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**Online Cognitive Assessment of 15q11.2 Deletion Carriers
Reveals Domain Specific Impairments**

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Capstone Project

May 2015

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Introduction

Advanced genetic testing has enabled detection of copy number variations (CNVs) which were previously undetectable. The 15q11.2 microdeletion is an example of this sort of CNV. Chromosome 15q11 to q13 is known to be a highly unstable region and therefore associated with high frequency of mutation (Murthy et al, 2007). Specifically, the presence of repeat sequences in low copy numbers at some regions within 15q11 to q13 has created common break point regions including BP1, BP2, and BP3 (Murthy et al, 2007). 15q11.2 microdeletions encompass a lost copy from BP1 to BP2. The four genes in this region are *NIPA1*, *NIPA2*, *CYFIP1*, and *TUBGCP5* (De wolf et al, 2013), and the deletion spans from 20,306,549bp to 20,777,695bp on chromosome 15, or approximately about 470 kb (Stefansson et al, 2008). Although 15q11.2 is next to the region associated with Prader-Willi syndrome and Angelman syndrome, it is not overlapping. These two conditions are related specifically to the region between BP2 and BP3. None of the four genes in 15q11.2 region are known to be imprinted, in contrast to some genes in adjacent bands.

Deletions in 15q11.2 are known to increase the risk of neurodevelopmental disorders. Specifically, 15q11.2 deletions have been associated with conditions such as developmental delay, autism spectrum disorder, schizophrenia, epilepsy, dyslexia, and dyscalculia (Burnside et al, 2011; Cooper et al, 2011; De Kovel et al, 2010; De wolf et al, 2013; Doornbos et al, 2009; Murthy et al, 2007; Stefansson et al, 2008; Stefansson et al, 2014; Von der Lippe et al, 2010). However, like many other recently detected CNVs, 15q11.2 deletions lack phenotypic specificity. This deletion can manifest with different symptoms in different individuals. To further complicate the matter, 15q11.2

deletions, like many other newly detectable CNVs, are present in the population among those who do not present with any clinically significant symptoms (Stefansson et al, 2014). Therefore, having this deletion creates a susceptibility to some neurodevelopmental disorders, but it is not necessarily causal. Lack of any direct associated phenotype in some carriers of this deletion makes it difficult to predict outcomes. Therefore, it can leave clinicians, such as genetic counselors, challenged to interpret and communicate the meaning of these results to the patients and families (Burnside et al, 2011; Chaste et al, 2014; De wolf et al, 2013).

There has been some speculation regarding the possible presence of intermediate phenotypes in 15q11.2 deletion carriers who are not affected (De Wolf et al, 2013, Stefansson et al, 2014). This hypothesis was examined in a paper published in 2014 by Stefansson et al. Stefansson looked for relationships between individuals harboring CNVs known to increase risk for neurodevelopmental disease and altered cognition. The selection of CNVs was based on a literature review to identify those known to be associated with schizophrenia or autism, including 15q11.2 deletions. Subjects were recruited from four groups: carriers of a CNV associated with a neuropsychiatric disorder, including 15q11.2 deletion carriers, carriers of other CNVs not associated with neuropsychiatric disorders, controls with no CNVs, and patients with schizophrenia. Subjects were all between 18 to 65 years old (Stefansson et al, 2014).

Participants were tested for cognitive functions including attention, spatial working memory, logical memory, executive functioning, cognitive flexibility, language and speed processing, using standardized tests such as Mini International Neuropsychiatric Interview (M.I.N.I.)(Stefansson et al, 2014). According to Stefansson

these cognitive functions are known to be affected in individuals with schizophrenia. In addition, subjects were tested for dyslexia and dyscalculia (Stefansson et al, 2014).

In this study, Stefansson found that 15q11.2 deletion carriers' performance on tests of cognitive function fell between those of general population and patients with schizophrenia. The discrepancy with the general population was greatest for dyslexia and dyscalculia (Stefansson et al, 2014). Stefansson deduced that the cognitive activity of carriers fell somewhere between the non-carriers and patients with schizophrenia, providing support for this hypothesis (Stefansson et al, 2014).

In order to further study the effect of CNVs on a carrier's brain, Stefansson, utilized magnetic resonance imaging (MRI). Carriers of a 15q11.2 deletion were found to have reduced grey matter volume in anterior cingulate cortex and left insula, reduced white matter volume in temporal lobe, and increased corpus callosum volume. Interestingly, the reduced grey matter observed in these carriers is similar to that found in individuals with dyslexia and dyscalculia. Stefansson concluded that perhaps 15q11.2 events are associated with specific aspects of cognition and brain structure (Stefansson et al, 2014).

Prior to Stefansson's work, Murthy et al, in 2007, published the first case report on a three and a half year old boy with a 253 Kb deletion in 15q11.2, between bp1 and bp2. Prior to this report, other reported cases of 15q11.2 deletions were larger and not limited to the region between bp1 and bp2 (Butler 2004, and Milner 2005). Those cases had deletions that included the region between BP2 and BP3, and hence usually a diagnosis of Prader-Willi syndrome or Angelman syndrome.

Murthy reported on a patient with mental retardation, developmental delay and speech problems. The deletion was found to be paternally inherited. The child's father had similar but milder symptoms (Murthy et al, 2007). However, Murthy did not speculate any reason for the milder presentation in the father.

Doornbos et al, published the second case report, reporting on 9 cases in 2009. Probands all harbored 15q11.2 deletions and manifested developmental delay, mental retardation, dysmorphic facial features and behavioral problems. Behavioral problems encompassed autism, attention deficit hyperactivity disorder (ADHD), and obsessive-compulsive disorder (OCD). A control population of 350 was screened, and no deletion carriers were found. This group concluded that there might be a correlation between 15q11.2 deletions and developmental delay and mental retardation. In this study, 7 of the 9 reported patients were noted to have inherited the deletion from an unaffected or a mildly affected parent (Doornbos et al, 2009). Again, no rationale for the milder presentation of these individuals was offered.

In 2010, Von der Lippe et al, reported on 7 patients with the same symptoms as those described by Doornbos patients, except facial dysmorphism. This study provided additional support for the association of developmental delay, mental retardation and behavioral problems with 15q11.2 deletions (Von der Lippe et al, 2010).

The first large study of 15q11.2 deletions was done in 2008, a year after the first case report. Investigators were interested to know whether there was an association between schizophrenia and three recently discovered common deletions, including 15q11.2. They screened a population of 4,718 patients with schizophrenia for the three

deletions, and compared it to the prevalence of the deletion in a control population of 41,194. With regards to 15q11.2 deletions, 26 of 4,718 (0.55%) patients with schizophrenia and psychosis were carriers while only 79 of 41,194 (0.19%) controls had the deletion (Stefansson et al, 2008). This group concluded that indeed there was an association between schizophrenia and 15q11.2 deletions.

In 2012, Van Den Bossche et al, confirmed this association by screening a different population of patients with schizophrenia as well as patients with bipolar disorder, major depressive disorder, and intellectual disability, for deletions in 15q11.2. 15q11.2 deletions were found to be associated with increased susceptibility to both schizophrenia and intellectual disability. This group speculated that CNVs in this region could cause disturbances in brain development, which consequently can increase predisposition to different neuropsychiatric conditions (Van Den Bossche et al, 2012).

In 2010, De Kovel et al looked at the association of five commonly reported deletions, including 15q11.2 deletions, with epilepsy. This study looked at the prevalence of these deletions in a patient population with common idiopathic generalized epilepsy syndrome, and 12 of 1234 (1%) patients and 6 of 3022 (0.2%) controls were found to have 15q11.2 microdeletions (Kovel et al, 2010). Therefore, this group concluded a susceptibility to epilepsy did exist for carriers of this deletion. All these cases were inherited from a non-affected parent, and again no explanation for this finding was offered.

In 2011, Cooper et al, screened a large sample of 15,767 children with intellectual disability and developmental delay for the presence of 15q11.2 deletion, and

compared it to 8329 unaffected adults patients. This group found the 15q11.2 deletion in one out of every 167 affected patients with intellectual disability and developmental delay, providing support for the association of 15q11.2 deletion with intellectual disability and developmental delay (Cooper et al, 2011).

Additionally, Burnside et al, in the same year, screened a total of 3,992 patients. Patients were affected with autism, developmental delay, motor and language delays, and behavioral problems. A total of 0.86% of the 3,992 were found to carry either duplication or a deletion (0.41% deletion) in the 15q11.2 region. However, only 0.38% of 6,329 controls were found to carry a mutation in 15q11.2 (Burnside et al, 2011). Most of the mutations in Burnside study were inherited from unaffected parents. Possible explanations for these results included “reduced penetrance, altered gene dosage on a particular genetic background, or a susceptibility region as reported for other areas of the genome implicated in autism and behavior disturbances” (Burnside, 2011).

The current study assessed the cognitive phenotypes of 15q11.2 deletion carriers. As demonstrated above, unaffected parents harboring a 15q11.2 deletion were observed in most of the studies. Finding a possible intermediate or associated phenotype in the 15q11.2 deletion carriers would not only provide important insight into this deletion’s neurobiology, but also aid clinicians to interpret the outcome of such deletions for patients with increased certainty.

Materials and Methods

A cohort of 27 individuals with 15q11.2 deletion was recruited, using online social media tools, including Facebook. Sex, age and education level of participants are

summarized in Table 1. 74.1% of this cohort consists of individuals without a clinical diagnosis, who harbor a 15q11.2 deletion, and are family members (parents and siblings) of individuals with a diagnosis.

All participants have deletions that include the 4 genes. The break point of all deletion carriers are (Hg18) = chr15: 20,316,792-20,851,728 (plus or minus 100kb either side) or (Hg19) = chr15: 22,748,621-23,328,986 (plus or minus 100kb either side). Blood or spit samples were collected from the subjects. DNA prepared from these samples was tested in the Abrahams lab for the presence of 15q11.2 deletion using TaqMan technology.

To investigate cognitive function in 15q11.2 deletion carriers we used an online platform, called Lumosity, which employs well established neuropsychology tests to look at cognitive functions including memory, speed, attention, flexibility, and problem solving. We asked participants to complete a Brain Performance Test (BPT) to measure their cognitive ability. In order to do the test, individuals had to sign into Lumosity using their electronic devices. Individuals were not asked to travel to our lab to do the test. The BPT includes 10 different tasks. Each task assesses a unique cognitive ability (Table 2). For each task, participants get a separate score or time or both.

We matched each one of our subjects to 100 controls based on sex, age, and level of education. The results of BPT tests for matched controls were received from Lumosity. We assumed that controls did not have a 15q11.2 deletion, since the prevalence of this deletion in general population is known to be low. We calculated the mean of BPT scores of controls in each group. We compared each subject's score or

finish time to a mean score for a population of 100 matched controls. We tested for significant differences between deletion carriers and controls using one-tailed Wilcoxon Signed-Rank test. A threshold of $p < 0.05$ was employed to assess significance.

Table 1: Sex, Age, and Education Level Breakdown of Participants

Sex	Female	19
	Male	8
Age	10-20	8
	20-30	2
	30-40	10
	40-50	2
	50-60	5
Education level	Some school	9
	High school	7
	Associates degree	3
	Bachelors degree	2
	Master's degree	4
	PhD	2

Table 2: List of Tasks in BPT and What They Measure For

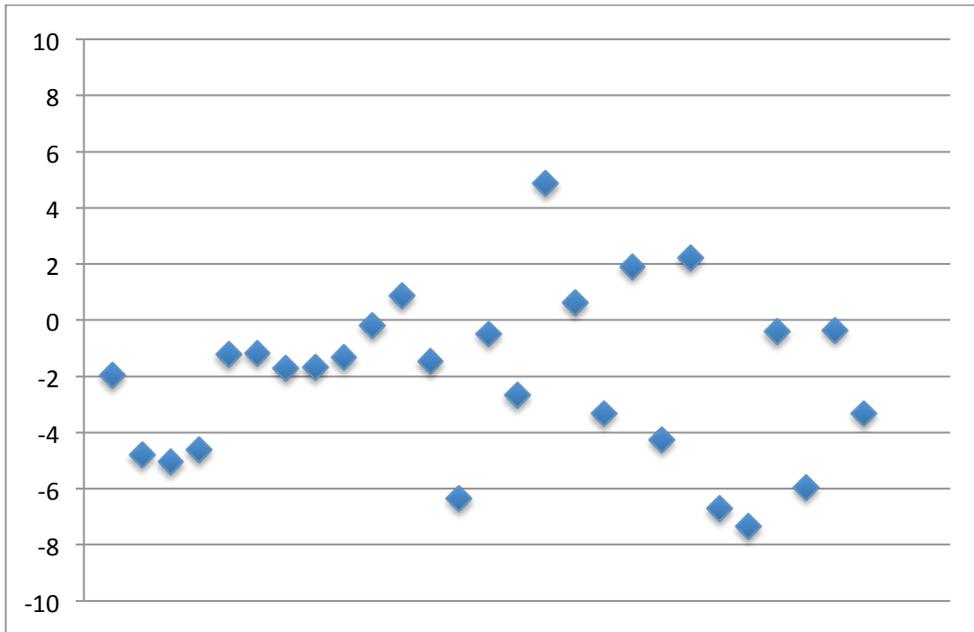
Task	Cognitive Skill assessed	Description	Measure
Digit Symbol Coding	Visual Speed of processing	Enter the number corresponding to the symbol.	Net number correct
Divided Visual Attention	Divided visual attention, field of view	Attend to two target letters. Four letters are briefly flashed inside four circles at a particular eccentricity, followed by a mask. Click on circles that contained target letters.	Minimum presentation time
Grammatical Reasoning	Logical reasoning	Respond whether logical statement is true or false.	Net number correct
Progressive Matrices	Flexibility	Complete a final element in a 3 by 3 grid by determining the pattern that relates other elements in the grid to each other.	Net number correct
Go/no-go Reaction	Response inhibition and speed of processing	Press the spacebar as fast as possible when a target stimulus appears, and avoid responding to distractors.	Mean response time
Span Board (Forward and Reverse)	Visual-spatial working memory	Recall the spatial location and sequence of highlighted boxes by clicking in the forward order (Forward). Recall the sequence in reverse order (Reverse).	Maximum span
Trail Making A and B	Visual-spatial search, visual scanning, task-switching	Trace a path connecting numbers from smallest to largest (A). Trace a path from smallest to largest, alternating between numbers and letters (B).	Completion time
Wordy Equations	Arithmetic problem solving	Answer arithmetic questions written in words with a numeric value.	Net number correct

Results

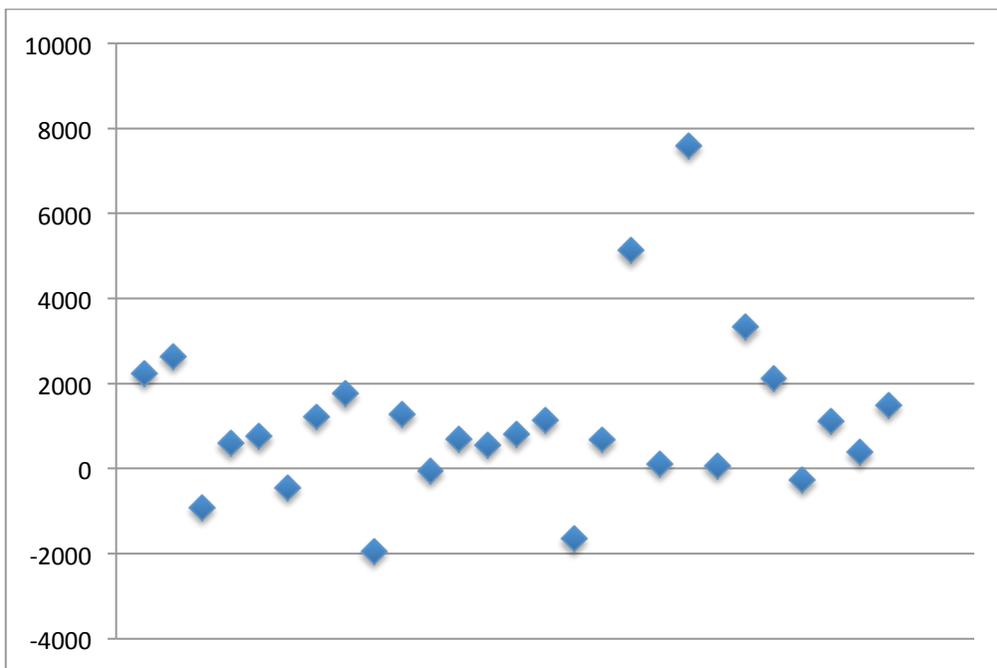
Table 3: Results, Significant Findings in Bold

Task	Mean for deletion carrier participants	Mean controls	P value (Wilcoxon test, One-tailed)
Digit Symbol Coding	Score: 40 Time: 2569	Score: 44 Time: 2129	Score: 0.00734 Time: 0.03216
Divided Visual Attention	Time: 436.41	Time: 369.26	Time: 0.18141
Grammatical Reasoning	Score: 5.48 Time: 5177.67	Score: 7.55 Time: 4054.53	Score: 0.00187 Time: 0.00135
Progressive Matrices	Score: 9.44	Score: 9.63	Score: 0.49202
Go/no-go Reaction	Time: 451.67	Time: 443.23	Time: 0.40517
Span Board Forward and Reverse	Forward score: 5.37 Reverse: 4.15	Forward score: 5.57 Reverse: 4.98	Forward: 0.0951 Reverse score: 0.00347
Trail Making A and B	A: 24571.30 B: 50438.52	A: 23906.35 B: 43448.54	A Time: 0.23576 B Time: 0.42465
Wordy Equations	Score: 11.11	Score: 13.47	Score 0.00144

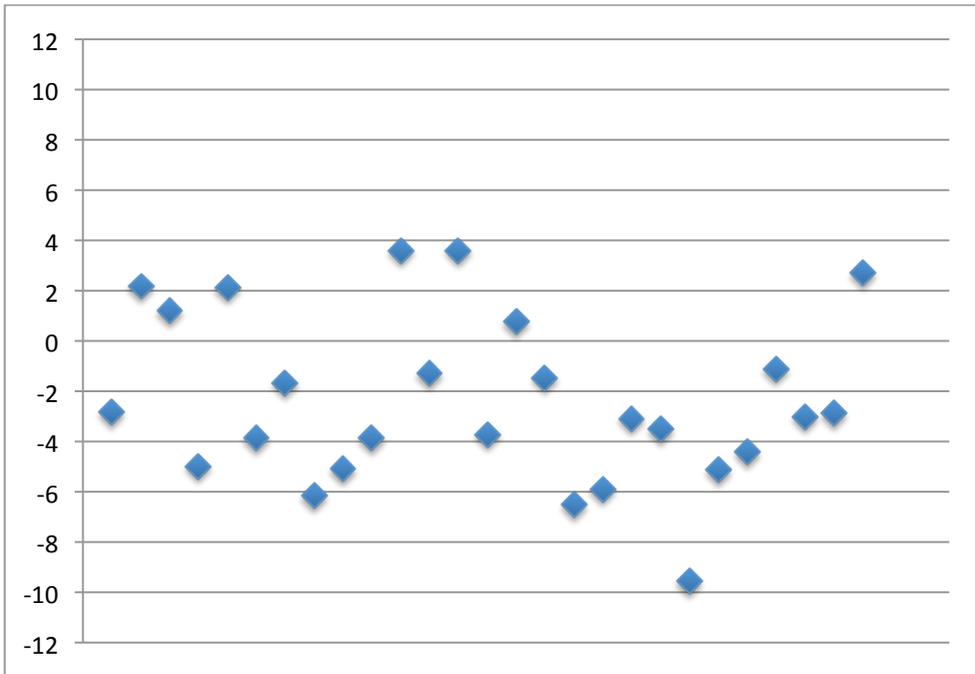
Graph 1: Grammatical Reasoning Score, deletion score minus controls score



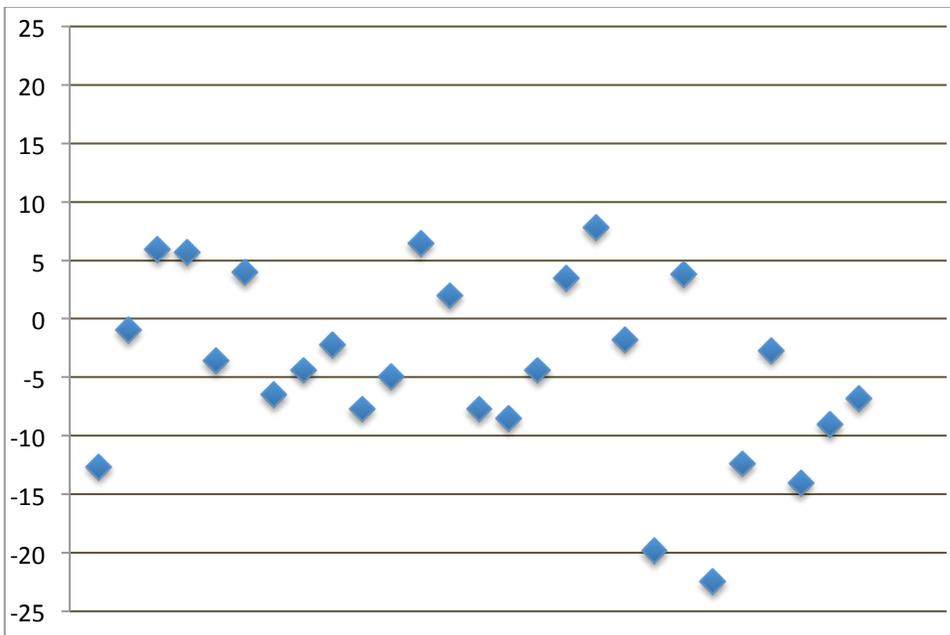
Graph 2: Grammatical Reasoning Time, deletion time minus controls time



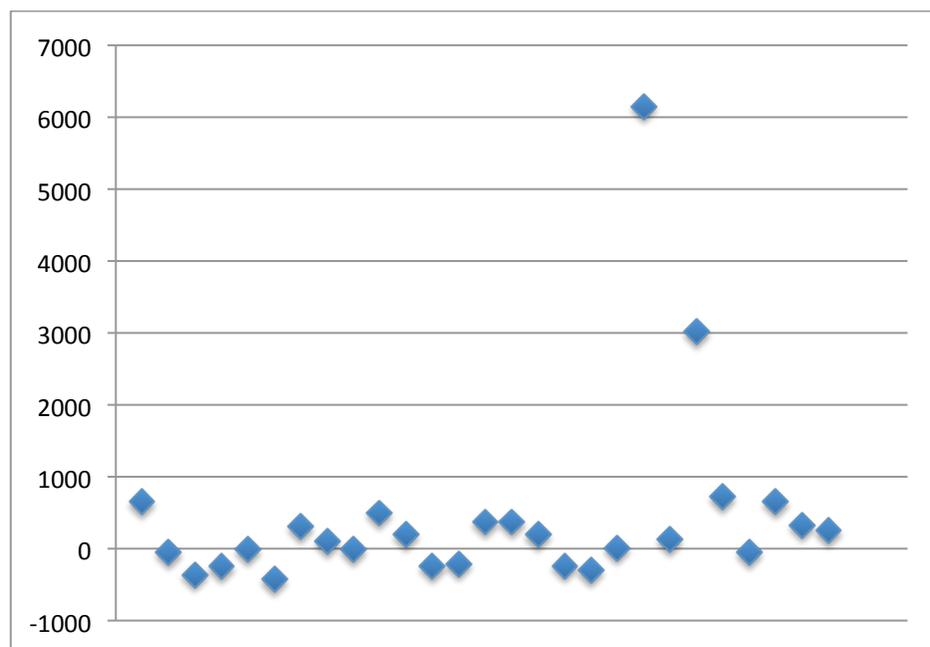
Graph 3: Wordy Equations: Deletion score minus controls score



Graph 4: Digit Symbol Coding, Deletion score minus controls score



Graph 5: Digit Symbol Coding, Deletion time minus controls time



Discussion

We report here on the cognitive ability of a cohort of 27 individuals with 15q11.2 deletion, who are not affected or are minimally affected. We compared the performance of our participants to controls matched to each participant based on age, education level and sex on 10 different tasks included in the BPT. We found statistically significant differences between our cohort and the control populations, using Wilcoxon Signed-Rank test, in four cognitive tasks: Grammatical reasoning, Wordy equations, Digit symbol coding, and Reverse span board (Table 3). We performed a statistical analysis excluding outliers, and still found significant differences for the aforementioned tasks.

As described in table 2, in the Grammatical Reasoning task, designed to assess logical reasoning, individuals were asked to answer true or false to logic questions. Both

the net correct number (score) and the time to complete the task were recorded for each individual. In comparing individuals with a deletion against the mean scores of matched controls, individuals with a deletion consistently answered fewer questions correctly and had slower times. Collectively, the differences in score and time were significant, with p values of 0.00187 and 0.00135 respectively. Each point in Graphs 1 and 2 represents a deletion carrier score or time minus the mean score or time of the 100 controls that matched the participant based on covariates. In Graph 1, 22 out of 27 points lie under the zero, demonstrating that the majority of deletion carriers performed worse. In Graph 2, 21 out of 27 points lie above the zero line for time, demonstrating that the majority of deletion carriers took more time to finish the task.

In the Wordy Equation task, participants were asked to answer arithmetic questions to assess arithmetic problem solving ability (Table 2). Individuals with 15q11.2 deletion had lower scores than individuals with the same age, sex, and education level in arithmetic problem solving tasks in most instances, and collectively the differences were significant, with a p value of 0.00144. Graph 3 presented individual level data for all deletion carriers. Each point in Graph 3 represents a deletion carrier score minus the mean of 100 scores for matched controls, and 20 out of 27 points lie under the zero line.

In the Digit Symbol Coding task, designed to assess visual speed of processing, individuals were asked to determine how many items appeared on the screen. Although the p value of 0.00734 calculated for the Digit Symbol Coding task is significant, and 19 out of 27 points in graph 5, which represent deletion carrier score minus the controls, lie

under the zero line, the differences are less pronounced than those in tests of arithmetic problem solving and logical reasoning. In addition, the time component of this test, while slower on average for most deletion carriers (Graph 5), was not statistically significant overall. Further studies are required to confirm the association between 15q11.2 deletion and decreased ability of visual speed of processing.

In the Span Board and Reverse Span Board tasks, individuals were asked to recall the location and sequence of highlighted boxes and click in the forward or reverse order, respectively (Table 2). Deletion carriers correctly identified location and sequence less often than matched controls in both the Span Board and Reverse Span Board tests, but the p value for Reverse Span Board test was significant ($p=0.00347$) while the p value for span board test was not ($p=0.951$). Since both tasks are very similar and both measure visual-spatial working memory, the lack of concordance suggests that current data is inadequate to determine the extent of cognitive differences between participants and the control population. Since the Reverse Span Board task is more difficult than the forward Span Board task, it may be that deletion carriers and controls perform equally well in visual-spatial working memory tasks when those tasks are routine, and less well in tasks that are more challenging. Further studies are needed to investigate this hypothesis.

Although on average deletion carriers scored lower and performed slower in all the tasks included in BPT (Table 3), in addition to the tasks mentioned above, the difference was not significant for Divided Visual Attention, Progressive Matrices, Go/No-go Reaction, and Trail Making And B tasks. These tasks were designed to assess divided visual attention, flexibility, speed of processing and task switching. The absence

of significant finding in these tasks could be due to the fairly small sample size of this study. Further investigations in the future with larger sample sizes may be beneficial.

As discussed, Stefansson et al, in 2014, showed that the performance of 15q11.2 carriers on select tests fell between that of non-carriers and patients with schizophrenia. Stefansson used traditional approaches, such as the M.I.N.I test for assessing cognitive ability (Stefansson et al, 2014). Typically, only a limited and homogeneous sample could be studied with this approach, since the participants were required to physically travel to the research lab. Our study utilized an online research database, Lumosity, which permitted a more heterogeneous population. In fact, with regards to geographical location, the cohort for the present study has been recruited from across the United States and Canada.

Since the emergence of Lumosity in 2007, there have been several studies suggesting Lumosity's effectiveness with regards to measuring cognitive ability (Sternberg, 2013; Tartaglione, 2014). Recently, Tartaglione et al, compared usage of Lumosity training games to currently widely used psychometric tests to investigate the cognitive differences. Tartaglione concluded that Lumosity games could be a useful tool to test for small cognitive impairments, which sometimes cannot be detected by more conventional testing (Tartaglione, 2014). Therefore, using Lumosity in this study, may have helped to detect previously unobserved small cognitive differences between 15q11.2 deletion carriers and controls.

In the future, the use of online cognitive training games could be investigated as a potential vehicle to improve the Logical reasoning and arithmetic problem solving skills of individuals with 15q11.2 deletion.

Conclusion

15q11.2 deletion has been reported to be associated with a number of neurobehavioral phenotypes. Some carriers of this deletion manifest clinical symptoms, while others do not. In this study, we showed that symptomless individuals with 15q11.2 deletion perform worse than the general population in tasks that involve arithmetic problem solving and logical reasoning, providing evidence for the presence of an intermediate cognitive phenotype in all individuals with 15q11.2 deletion.

This study suggests more complete penetrance for lowered problem solving and logical reasoning ability associated with 15q11.2 deletion. Individuals however, show variable degrees of expression for these cognitive phenotypes, ranging from mildly affected individuals who appear to be symptomless to individuals who are severely affected and have diagnosis of cognitive disabilities. Therefore, even though some individuals with 15q11.2 function within the norm in the general population, their problem solving and logical reasoning may be affected.

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