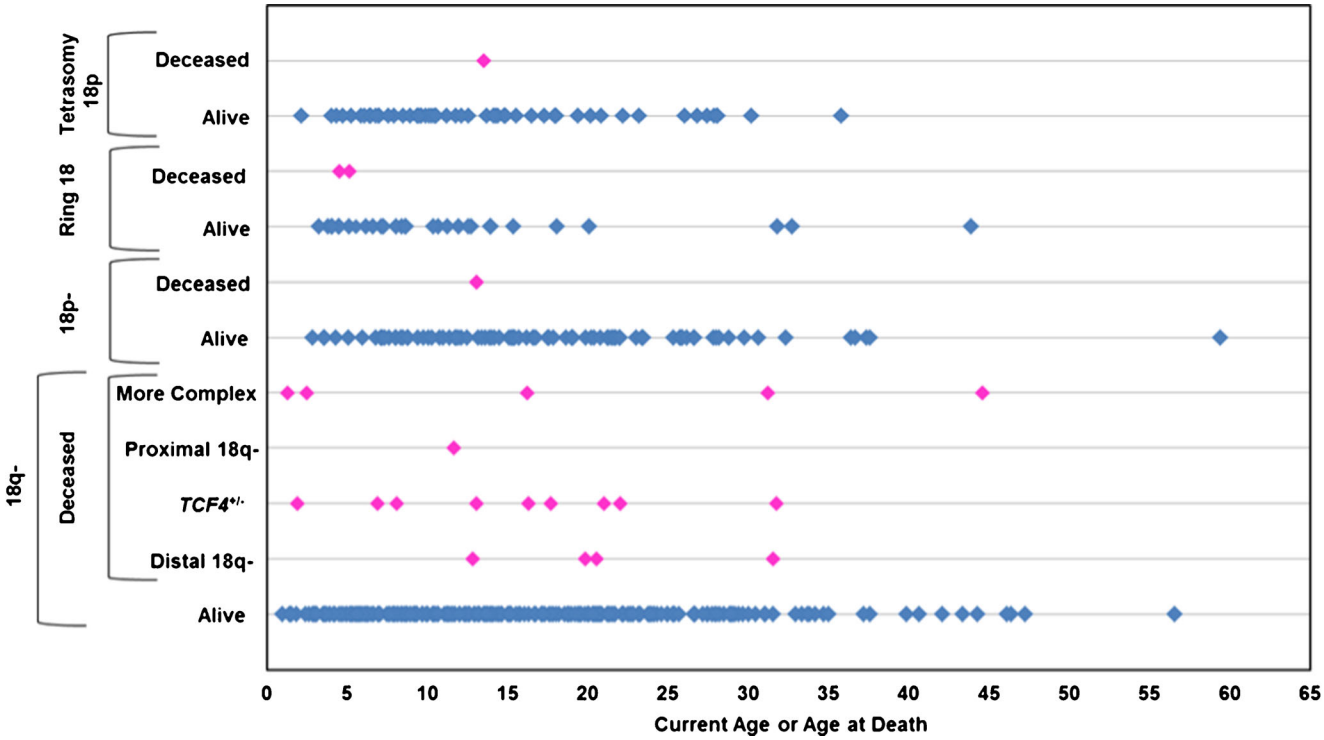

Fig. 3 Current ages and age at death of study participants. Each *diamond* indicates the current age or the age of death for the participants as indicated by their specific chromosome 18 condition

Lifespan

The average age of the Ring 18 population is 11.4 years. Within this group, two have died from major organ failure (Table 4 and Fig. 3). One of these individuals had large duplications of both the p and q arms integrated into the ring chromosome (Cody et al. 2009). This individual had a relatively small deletion of both 18p and 18q, but they also had duplications of most of the remaining p and q arms as well. For all practical purposes this person's genotype and phenotype were more like trisomy 18 for which there is a significantly reduced lifespan.

Table 1 Percentage of individuals in the cohort with behavior that is either at-risk or a significant area of concern from the BRIEF-A, informant report - adults

	Tetrasomy 18p	Ring 18	18p-	18q-
Number of participants	12	2	26	68
Behavioral regulation index	33	0	30	38
Inhibit	58	0	10	26
Shift	58	50	70	51
Emotional control	0	50	30	34
Self-monitoring	50	0	30	26
Metacognition index	75	50	60	44
Initiate	67	0	60	46
Working memory	92	50	45	50
Plan / Organize	58	50	55	46
Task monitor	83	50	70	54
Organization of material	50	0	45	26
Global executive composite	58	50	50	43

Table 2 Percentage of individuals in the cohort for whom this behavior is either at-risk or a significant area of concern from the BASC

	Tetrasomy 18p	Ring 18	18p-	18q-
Number of participants	12	3	23	63
Withdrawal	33	67	39	41
Poorly developed daily living skills	58	33	30	49
Poor leadership skills	42	33	39	41
Poor functional communication	50	33	35	33
High atypicality	50	0	39	25
Poor social skills	33	0	43	33
Hyperactivity	58	0	22	24
Attention problems	42	0	13	16
Depression	0	33	17	21
Anxiety	0	33	13	16
Poor adaptability	0	0	35	19
Somatization	0	0	13	21
Aggression	0	0	13	11
Conduct problems	0	0	4	13

Educational Attainment and Living Situation

Like the group with Tetrasomy 18p, both adults with Ring 18 live with their parents, are not married, and have never had any children (Table 3). Educationally, both have completed high school or high school equivalent. One has attended college for a time. One works part-time as a book room resource assistant in an elementary school. She also does volunteer work at another private school. The other goes to an adult workshop and performs assembly work, part-time, for 30 h a week.

Table 3 Current living situation, marital and parental status, education level, and work situation as reported by study participants

	Tetrasomy 18p	Ring 18	18p-	18q-
Number of participants	14	5	29	103
Living situation				
With parents	8	3	19	59
With spouse / partner	0	0	0	3
Independent	1	0	4	6
With roommates	1	0	2	2
Foster / Respite home	1	0	0	1
Group home	1	0	0	4
Host family	0	0	0	1
Unknown	2	2	4	27
Marital status				
Never married	9	3	23	54
Married	1(engaged)	0	0	3
Separated / Divorced	0	0	0	2
Unknown	4	2	6	44
Parental status				
Live births	0	0	0	3
No children	10	3	23	56
Unknown	4	2	6	44
Highest educational level				
Did not complete high school	0	0	4	12
Attending high school	4	0	2	7
High school graduate (certificate)	4	1	4	9
High school graduate (diploma)	0	1	6	16
High school graduate (unknown)	2	0	1	8
Attending vocational school	0	0	0	4
Attended vocational school (no degree)	0	0	2	3
Vocational school degree	1	0	1	3
Attending college	1	0	1	7
Attended college (no degree)	0	1	1	3
Associate degree	0	0	3	1
Bachelors degree	0	0	0	1
Masters degree	0	0	0	1
Unknown	2	2	4	28
Work (Volunteer, pair, part-time, full-time)				
Yes	7	2	16	37
No	4	1	7	28
Unknown	3	2	6	38

Behavioral Outcome

Regarding the two adults with Ring 18, one parent or caregiver reported problems with behavior regulation (shifting behaviors and emotional control) and concerns with metacognition (working memory, planning and organizing tasks, and monitoring successes and failures) (Table 1). There were no concerns noted on the BRIEF-A for the other adult with Ring 18.

The most common behavioral concern in the Ring 18 group was withdrawal related to avoidance of social and peer interactions; however, as discussed, the small sample size limits the ability to draw conclusions from these data (Table 2).

18p-

The group of individuals with 18p deletions has a great deal of genotypic variability. Approximately half of the people with 18p deletions have breakpoints at the centromere and therefore are hemizygous for the entire p am of chromosome 18. The other half of the 18p- population has smaller deletions with each person having a unique breakpoint (Sebold et al. 2010). There are 91 individuals with 18p deletions in the study cohort, 29 of which are over 18 years of age.

Lifespan

The average age of the 91 individuals with 18p deletions in the study cohort is 17.5 years. Only one individual has died within this group (Table 4 and Fig. 3). This individual had a complex congenital heart abnormality and died due to complications arising from cardiac surgery. Of interest, she also had Goldenhar syndrome, which is not a common feature of 18p deletions but has been described previously (Buffoni et al. 1976).

Educational Attainment and Living Situation

Most of the adults live at home with their parents or guardians; however, a few have moved out and live independently and few and moved in with roommates. No marriages or children have been reported. The majority of our adult 18p- study participants have completed high school and a few have even received associate degrees. Most of the adults who do work are holding part-time jobs. One works in restaurants stocking and cleaning. Another works in an insurance office doing clerical work. One works full-time in sales as a cashier. Lots

Table 4 Cause of death

	Age deceased	Gender	Cause of death	Past medical history*
Tetrasomy 18p	13 years 5 months	F	Sudden heart arrest. One day of history of nausea, vomiting and lethargy. Autopsy: significant dilatation of her colon	Significant constipation; question of seizures; a small VSD that closed on its own
Ring 18	4 years 5 months	F	Lung failure	ASD; seizures; cerebellar stroke; coloboma of Iris; spastic quadriparesis; pulmonary hypertension; respiratory insufficiency; aspiration pneumonia; asthma
	5 years 1 month	F	Had been vomiting prior to death. No acute cause of death	Hydrocephalus; severe hypotonia; poor cough reflex with hypoventilation; history of heart failure
18p-	13 years	F	Brain bleed post cardiac surgery	Goldenhar syndrome; complex congenital heart disease
18q-& complex rearrangements	15 months	F	N/A	Multiple congenital heart defects; hernia repair; intestine malrotations; hydrocephalus; severe sleep apnea
	2 years 6 months	M	Heart complications after heart surgery	Multiple heart surgeries; malrotated bowel; reactive airway disease
	16 years 3 months	M	Kidney and heart failure	Profound developmental delay; mitral and aortic valve insufficiency; bilateral hypoplastic kidneys; chronic renal insufficiency
	31 years	F	N/A	N/A
	45 years	F	Choking due to a recurrent habit of retaining food in her cheeks.	N/A
18q- interstitial proximal	11 years 7 months	M	Seizure complications	Spastic cerebral palsy; epilepsy; aspirating pneumonia; Nissen Fundoplication
TCF4$^{+/-}$	22 months	F	Admitted to the hospital for central apnea. Developed tachycardia	Respiratory distress; central apnea; silent aspirations; failure to thrive; oropharyngeal dysphagia
	6 years 10 months	M	Aspiration (at the time of death had cold/congestion). Admitted to the Hospital for not breathing. Cause of death: aspiration	Reactive airway disease; pneumonia; ASD which was closed spontaneously
	8 years	M	Sepsis	Poor immune system; developed interstitial lung disease and asthma; apnea; obstructed bowels; aspiration secondary to GERD. ASD; seizures; corneal staphyloma (Right)
	13 years	M	Sepsis (developed an infection on his liver which was not able to get controlled and spread to other organs)	Immature lung development as a newborn; cortical blindness; pneumonia very often; silent aspirations; central apnea
	16 years 3 months	F	N/A	Bronchitis always turned into bronchial pneumonia', at about 3 times a year; one lung functions only at 10 % due to scarred tissues from pneumonia; asthma
	17 years 8 months	F	Sudden death. The cause of death was considered "natural causes". Death certificate:" cardiac arrest"	Intra uterine growth retardation; medical records not available after 3 months of age
	20 years 11 months	F	Vomiting; poor feeding tolerance; worsening apneic episodes; adynamic illeus	Recurrent aspiration pneumonia; central apnea; irregular breathing cycles; history of cyclical vomiting; constipation; malrotation of intestine; pulmonary stenosis
	22 years	F	N/A	Pneumonia in multiple times; asthma; alopecia totalis; fused kidneys; trouble with swallowing and controlling secretions
	31 years 8 months	M	N/A	History of seizure; pancreatitis/vomiting attacks

Table 4 (continued)

	Age deceased	Gender	Cause of death	Past medical history*
Distal 18q-	12 years 9 months	M	N/A	Records only at a very young age (2 years old): episodes of apnea; pyloric stenosis; silent aspirations; jejunostomy tube; oropharyngeal dysmotility
	19 years 9 months	M	Sudden death. Autopsy: result of a sudden death	History of heart murmur; history of pulmonary valve stenosis; MRI: Chiari I malformation.
	20 years 6 months	F	Report per mother: unexpectedly	Records available only at a very young age: history of gastroenteritis; failure to thrive
	31 years 6 months	F	Sudden, persistent epileptic event	Meningitis; asthma; mitral insufficiency; history of seizures; periventricular leukomalacia (MRI)

N/A not available

of adults volunteer their time doing things such as: sorting movies at the library; hanging clothes in a thrift store; cleaning a pub; and rotating snack supplies at a local blood bank.

Behavioral Outcome

The most common executive functioning challenge within the adult 18p- cohort included problems with shifting behaviors and monitoring successes and failures (Table 1). Seventy percent of the cohort showed problems in these two areas. Sixty percent showed problems with initiating tasks and 55% had trouble planning and organizing tasks. Only a few had trouble with inhibiting impulses, adjusting emotional responses, and self-monitoring.

The most common behavioral challenge in the adult 18p- group was poor social skills followed by withdrawal, poor leadership skills, as well as high atypicality (Table 2). High atypicality can be defined as having "odd behaviors," and can include issues related to reality testing or autistic-like behaviors. However, these behaviors occurred in less than half of the participants and none of our participants have a major psychiatric diagnosis.

18q-

The 18q- groups is by far the largest, with a total of 306 individuals. It is also the most genotypically diverse. No two unrelated individuals with 18q- have the exact same genotype, as all have unique breakpoints. In addition, some in the 18q- cohort have gains or losses on other chromosomes. Lastly, although the grand majority of participants have deletions distal to position 44 Mb (18q12.1) (distal 18q-), there is a group of ten individuals with interstitial deletions proximal to 44 Mb (proximal 18q-); with a small region of the chromosome between these two groups that is not hemizygous in anyone. Approximately one-third of this 18q- cohort is over 18 years old.

Lifespan

The mean age of the individuals in our cohort of 306 individuals with 18q deletions is 16.3 years. The deceased individuals in this group have been subdivided into additional genotype-based groups (Table 4 and Fig. 3). There were 25 individuals with a loss or gain of chromosomal material from another chromosome arm. Five of 25 (20 %) are deceased. One person with proximal 18q (10 %) is deceased. The distal 18q- group consists of those individuals with deletions within the distal 31 Mb of 18q (q21.1–q23). This large group was subdivided into two groups; those with deletions including the *TCF4* gene, which is known to be associated with Pitt-Hopkins syndrome, and those with 2 copies of *TCF4*. The group whose deletion encompassed *TCF4* included 36 individuals, nine of whom have died (25 %). The group with distal

18q deletions with two copies of *TCF4* gene includes 235 individuals and 4 (1.7 %) have died.

Educational Outcome and Living Situation

Most of the adults live at home with their parents or guardians; however, a few have moved out and live either with their spouses, independently, with a roommate, or in a group home. There are a few marriages and divorces within this population. A few of our female adult participants have given birth to both affected and non-affected children. The education statuses of our 18q- vary considerable. While some have not completed high school, the vast majority are either currently still high school students or have completed high school. Several have gone on to attend and complete both vocational school and college.

Although very few work full-time, many work either part-time or do volunteer work. Some of the part-time jobs that our 18q- adults hold are: doing administrative work at a local university; straightening shelves up at a large discount store chain; keeping food bar clean and simple cooking for a restaurant chain; greeting customers and bagging groceries at a grocery store; working as a skilled worker in a small goods factory; working as a preschool teacher assistant and working as a dietary aide in a kitchen in a nursing home making sandwiches and salads and assisting the cook. A few volunteer jobs that are being held are: child care assistant at a local YMCA; organizing and prepping materials one afternoon a week at a glass art studio; and putting away food at a local food pantry. Some of the full-time jobs include: working for the past 9 years as a cashier at a department store and designing website business cards for the pharmaceutical medical industries

Behavioral Outcome

Although executive functioning problems are found among the 18q- population, only half of the participants report problems with shifting behaviors, working memory, and monitoring successes and failures (Table 1). One in four have problems with inhibiting control, self monitoring, and organization.

Participants with 18q deletions displayed behavior problems in fewer than half of the cohort (Table 2). The main challenges were poorly developed daily living skills, poor leadership skills, and withdrawal. Although aggression and conduct problems are commonly mentioned in case reports of people with 18q deletions (Jones 1997), these were not common findings in this group of adults.

Discussion

When meeting a family with a new diagnosis, one of the major challenges a genetic counselor faces is to give a family an idea of what to expect in concrete, understandable terms. Of course, the counselor can discuss the potential range of mental impairment, explain that there might be behavioral issues of some kind, and review the concepts of incomplete penetrance and variable expressivity. However, it is hard for many families to imagine the implications of this information for their child's future. As one of our patients stated, "I understand that you expect borderline to mild mental impairment for my son. What I don't understand is what that *looks* like. Will he go to school? Will he be able to live on his own? Will he get married? Can he hold a job? If he's healthy now, can I expect him to live a long life? Or will something pop up later?" For many conditions, these questions have been answered. However, in the case of chromosome 18 conditions, data on the long-term outcome is sparse. The goal of this paper is to give genetic counselors the tools to describe, in relatable terms, the implications of a chromosome 18 condition.

The Chromosome 18 Clinical Research Center has been enrolling individuals with chromosome 18 abnormalities for over 20 years. As we have enrolled older individuals and as the younger members of our cohort have grown into young adulthood, we are able to address the questions regarding long-term outcome of individuals with one of these rare chromosome abnormalities. We have accumulated a large amount of data from medical and educational records, surveys, our own clinical and psychological evaluations, as well as high resolution molecular analysis of chromosome content on over 500 affected individuals. Consequently we are able to learn about the behavioral, educational, and life courses as these individuals reach adulthood.

One of the primary concerns of a family with a new diagnosis of a chromosome 18 condition is lifespan. Based on the data presented here, 18q-, 18p-, Ring 18, and Tetrasomy 18p do not seem to confer a dramatically reduced lifespan. The exception seems to be individuals with distal 18q- whose deletions include *TCF4* as well as individuals with additional chromosomal imbalances (Table 4). In the group with distal 18q- with deletions inclusive of *TCF4* and those with more complex rearrangement, 25 % and 20 % of our cohort has died. This is in sharp contrast to the remainder of the distal 18q- group in which 1.7 % have died. Of course, since the mean age in each of our different chromosome 18 condition cohorts is between 11 and 18 years, these are young groups from which to draw definite longevity conclusions. However, it is clear that the vast majority of individuals with these conditions live at least into the teenage years with little evidence to suggest an early death in the majority of individuals.

We also present data regarding the living situation and educational status of our population. As may be expected, the majority of the individuals in each condition group still live at home with their parents or caregivers. This is perhaps not surprising given that many individuals without chromosome changes live with their parents in their late teens and early twenties. That being said, a significant minority of our

patient population have been able to move out of their families' homes and are either living independently, with a roommate, or in a supervised setting. In addition, the grand majority have at least completed high school, and many are pursuing post-secondary school education. Of course, many are still in the public school system or are current students in a higher education program. This means that their current highest level of education may not be their ultimate highest level of education. Lastly, more than half of the individuals that we have data for are working, either in a paid position or as a volunteer.

Data regarding executive function and behavioral issues are also presented. These data were collected using validated scales and measures. Below, we provide a description of some of the typical problems that individuals with these conditions may encounter, based on the data presented in this manuscript.

Tetrasomy 18p Adults with Tetrasomy 18p will often have trouble initiating activities and/or tasks. They frequently have difficulty making plans and keeping track of time. Retaining information may be difficult for them, and keeping track of their material belongings can be a challenge. They may need to be reminded to groom themselves. Although the majority of the adults are verbal, they may have trouble getting their point across using spoken language. They may not realize how their behavior affects others, and, in fact, their behavior may seem odd to their peers. It might be difficult for these individuals to switch from one activity to another. Hyperactivity and impulsivity are also frequently reported in adults with Tetrasomy 18p.

Ring 18 The few adults with Ring 18 in our study reported having problems transitioning from one activity to another. They also have trouble recognizing due dates of projects, getting to work on time, bringing the appropriate materials to class, and adapting to changes in schedule or routine. Beginning a new task may be difficult. Behaviorally, they have poor social skills, so interacting with their peers may prove to be challenging.

18p- Similar to adults with Tetrasomy 18p, adults with 18p- will have trouble initiating activities and/or tasks. However, in contrast to the adults with Tetrasomy 18p, adults with 18p- tend to have higher cognitive ability. They also often have difficulty making plans and keeping track of time. Retaining information may be difficult for them, and they may lose their belongings. Switching from one activity to another can also be difficult. Behaviorally, they frequently have poor social skills which are essential for interacting effectively with peers and other adults at home, school, or in a workplace.

18q- Adults with 18q- often have trouble moving from one task to another. They will have trouble retaining information. Managing daily and future tasks will prove challenging for them. Some will have trouble starting a task and coming up with problem solving strategies for themselves. Behaviorally, you may see them having trouble completing basic daily living skills tasks, such as brushing their teeth and combing hair. Many are withdrawn and will try to avoid social situations. Their leadership skills are weak, but this might be attributable to their withdrawn nature.

Additionally, the groups reported here have a significant amount of genetic heterogeneity, with the exception of Tetrasomy 18p. Of the 56 individuals with Tetrasomy 18p genotyped, all but 2 have the exact same duplication of the entire p arm (Sebold et al. 2010). In the group with 18p deletion, approximately half of the individuals have deletions of the entire p arm and the other half has unique small deletions (Schaub et al. 2002) (Sebold et al. 2010). In the group of 306 with 18q deletions every unrelated individual had a different 18q deletion (Heard et al. 2009) ranging in size from 0.5 to 30 Mb of DNA. Even more variable are the group with Ring 18. They not only have genetic heterogeneity with regard to their deletions of both the p and q arms, but many are also mosaic for several derivative cell lines as well (Cody et al. 2009). However, despite these limitations, these data are critical for the purposes of providing anticipatory guidance to families with a diagnosis of a chromosome 18 condition.

We appreciate that this information will change with time as the age of the cohort increases and the interventions and behavioral interventions improve. However, these data can serve as a baseline for the purpose of counseling families with a diagnosis of a chromosome 18 condition.

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Conflict of Interest Bridgette Soileau, Minire Hasi, Courtney Sebold, Annice Hill, Louise O'Donnell, Daniel E. Hale, and Jannine D. Cody declare that they have no conflict of interest.

Human Studies and Informed Consent All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (instutional and national) and with the Helsinki Declaration of 1975, as revised in 2000 (5). Additional Informed consent was obtained from all patients for which identifying information is included in this article.

Animal Studies No animal studies were carried out by the authors for this article.

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