I, Ashley Brazil, hereby submit this original work as part of the requirements for the degree of Master of Science in Genetic Counseling.

It is entitled:
Delineation of 1p36 Deletion Syndrome in Adolescents and Adults

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Delineation of 1p36 Deletion Syndrome in Adolescents and Adults

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Abstract

Background: 1p36 deletion syndrome, also known as monosomy 1p36, is the most common terminal deletion syndrome, with an incidence of 1/5,000 – 1/10,000. Current literature describes 1p36 deletion syndrome in infancy through adulthood; however, the progression of the disease is unclear. The purpose of this study was to further describe the progression of 1p36 deletion syndrome in adolescents and adults. Methods: A 133 item questionnaire was developed to assess baseline values of medical problems and developmental and functional problems of individuals aged 12 or older with 1p36 deletion syndrome, and participants of the survey were primary caregivers of the individuals with 1p36 deletion syndrome. Questionnaires were distributed electronically through the 1p36 Deletion Support & Awareness Group, UNIQUE, and Chromosome Disorder Outreach, Inc., and via mail through the Cincinnati Children’s Hospital Medical Center cohort. Results: 38 surveys (n=11 males, n=29 females) were completed, and two additional surveys (1 male, 1 female) were mostly completed and were thus included in analysis. Among the medical problems reported, 78% of individuals had a history of seizures, with 42% of these individuals currently having seizures; additionally, 65% of individuals were currently hypotonic. 35% of individuals were reported to have strabismus, and 38% had myopia. Hearing loss, acquired cardiovascular complications, and no occurrences of cancer were also reported. Among developmental and functional problems, 43% of patients were able to talk, and the majority (71%) could use over 100 words; additionally 62% of individuals used sign language as their sole form of communication. 82% of males and 79% of females with 1p36 deletion syndrome were reported to walk independently. Individuals were also reported to receive the majority of their nutrition orally, have some speech problem diagnoses, some pubertal development, and behavioral concerns. Conclusions: We have corroborated some of the same medical concerns in adolescents and adults with 1p36 deletion syndrome, yet we also have identified that as individuals with 1p36 deletion syndrome age, they are able to achieve many milestones including walking and talking to a greater degree than is reflected in the previous studies. Constant monitoring for lifelong health concerns such as seizures is imperative; however, the long-term prognosis for these patients is promising. We show with proper medical care and support, individuals with 1p36 deletion syndrome appear to make significant developmental progress as well as achieve a level of independence.

Key Words: 1p36 deletion syndrome, monosomy 1p36, progression, chromosome 1 deletion, 1pter deletion, 1p36 – 1pter deletion
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Introduction

Recent research indicates that 1p36 deletion syndrome, also known as monosomy 1p36, is the most common terminal deletion syndrome, with an incidence of 1/5,000 – 1/10,000 [1-3]. Heilstedt et al (2003) reported most breakpoints occur 4.0 – 4.5 Mb from the telomere, and are from the maternally-derived chromosome [3]. The most common traits associated with 1p36 deletion syndrome include characteristic craniofacial features, gastrointestinal anomalies/problems, seizures, vision and hearing problems, cardiovascular complications, speech and communication problems, feeding difficulties in infancy, cognitive impairment, limited mobility, and behavioral problems. Many of the features vary in severity from person to person [4], and most of them can be managed with some assistance. Many studies (Battaglia et al, Gajecka et al, Heilstedt et al (2003), UNIQUE) describe the overall clinical features, both medical and non-medical, of people with this syndrome from infancy to late childhood; however, information regarding the specific medical and functional problems adolescents and adults have with 1p36 deletion syndrome is scarce. The purpose of this report is to begin to describe the natural progression of 1p36 deletion syndrome, which can be used to further additional research opportunities and address families’ and clinicians’ questions.

Methods

Participants and Procedures

The study is a cross-sectional descriptive study of a cohort of adolescents and adults with 1p36 deletion syndrome, assessing their medical problems and developmental and functional problems. The target populations are adolescents, aged 12 years old and up, and adults with 1p36 deletion syndrome; however, the survey was filled out by primary caregivers of the adolescents and adults with 1p36 deletion syndrome. Individuals with the deletion syndrome must have received genetic testing
(karyotype, fluorescence in situ hybridization [FISH] analysis, microarray) to confirm a diagnosis of 1p36 deletion syndrome (or a 1p36 – 1pter deletion), and must be at least 12 years old for inclusion. Families with adolescents and adults with 1p36 deletion syndrome were identified through e-mail by information liaisons for three online support groups, {1p36 Deletion Support & Awareness Group, UNIQUE, and Chromosome Disorder Outreach, Inc.}, as well as posting on the 1p36 Deletion Support & Awareness Homepage, and locally through Cincinnati Children’s Hospital (about 6-8 adolescents and adults with 1p36 deletion syndrome).

Survey Development

A 133 item questionnaire was developed to assess baseline values of medical problems and developmental and functional problems of individuals aged 12 or older with 1p36 deletion syndrome. The survey contained 72 close-ended questions and 61 open-ended questions (see Appendix). The questionnaire was developed based on a thorough literature review of 1p36 deletion syndrome documented in case reports and characterizations of patients with 1p36 deletion syndrome, mostly under the age of 12, as well as anticipated medical problems adolescents and adults may experience, such as cancer diagnoses. The survey inquired about the progression of medical problems, such as progressive hearing and vision loss, or progressive of heart disease, and treatments for identified problems. The age of onset was documented for each medical problem shared.

Survey Measures

The survey was separated into 12 sections of questions: demographic, medical history, central nervous system, hearing and vision, cardiovascular, physical abnormality, cancer, puberty, mobility, feeding and toileting, speech and communication, and behavioral. Questions used a combination of open and close-ended questions; skip-logic was utilized so participants did not have to answer questions
that were not applicable to the person under their care. RedCap®, an electronic data collection tool, was utilized for the survey construction, distribution, and analysis of surveys.

An e-mail was sent to eligible participants including a cover letter detailing the purpose of the research and a URL to access the online survey (see Appendix). One month after the initial disbursement of the survey, another e-mail was sent to the same recipients, as a reminder to complete the survey.

**Data Analysis**

The survey was conducted between September 2012 and January 2012. All survey responses (n=50) were collected electronically using REDCap®, an online system for surveys and databases. The data was sorted and prepared for analysis by the REDCap® software. Questionnaires left blank (n=7) and participants who indicated the person with 1p36 deletion syndrome was not aged 12 years or older (n=1) were excluded and removed from the final analysis. Two additional questionnaires only had demographic information filled out and were subsequently excluded as well. Two more questionnaires completed all but the behavioral questions; these were included in the final analysis for all sections, except behavioral.

Summary statistics were calculated using the SAS system (version 9.3 for Windows). For categorical variables, these included counts and frequencies, and continuous variables included means and standard deviations. Differences among subgroups were tested for statistical significance using the appropriate method: either a chi-square test or t-test. Differences among treatment arms were not tested, so power and sample size were not relevant factors.
Results

Forty questionnaires meeting inclusion and exclusion criteria were included in the analysis of all sections except behavioral; 2 were excluded from the behavioral section due to blank surveys. So 38 surveys were included in the analysis of behavioral questions. Eleven individuals with 1p36 deletion syndrome were male (27.5%) and 29 were female (72.5%). For males, ages ranged from 13 - 34 years old, with an average age of 19.2 years old; for females, ages ranged from 12 – 46 years old, with a mean age of 19.7 years old. No statistical significance was found between the ages of males and females (Chi square, P=0.8738). Approximately 18% (n=7) were diagnosed using microarray analyses, 25% (n=10) were diagnosed by karyotype, and 58% (n=23) were diagnosed by FISH. Approximately 70% of respondents (n=28) claimed residency in the United States, and 30% (n=12) lived outside of the United States (Australia, New Zealand, and the UK).

Medical History

Approximately 27% of males (n=3) and 17% of females (n=5) reported gastroesophageal reflux as a problem within the past month, 40% of males and females (n=3 and n=13, respectively) reported constipation as a problem within the past month. Ulcers, abdominal pain, and diarrhea were less commonly reported problems, reported at a frequency of 5%, 20%, and 25%, respectively. One female with 1p36 deletion syndrome was born with gastroschisis and an imperforate anus; another female was diagnosed with celiac disease at age 14. In addition, 3 males (27%) and 6 females out of 28 respondents (21%) reported having had a kidney infection.

Central Nervous System

Approximately 78% of respondents (n=40 total responses, n=7 males, n=24 females) reported a history of seizures, with 21 participants reporting an onset of seizures within the first 6 months of life.
One male and one female patient were reported to have an onset of seizures over the age of 15. When asked if these individuals still have the seizures, 4 out of the 7 males responded no (57%) and 14 out of the 24 females responded no (58%). Approximately 55% of males (n=6) and 69% of females (n=20), totaling 65%, were reported with hypotonia. Three males were reported to currently have spasticity, while two males were reported to have contractures. Six females were reported to currently have spasticity (21%), and 8 out of 26 (31%) females had contractures. Five males (45%) reported no physical brain abnormalities; two males (18%) were reported with hydrocephaly, and one male was reported with microcephaly diagnosed at age 13 (three males did not respond to the question).

Eighteen females (62%) were reported to have no brain abnormalities; one female was reported to have decreased myelination, one female was described with a benign arachnoid cyst, and another female was reported with enlarged ventricles in utero. Seven females did not respond to the question.

Vision and Hearing

The majority (55%) of participants reported no hearing problems (n=5 males, n=17 females). Two males and 5 females (n=39) were reported with conductive hearing loss (18%), 13% (n=5) of individuals were reported with sensorineural hearing loss, and 8% (n=3) reported mixed hearing loss.

Approximately 73% of males (n=8) and 83% of females (n=24) were reported with vision problems. Three males (27%) and 11 females (38%) with 1p36 deletion syndrome were described to have strabismus, and 6 males (55%) and 9 females (31%) were reported with myopia. It should be noted that the categories were not mutually exclusive; thus the participants could select all the diagnoses/options that were applicable to the person with 1p36 deletion syndrome. Hypermetropia was reported less commonly; 1 male and 3 females were described to have this.
Cardiovascular

With respect to heart defects, 64% of males (n=7) and 48% of females (n=14) were reported with congenital heart defects. Among the responses, ventricular septal defects (VSDs), and patent ductus arteriosus (PDAs) were the most common (n=7 and n=6 respectively). Three males (27%) and 5 females (17%) were reported with an acquired heart disease. One male was reported with a new “hole” (diagnosed at age 13) in his heart that resolved on its own, and another male was reported with cardiomyopathy diagnosed at age 24 that has improved with medication, but is currently still a problem. The last male was diagnosed with cardiomyopathy at age 12, has been treated with medication, but his cardiomyopathy has worsened over time (he was 25 at the time of the survey). One female also was described to have a new hole in her heart (diagnosed at age 13), and another was reported to have a dilated aortic and pulmonary root diagnosed at age 5; both of these acquired conditions have improved over time. One female was reported to have “problems” with her left ventricle (diagnosed at age 13), with no change in her condition over time, and another was diagnosed with cardiomyopathy at age 16, which has worsened over time. The last female was diagnosed with unspecified congestive heart failure at 4 months of life.

Physical Development

Using Tanner Stage as a reference, 2 males (18%) were reported to be in stage 2 at the age of 16 and 25, 1 male (9%) was reported to be in none of the above at the age of 13, and 8 males (73%) were reported to be in stage 5 at an average age of 12. The average age of onset of puberty was 12.5 years old, and the range was 8 – 16 years old. Of the females, 1 out of 28 (4%) was reported to be in none of the stages by age 12, three of 28 (11%) were reported to be in stage 3, 6 of 28 (21%) were reported to be in stage 4, and 18 of 28 (64%) were reported to be in stage 5. The average age of onset of puberty was 11 years old, while the range was from 6 – 16 years old. The average age of onset of menses for
females was 11.3 years old, with 7 out of 20 responses noting excessive bleeding during menstruation. One participant noted the female under their care would menstruate for weeks at a time. It should be noted that five females were prescribed medication to cease menstruation, and one underwent a uterine ablation. When asked about atypical pubertal development, one male was reported to have early onset of pubic hair, two males with inverted penises and small genitalia, one with breast tissue development, and one with a strangulated testicle that was subsequently removed. Two females were reported to have early development of breast tissue, and two females reported precocious puberty at ages 6 and 8.

Cancer

No cancers or tumors were reported among any of the participants responding on behalf of the individuals with 1p36 deletion syndrome (0%, 0 out of 40).

Speech and Communication

Approximately 43% of participants (17 participants; 4 males (36%) and 13 females of 28 (46%)) are able to talk, with 71% of these using over 100 words. 1 female spoke fewer than 10 words, while 2 people (1 male and 1 female) spoke between 11 – 50 words, and 2 females spoke between 51 – 100 words. All but one of the individuals reported with the ability to speak were reported to speak in sentences. Approximately 75% of participants (n=30) were able to imitate sounds, and 53% (n=21) utilize sign language as an alternative form of communication. It should be noted that questions asking about verbal speech and sign language were not mutually exclusive; therefore, participants had the opportunity to answer both if the person with 1p36 deletion syndrome could both speak and use sign language as a means of communication. However, only 8 out of the 21 respondents who utilized sign language as a method of communication also were able to verbally speak; thus, 62% of individuals who used sign language (13 out of 21) did so as their sole form of communication. Four males (36%) and 12
females of 28 (43%) were diagnosed with a specific speech problem; apraxia (or a form of apraxia ranging from "suggested" to severe) was described in 8 cases, while other responses included articulation problems, dyspraxia, and aphasia.

**Feeding and Toileting**

When asked if individuals with 1p36 deletion syndrome ever needed to be fed through a tube (either G-tube or NG-tube), 73% of males (n=8) and 79% of females (n=23) never needed to be fed with a tube (total 78%). Only 3 males (27%) were reported to be fed through a G-tube in the past, and 2 of these males (18%) were currently being fed through a G-tube; 5 females (17%) were reported to be fed through a G-tube in the past and 1 (3%) was fed through a NG-tube in the past; currently only 2 females (7%) were being fed through a G-tube. Thus, currently, 81% of males (n=9) and 90% of females (n=26) were completely orally fed (total 88%). Approximately 95% of all individuals with 1p36 deletion syndrome were receiving the majority of their nutrition orally (91% of males, n=10, and 97% of females, n=28). All 10 males with 1p36 deletion syndrome (one participant did not respond) and 28 out of 28 females with 1p36 deletion syndrome (one participant did not respond) were reported to be able to hold a cup or a spoon. Approximately 90% of males (9 out of 10 responses) and 85% of females (23 out of 27 responses) also were reported to be able to feed themselves (total 86%, 32 out of 37 responses).

When asked about potty training, participants reported that 45% of males (n=5) and 41% of females (n=12) were trained for both stool and urine, with a range of training 2 -10 years old and an average of 5.7 years old for the males, and a range of training 3 – 11 years old and an average of 5 years old for females. One male (9%) was reported to be trained for only urine at the age of 12, and 2 females (7%) were reported to be trained for only urine at the age of 8. By report 45% of males (n=5) and 48% of females (n=14) were not potty trained (one participant for the female group did not respond). Accidents were noted to occur anywhere from 1-2 times per week, to a few times a month; one
participant described the male with 1p36 deletion syndrome to have accidents more frequently when he gets upset.

**Mobility**

By report, 91% of males (n=10) and 100% of females (n=29) with 1p36 deletion syndrome were able to sit independently (total 98%), with an average age of onset for males at age 1.5, and for females at age 2.2. Approximately 82% of males (n=9) and 79% of females (n=23) were reported to walk independently (total 80%), with an average age of onset for males at age 3.4, and for females at age 3.7. Some individuals were reported to use assistive equipment such as walking frames, leg braces, and orthotics. When asked about the use of a wheelchair, 70% of males (n=7 out of 10) and 62% of females (n=18) did not use a wheelchair to help with mobility (total 64%). Two males and 10 females were reported to use a manual wheelchair. There were no responses for 2 males and 1 female to the question.

**Behavioral**

All individuals with 1p36 deletion syndrome (n=38) were reported to be able to smile and differentiate between familiar faces and strangers. When asked about behavioral trends within the past year, 80% of males (n=8) and 61% of females (n=17) were reported to seek attention very often, and 79% of individuals were reported to seem happy/content very often or often. 26% became agitated somewhat often and two males (20%) and were reported to become agitated very often, while 26% became agitated somewhat often, and 24% of individuals became agitated often. Approximately 50% of females (n=14) and 20% of males (n=2) were reported to become angry very often, while 29% of females (n=8) and 10% of males (n=1) were described to become angry somewhat often. Unexplained fussiness (rarely) was reported in 32% of individuals, frequent unexplained fussiness was reported in 29% of individuals, and 21% were reported to experience unexplained fussiness somewhat often. Self-injurious
behavior was never exhibited in 34% of the individuals, while 29% of individuals with 1p36 deletion syndrome were described to exhibit self-injurious behavior very often.

Discussion

Medical History

Gastroesophageal reflux and constipation are the two most common GI difficulties people with 1p36 deletion syndrome report. In a descriptive survey conducted by UNIQUE (2011), which asked 74 family members of an individual with 1p36 deletion syndrome about the individual’s medical and developmental problems/delays, about 70% of families reported gastroesophageal reflux as a main problem in babies with 1p36 deletion syndrome, and 61% of families reported constipation as another central problem in babies and children [4]. Gajecka et al (2007) found that 56% (23/41) people with the deletion syndrome examined hadesophageal reflux, and 28 out of 43 individuals examined reported constipation as a problem (65%) [5]. Other gastrointestinal problems included general discomfort, ulcers, and hiatal hernia [5, 6].

Gastroesophageal reflux and constipation were both reported much less commonly among patients in our study (total 20% and 40%, respectively). Gastroesophageal reflux is typically more frequently associated with infancy and childhood; here we show that it is possible gastroesophageal reflux is not a prominent medical problem in adolescents and adults with 1p36 deletion syndrome.

Previously reported renal abnormalities include unilateral renal pelvis with hydrenephrosis of the upper pole, kidney ectopia with right kidney cyst, and unilateral pelvic ectasia, kidney reflux, kidney stones, and calcium accumulation in one kidney [4, 6]. Data collected through our study illustrate that females with 1p36 deletion syndrome were reported more commonly to have had recent kidney
infections in their adolescence and adulthood; this may be due to pubertal onset or other hormonal factors.

Central Nervous System

Seizures are a commonly reported problem among patients with 1p36 deletion syndrome, with a variable onset from infancy to later in childhood. Studies report seizures in 50% - 79% of individuals with 1p36 deletion syndrome [4, 5, 7], and Knight-Jones et al (2000) described four case reports, all of whom experienced seizures with an age of onset ranging from three months to two years old [8]. Infantile spasms also account for about 20% of seizures among people with 1p36 deletion syndrome [1]. Congenital brain malformations may also be a problem for people with 1p36 deletion syndrome. Some documented abnormalities include polymicrogia, leukoencephalopathy, generalized atrophy, and prominent ventricles [5].

The history of seizures in our population of people with 1p36 deletion is in concordance with previously published literature; however, we document the onset of seizures in late adolescence/early adulthood in two of our cases. It also appeared as these individuals aged, seizures may decrease in frequency or stop in many patients. This may be due to finding an appropriate balance of medication or proper treatment, or the individuals may have outgrown them as well. The majority of males and females with 1p36 deletion syndrome also were reported to currently have hypotonia; this feature did not appear to decrease in frequency with aging. This had not been previously studied in aging individuals with 1p36 deletion syndrome. Although the seizures appear to lessen over time, individuals with 1p36 deletion syndrome remain at a high risk for neurologic problems. They may benefit from physical therapy services to assist with hypotonia.
Vision and Hearing

Strabismus is present in about 30% - 50% of patients with 1p36 deletion syndrome currently documented in the literature [3, 4, 6, 7]; however, it has been reported in up to 67% of a studied population [5]. Hypermetropia may range from 41% - 67% [3, 5], and myopia may have up to a 40% prevalence among people with 1p36 deletion syndrome [5]. Hearing loss also has been documented to affect up to two-thirds of people with the deletion syndrome [4]. Heilstedt et al (2003) reported general hearing loss in their cohort of up to 82% [3]; Gajecka et al (2007) reported a 46% prevalence of conductive hearing loss, and a 58% prevalence of sensorineural hearing loss among the participants in their cohort [5].

Within our results, over 70% of males and over 80% of females with 1p36 deletion syndrome were reported to have vision problems, with strabismus and myopia being the most common, but falling within the 30% - 50% range as previously reported. However, hearing loss was not reported in our study as frequently as it was in the literature. This may be due to frequent otitis media as children, which they have now outgrown, or an over-estimate from previous literature. Routine ophthalmologic and audiology exams should still be performed.

Cardiovascular

Complications within the cardiovascular system are prevalent among people studied with 1p36 deletion syndrome (aged newborn to 24 years old). Reported estimates of cardiomyopathy range from 23% - 31% [3, 5, 6], and is reported in numerous case studies [9]. Congenital heart defects have been documented in up to 75% of individuals with 1p36 deletion syndrome [5, 6]; however, Shapira et al (1997) reported only 17% participants with a congenital heart defect [5-7]. Anomalies from fetal heart structures, such as patent ductus arteriosus and patent foramen ovale, also may persist [5].
Results from our study indicate that there is a higher prevalence of congenital heart defects in patients with 1p36 deletion syndrome; however, the majority of the congenital heart defects do not persist into adulthood. However, new occurrences of heart disease had occurred after infancy, specifically cardiomypathy (reported in three individuals). In addition, we know of one male with 1p36 deletion syndrome who was diagnosed with cardiomyopathy at age 21 from the Cincinnati Children's Hospital cohort; however, he died at the age of 23 from respiratory failure/sepsis. Consultation with cardiology should occur once every 2-3 years for a newly onset cardiac disease in the individual with 1p36 deletion syndrome.

Physical Development

Little literature describing the course of puberty in people with 1p36 deletion syndrome exists. Shapira et al (1997) documented 3 out of 4 people with 1p36 syndrome entered into reported precocious puberty, two of whom were females aged 10 and 11 years old, and began menses at 10 years old [7]. Families with someone who has 1p36 deletion syndrome belonging to UNIQUE report puberty among girls occurred from 9-11 years of age [4]. However, a delay in puberty may be true of young men; Knight-Jones et al (2000) reported a case of a male who did not show signs of puberty at 17 years of age [8].

The results of our study show varying degrees of an onset or delay of puberty in both males and females. Two males were reportedly delayed in puberty and in stage 2 of the Tanner Stages at ages 16 and 25. However, the majority of males were reported to be in stage 5 of puberty, with one male reaching stage 5 at the age of 8. For females, the average age of onset of puberty was typical for females, but the range was 6 – 16 years old; two females at the ages of 6 and 8 entered into precocious puberty. Some males were also reported to have malformations associated with their genitalia, while quite a few females with 1p36 deletion syndrome were reported to have experienced excessive
menstrual bleeding. Our results indicate that the onset of puberty is quite variable and difficult to predict; however, future studies should try and illuminate the course of puberty and complications from pubertal onset in individuals with 1p36 deletion syndrome.

Cancer

Deletions of the 1p36 region have been documented in various tumor tissues, including neuroblastoma, prostate cancer, lung cancer, ovarian cancer, and non-Hodgkin lymphoma [3]. Neuroblastoma is one cancer more commonly associated with a deletion involving 1p36. White et al (1995) reported 26% of primary neuroblastoma tumors with deletion of 1p36[10]. Two case reports link neuroblastoma and children with 1p36 deletion syndrome as well: one described a deletion of D1S47 locus, bound distally by the D1Z2 gene and proximally by the APNH gene [11], and the other a deletion of a possible neuroblastoma suppressor gene [12]. However, White et al proposed four candidate genes in the 1p36.2–1p36.3 region: DAN, ID3, (heir-1), CDC2L1 (p58), and TNFR2 that are linked to neuroblastoma.

No cancers or tumors were reported among any of the participants responding on behalf of the individuals with 1p36 deletion syndrome (0%, 0 out of 40); however, this does not establish a low risk for developing cancer among these individuals, and physicians caring for these patients should be aware of a potentially increased risk for developing cancer.

Speech and Communication

Delays in speech development are almost universal among patients with 1p36 deletion syndrome, though they vary in severity [4, 5]. Current literature indicates children and adolescents may be able to form first word associations, or understand and speak a few isolated words, yet others may be completely non-verbal their whole lives [3, 5, 6, 8]. Only two individuals with 1p36 deletion syndrome
have been reported to have complex speech abilities [3]. The findings from our study greatly contrast previous assumptions.

Almost half of males and females with 1p36 deletion syndrome are able to speak, with over 70% of these individuals using over 100 words. However, verbal communication is not the only way these individuals are able to communicate; 21 individuals with 1p36 deletion syndrome utilized sign language, and 62% of these 21 used it as their sole form of communication. We were unable to characterize the number of words or sentences patients used during sign language; this is an area that may be studied in future research. Thus, patients with this deletion syndrome are able to communicate over time, and interventions to maximize communication should be offered to these individuals. We also looked at diagnosed speech problems which no study had previously done: over 40% were reported with a specific speech problem (i.e.: apraxia).

Feeding and Toileting

Babies with 1p36 deletion often have difficulty feeding during the first year of life. Approximately 47% - 77% of infants may have problems feeding when cleft lip/palate is not present [3, 5, 7]. Outcomes of feeding have not been well documented. We found that most individuals never needed to be fed through a G-tube or NG-tube. Approximately 88% were currently receiving all of their nutrition orally, and 86% were able to feed themselves. About half of individuals were reported to be able to be toilet trained, though it varied if it was for urine, stool, or both. While toilet training is an area that appears to be a slight struggle for individuals with 1p36 deletion syndrome, most individuals are able to feed themselves and do not need to be fed through a G- or NG-tube. For individuals that are having difficulty learning to self-feed, occupational and speech therapy may help develop oromotor skills and sensory integration.


Mobility

Mobility in people with 1p36 deletion syndrome has been documented as usually delayed, most likely due to hypotonia and achieving developmental milestones at a later age. Previous studies reported that most children will skip crawling after achieving independent sitting, and begin to move around by “bottom-shuffling” [4, 8]. It has also been reported that many children may be non-ambulatory and wheelchair dependent [6, 8], while others may achieve independent walking by late childhood [6, 8, 13].

An overwhelming majority of participants in this study reported the individual with 1p36 deletion syndrome was able to walk independently, with an average age of 3.4 – 3.7. Some individuals may still use wheelchairs to assist in mobility, but could walk by themselves for at least short distances. Physical therapy would be important to help develop muscle tone, especially in children with hypotonia, to aid in independent walking.

Behavioral

About 50% of people with 1p36 deletion syndrome documented in current literature exhibit behavioral problems, ranging from a placid, happy temperament, to having autistic-like features, and slightly less commonly displaying self-injurious behavior [4-6]. 1p36 deletion syndrome may be misdiagnosed as Prader-Willi Syndrome or Smith-Magenis Syndrome due to behavioral manifestations [2, 13, 14]. Our results show that individuals with 1p36 deletion syndrome may frequently seek attention, and be very happy/content. Unexplained fussiness, agitation, and anger weren’t reported as frequently, but were of concern. Self-injurious behavior was reported 30% of the time.
Limitations and Conclusions

There are several limitations to this study. Studies report an association between 1p36 deletion syndrome and obesity [8, 13-15]; however, quantifying obesity among our cohort of individuals with 1p36 deletion syndrome was omitted from the administered survey. This is an area that needs to be explored in future studies. Individuals with 1p36 deletion syndrome that were classified during the study were not able to be evaluated by a geneticist, and the surveys were subjectively answered by primary caregivers of these individuals. Recall bias, misclassification bias, or possibly ascertainment bias may be present; thus a further, more detailed, evaluation of these individuals by a clinical geneticist would be warranted to validate the data. Due to the unique population, a quantitative survey tool was developed by the research team; however, the survey has not been formally validated.

Previous literature delineating 1p36 deletion syndrome illustrates individuals with a complex medical phenotype, and limited function and mobility [1, 5-7, 16, 17]. Seizures, vision problems, and congenital heart defects have been some of the most common medical problems reported; questions regarding neuroblastoma and cancer development also have been raised. Speech delays and oral-motor concerns have been documented as well for these children. Our study has been able to corroborate some of the same medical concerns in adolescents and adults with 1p36 deletion syndrome, yet we also have identified that as individuals with 1p36 deletion syndrome age, they are able to achieve many milestones including walking and talking to a greater degree than is reflected in the previous studies. Constant monitoring for lifelong health concerns such as seizures is imperative; however, we have illustrated that the long-term prognosis for these patients is promising. It should be noted that there are known deaths from 1p36 deletion syndrome, but we were unable to document the number of patients who have died prior to adolescence in this study. Nevertheless, with proper medical care and
support, individuals with 1p36 deletion syndrome appear to make significant developmental progress as well as achieve a level of independence.
References

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Appendix A

Delineation of Medical Problems and Developmental and Functional Problems in Adolescents and Adults with 1p36 Deletion Syndrome

Online Questionnaire

You are about to begin the survey "Delineation of Medical Problems and Developmental and Functional Problems in Adolescents and Adults with 1p36 Deletion Syndrome". Your participation is voluntary; you may choose to end the survey or skip questions at any time and still be eligible to donate to one of the support organizations provided. If you agree to participate, please begin the survey below. Thank you again for your time and consideration.

Demographic Questions

Are you an individual aged 12 years or older with 1p36 deletion syndrome, or the primary caregiver of an adolescent or adult (aged 12 years old and up) with 1p36 deletion syndrome?

☐ Yes
☐ No

For the remainder of the survey, the person with 1p36 deletion syndrome or the primary caregiver of the individual with 1p36 deletion syndrome may fill out the questionnaire.

The following questions pertain to the person with 1p36 deletion syndrome under your primary care:

How old is he/she? Please list the age in years.

How old was he/she when diagnosed? Please list the age in years. If diagnosed at less than a year old, please round to the nearest quarter of a year (i.e.: 0.25, 0.5, etc)

How was the diagnosis of 1p36 deletion syndrome confirmed?

☐ Karyotype
☐ FISH Analysis
☐ Microarray
☐ Other

Please specify how the diagnosis was made:

What is his/her sex?

☐ Male
☐ Female

What country does he/she live in?

If he/she lives within the United States, what state do they live in? Please write N/A if this does not apply.

How much time (please round to the nearest hour) does it take he/she to get to the nearest major medical facility? Major medical facility is defined as a hospital that has a wide array of services, as well as various specialty clinics.

☐ Less than 1 hour
☐ 1-2 hours
☐ 2-3 hours
☐ More than 3 hours

Does he/she attend a genetics clinic or see a geneticist as part of medical follow up care?

☐ Yes
☐ No
Medical History

In the past month, has the person under your care had any of the following gastrointestinal (GI) problems? Please check all that apply.

- Reflux
- Ulcer
- Abdominal Pain
- Constipation
- Diarrhea
- Other

Please specify the type of gastrointestinal (GI) problems:

Has he/she ever required surgery to correct any of the following GI problems? Please check all that apply.

- Ompalocoele
- Gastrochisis
- Anteriorly Placed Anus
- Imperforate Anus
- Other

Please specify the type of GI problem he/she had that required surgery to correct it:

Has he/she ever gotten a kidney infection?

At what age did he/she last get a kidney infection(s)? Please state the age in years. If diagnosed at less than a year old, please round to the nearest quarter of a year (i.e.: 0.25, 0.5, etc.).

Central Nervous System Questions

Has he/she ever had a seizure?

- Yes
- No

How old was he/she when he/she had his/her first seizure?

- 0-6 months old
- 7-12 months old
- 13-24 months old
- 25-35 months old
- 3-5 years old
- 5-10 years old
- 10-15 years old
- Older than 15 years old

Does the person under your care still have seizures?

- Yes
- No

What type(s) of seizure(s) does he/she have? Please check all that apply

- Myoclonic
- Generalized tonic-clonic
- Right sided focal fits
- Simple partial
- Complex partial
- Infantile spasms
- Other

Please specify the type of seizure:

On average, how often does he/she have seizures?

How are the seizures being treated? Please check all that apply.

- Medication
- Ketogenic Diet
- Surgery
- They are currently not being managed

Please specify the type and date of surgery:
Low muscle tone (hypotonia)

Higher than average muscle tone (spasticity)

Has he/she ever developed contractures (permanently shortened muscles or joints)?

What body part(s) did he/she develop the contracture(s) in?

Did he/she receive treatment for his/her contractures?

What type of treatment did he/she receive for his/her contractures?

Did the contractures change after treatment?

Does the person under your care have any of the following congenital brain malformations? Please check all that apply.

Please specify the type of congenital brain malformation:

How old was he/she when the brain malformation was diagnosed? Please specify the age in years. If diagnosed at less than a year old, please round to the nearest quarter of a year (i.e.: 0.25, 0.5, etc).

Has the brain malformation changed since it was diagnosed?

☐ Yes, it has gotten better
☐ Yes, it has gotten worse
☐ No, it has not changed
☐ Unknown (malformation has not been re-evaluated since last diagnosis)
Hearing and Vision Questions

What type of hearing problems, if any, does the person under your care have? Check all that apply and please be prepared to list the age of diagnosis.

- No hearing problems known
- Conductive hearing loss, right ear
- Conductive hearing loss, left ear
- Sensorineural hearing loss, right ear
- Sensorineural hearing loss, left ear
- Mixed hearing loss, right ear
- Mixed hearing loss, left ear
- Legally deaf, right ear
- Legally deaf, left ear
- Other

Please list the age of diagnosis (in years) of conductive hearing loss in the right ear. If diagnosed at less than a year old, please round to the nearest quarter of a year (i.e.: 0.25, 0.5, etc.).

Please list the age of diagnosis (in years) of conductive hearing loss in the left ear. If diagnosed at less than a year old, please round to the nearest quarter of a year (i.e.: 0.25, 0.5, etc.).

Please list the age of diagnosis (in years) of sensorineural hearing loss in the right ear. If diagnosed at less than a year old, please round to the nearest quarter of a year (i.e.: 0.25, 0.5, etc.).

Please list the age of diagnosis (in years) of sensorineural hearing loss in the left ear. If diagnosed at less than a year old, please round to the nearest quarter of a year (i.e.: 0.25, 0.5, etc.).

Please list the age of diagnosis (in years) of mixed hearing loss in the right ear. If diagnosed at less than a year old, please round to the nearest quarter of a year (i.e.: 0.25, 0.5, etc.).

Please list the age of diagnosis (in years) of mixed hearing loss in the left ear. If diagnosed at less than a year old, please round to the nearest quarter of a year (i.e.: 0.25, 0.5, etc.).

Please list the age of diagnosis (in years) of legal deafness in the right ear. If diagnosed at less than a year old, please round to the nearest quarter of a year (i.e.: 0.25, 0.5, etc.).

Please list the age of diagnosis (in years) of legal deafness in the left ear. If diagnosed at less than a year old, please round to the nearest quarter of a year (i.e.: 0.25, 0.5, etc.).

Please specify the type of hearing problems, the ear in which it was diagnosed, and the age of diagnosis of this particular hearing problem. Please list the age of diagnosis in years, and if diagnosed at less than a year old, please round to the nearest quarter of a year (i.e.: 0.25, 0.5, etc.).

What type of treatment, if any, did he/she receive for his/her hearing problem?

- Yes, it has gotten better
- Yes, it has gotten worse
- No, it has not changed

Overall, has his/her hearing problem changed since it was diagnosed?
What type of vision problems, if any, does the person under your primary care have? Please check all that apply.

☐ No vision problems known
☐ Strabismus (cross-eyed)
☐ Myopia (near-sightedness)
☐ Hypermetropia (far-sightedness)
☐ Other

Please list the age of diagnosis of strabismus in years. If diagnosed at less than a year old, please round to the nearest quarter of a year (i.e: 0.25, 0.5, etc).


Please list the age of diagnosis of myopia in years. If diagnosed at less than a year old, please round to the nearest quarter of a year (i.e: 0.25, 0.5, etc).


Please list the age of diagnosis of hypermetropia in years. If diagnosed at less than a year old, please round to the nearest quarter of a year (i.e: 0.25, 0.5, etc).

Please specify the type of vision problem(s) and the age of diagnosis(es) in years. If diagnosed at less than a year old, please round to the nearest quarter of a year (i.e: 0.25, 0.5, etc).

What type of treatment, if any, did he/she receive for his/her vision problem? (Glasses, contacts, any surgeries, etc.)

Overall, has his/her vision problem changed since it was diagnosed?

☐ Yes it has gotten better
☐ Yes, it has gotten worse
☐ No, it has not changed
Cardiovascular Questions

Was the person under your care born with a heart defect or problem?

☐ Yes  ☐ No

What was the heart defect or problem? (If more than one defect or problem, please list them all)

Beginning at the age of 0.25 years, has he/she ever been diagnosed with a heart problem (not including the one they may have been born with)?

☐ Yes  ☐ No

How old was he/she when this diagnosis was made (age in years)? If diagnosed at less than a year old, please round to the nearest quarter of a year (i.e.: 0.25, 0.5, etc.).

What was their diagnosis(es)? (If more than one problem, please list them all)

Does he/she currently have this heart problem?

☐ Yes  ☐ No

Has he/she received treatment for his/her heart problem?

☐ Yes  ☐ No

What type of treatment did he/she receive?

☐ Medication  ☐ Surgery  ☐ Other

Please specify the type of treatment.

Has his/her heart problem changed since the initial diagnosis?

☐ Yes, it has gotten better  ☐ Yes, it has gotten worse  ☐ No, it has not changed

Physical Abnormality Questions

Was the person under your care born with any other physical birth defect that has not previously been mentioned? (Examples may include cleft lip, cleft palate, extra or missing fingers or toes, etc.)

☐ Yes  ☐ No

What birth defect(s) was he/she born with? Please list them all.

What treatment, if any, did he/she receive for the birth defect?
Cancer Questions

Has the person under your care ever had a cancer or tumor?
- Yes
- No

Has he/she had more than one cancer or tumor?
- Yes
- No

How many cancers or tumors has he/she had?

The following 7 questions pertain to the primary cancer or tumor.

Where was his/her first cancer or tumor located?

What type of cancer or tumor was it?

How old was he/she when his/her first cancer or tumor was found? Please write the age in years. If diagnosed at less than a year old, please round to the nearest quarter of a year (i.e. 0.25, 0.5, etc).

Was the cancer or tumor benign or malignant?
- Benign
- Malignant

Did the cancer or tumor metastasize?
- Yes
- No

What type of treatment did he/she receive? Please check all that apply.
- Chemotherapy
- Radiation
- Complete Removal
- None
- Other

Please describe the type of treatment.

Was the treatment successful?
- Yes
- No
- Not Applicable

The following 7 questions pertain to the secondary cancer(s) or tumor(s).

Where was his/her secondary cancer(s) or tumor(s) located?

What type of cancer(s) or tumor(s) was(were) it(they)?

How old was he/she when the secondary cancer(s) or tumor(s) was found? Please write the age in years. If diagnosed at less than a year old, please round to the nearest quarter of a year (i.e. 0.25, 0.5, etc).

Was the secondary cancer(s) or tumor(s) benign or malignant?
- Benign
- Malignant

Did the secondary cancer(s) or tumor(s) metastasize?
- Yes
- No

What type of treatment did he/she receive? Please check all that apply.
- Chemotherapy
- Radiation
- Complete Removal
- None
- Other

Please describe the type of treatment.

Was the treatment successful?
- Yes
- No
- Not Applicable
Developmental and Functional Questions

The following questions pertain to the person under your primary care with 1p36 deletion syndrome and their development and functional abilities.

Physical Development

Please use this picture to answer the following question.

[Inline image: "tanner stages - 2.gif"]

In reference to the picture above, what stage best matches his/her physical development?

- [ ] Stage 2
- [ ] Stage 3
- [ ] Stage 4
- [ ] Stage 5
- [ ] None of the above

What age did he/she start puberty? Please answer age in years or write N/A if he/she has not begun puberty yet.

__________________________

Has he/she ever experienced anything atypical or unusual with his/her physical/sexual development?

- [ ] Yes
- [ ] No

__________________________

What was the problem he/she had?

At what age did she begin menses (have their period)? Please write their age in years or write N/A if not applicable.

__________________________

How often does she have her period? Please write Not Applicable if she has not yet started her period.

__________________________

Does she experience excessive bleeding (more than you would expect) during menstruation?

- [ ] Yes
- [ ] No
- [ ] Not Applicable
Mobility Questions

Is the person with 1p36 deletion syndrome able to sit independently?

☐ Yes
☐ No

At what age did he/she begin to sit independently? Please write the age in years. If diagnosed at less than a year old, please round to the nearest quarter of a year (i.e.: 0.25, 0.5, etc).

Is the person under your care able to walk?

☐ Yes
☐ No

At what age did he/she start walking? Please write the age in years.

What type of assistive device, if any, does he/she require to help them walk?

Is he/she able to crawl or "bottom-shuffle" as a way to move around?

☐ Yes, he/she crawls to move around
☐ Yes, he/she "bottom-shuffles" to move around
☐ Yes, he/she can do both
☐ No, he/she cannot do either

Does he/she use a wheelchair?

☐ Yes, he/she uses an electric wheelchair (person with 1p36 can operate the chair themselves)
☐ Yes, he/she uses a manual wheelchair (person with 1p36 cannot operate the chair themselves)
☐ No, he/she does not use a wheelchair
### Feeding and Bathroom Questions

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<th>Question</th>
<th>Options</th>
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| Has the person under your care ever needed to be fed through a tube?     | □ Yes through a G-tube  
□ Yes, through a NG-tube  
□ No, he/she has not needed to be fed through a tube                     |
| Is he/she currently fed through a tube?                                  | □ Yes through a G-tube  
□ Yes, through a NG-tube  
□ No, he/she does not needed to be fed through a tube                     |
| Does he/she currently receive the majority of their nutrition orally (i.e. is he/she fed through their mouths most of the time and able to chew and swallow food)? | □ Yes  
□ No                                                                 |
| Is he/she able to hold a cup or spoon?                                   | □ Yes  
□ No                                                                 |
| Is he/she able to feed himself/herself?                                 | □ Yes  
□ No                                                                 |
| Is the person under your care toilet trained?                            | □ Yes, for both stool and urine  
□ Yes, for stool only  
□ Yes, for urine only  
□ No, they are not toilet trained                                         |
| At what age was he/she trained for both stool and urine? Please list age in years. |                                                                       |
| At what age was he/she potty trained for stool only? Please list age in years. |                                                                       |
| At what age was he/she potty trained for urine only? Please list age in years. |                                                                       |
| Does the person under your care have accidents with control of his/her bladder or bowels? | □ Yes  
□ No                                                                 |
| How frequently does he/she have accidents?                              |                                                                       |

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Speech and Communication Questions

Is the person under your care able to talk? □ Yes □ No

At what age did he/she begin to talk? Please write the age in years. If began at less than a year old, please round to the nearest quarter of a year (i.e: 0.25, 0.5, etc).

About how many words does he/she use? □ 10 words or less □ 11 - 50 words □ 51 - 100 words □ Over 100 words

Is the person with 1p36 deletion syndrome able to speak in sentences? □ Yes □ No

Is he/she able to imitate sounds? □ Yes □ No

Does he/she use sign language as a means of communication? □ Yes □ No

At what age did he/she start using sign language? Please write the age in years. If began at less than a year old, please round to the nearest quarter of a year (i.e: 0.25, 0.5, etc).

Does he/she use an assistive device to help him/her communicate? □ Yes □ No

At what age did he/she start using an assistive device? Please write the age in years.

Please describe the type of device he/she uses:

Has he/she ever been diagnosed with a specific speech problem (for example, apraxia)? □ Yes □ No

Please describe the type of speech problem that he/she was diagnosed with:

At what age was the speech problem diagnosed? Please write the age in years. If diagnosed at less than a year old, please round to the nearest quarter of a year (i.e: 0.25, 0.5, etc).

Has his/her speech problem changed since the initial diagnosis? □ Yes, it has gotten better □ Yes, it has gotten worse □ No, it has not changed
Behavioral Questions

Does the person under your care smile?

☐ Yes
☐ No

Is the person with 1p36 deletion syndrome able to differentiate between strangers and familiar faces?

☐ Yes
☐ No

In the last year, how often has he/she sought attention from others?

☐ Very Often
☐ Often
☐ Somewhat Often
☐ Rarely
☐ Never

In the last year, how often has he/she seemed agitated?

☐ Very Often
☐ Often
☐ Somewhat Often
☐ Rarely
☐ Never

In the last year, how often has he/she seemed happy/content?

☐ Very Often
☐ Often
☐ Somewhat Often
☐ Rarely
☐ Never

In the last year, how often has he/she seemed angry/mad?

☐ Very Often
☐ Often
☐ Somewhat Often
☐ Rarely
☐ Never

In the last year, how often has he/she had periods of unexplained fussiness, pain, or agitation?

☐ Very Often
☐ Often
☐ Somewhat Often
☐ Rarely
☐ Never

In the last year, how often has he/she had periods of self-injurious behavior?

☐ Very Often
☐ Often
☐ Somewhat Often
☐ Rarely
☐ Never
Does he/she currently take prescription medication to help manage behavioral problems?

☐ Yes  ☐ No

At what age did he/she begin taking medication to help manage his/her behavioral problems? Please list age in years.

Caregiver burden refers to the high level of stress that may be experienced by people who care for individuals with disabilities. As the primary caregiver for someone with 1p36 deletion syndrome, how would you describe the caregiver burden you experience?

As the primary caregiver of someone with 1p36 deletion syndrome, what are the most important problems you would like clinicians to learn more about and treat in the future?

Please select which organization you would like the research team to donate $5 to:

☐ 1p36 Deletion Support and Awareness ☐ Chromosome Disorder Outreach, Inc.  ☐ UNIQUE

Thank you for taking the time out of your day to complete the survey. Your input is extremely valuable as we work to help individuals with 1p36 deletion syndrome.