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Genetic factors and therapy outcomes in persistent developmental stuttering

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ABSTRACT

Purpose: We investigated whether outcomes of therapy for persistent developmental stuttering differ in individuals who carry a mutation in one of the known genes associated with stuttering compared to individuals without such mutations.

Method: We studied outcomes of an intensive fluency shaping-based therapy program in individuals with persistent developmental stuttering. We evaluated a cohort of 51 stuttering individuals with who carried a mutation in either the *GNPTAB*, *GNPTG*, *NAGPA*, or *AP4E1* gene. We compared therapy outcomes in these individuals with outcomes in 51 individuals matched for age, gender, and ethnicity, who stutter and underwent the same therapy program, and did not carry a mutation in any of these genes. Fluency pre- and post-therapy was evaluated using blinded observer-based quantitative stuttering dysfluency measures (Dysfluent Words Score, DWS), and by subjects' self-reported measures of struggle, avoidance and expectancy behavior associated with speaking (Perceptions of Stuttering Inventory, PSI). The difference between pre- and post-therapy fluency scores was taken as the measure of near-term therapy efficacy.

Results: Comparison of fluency measures showed a strong effect of therapy overall. Mutation carriers achieved significantly less resolution in PSI following therapy, with PSI scores showing significantly less improvement in individuals who carry a mutation ($p = 0.0157$, RR = 1.75, OR = 2.92) while the group difference in DWS between carriers and non-carriers was statistically not significant in the present study, the trend observed in the results warrants further research focused on this important issue.

Conclusions: These results suggest stuttering is more resistant to therapy in individuals who carry a mutation in one of the genes known to be associated with stuttering.

1. Introduction

A longstanding goal in the treatment of developmental stuttering has been to identify factors that can predict therapy success. Pre-treatment stuttering severity has repeatedly been shown to be one statistically significant factor relevant to therapy outcomes (Andrews & Craig, 1988; Block, Onslow, Packman, & Dacakis, 2006; Guitar, 1976), and other factors include lexical diversity and

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psychosocial impact (Cook, Donlan, & Howell, 2013) and language and motor abilities (Cook, 2011). However, several other factors that have been investigated, including head injury, family history, gender, handedness, and the existence of relatives who stutter have not been associated with therapy outcomes to date (Howell & Davis, 2011). Identifying such predictors is relevant, and they could inform therapy efforts and lead to the more efficient use of limited therapy resources.

An extensive literature supports a role for genetic factors in stuttering including twin studies (Andrews, Morris-Yates, Howie, & Martin, 1991; Dworzynski, Remington, Rijsdijk, Howell, & Plomin, 2007; Fagnani, Fibiger, Skytthe, & Hjelmborg, 2011; Felsenfeld et al., 2000; Godai, Tatarelli, & Bonanni, 1976; Howie, 1981; Ooki, 2005; Rautakoski, Hannus, Simberg, Sandnabba, & Santtila, 2012; van Beijsterveldt, Felsenfeld, & Boomsma, 2010), adoption studies (Bloodstein, 1961; Felsenfeld & Plomin, 1997), and familial aggregation studies (Cox, Kramer, & Kidd, 1984; Kidd, Heimbuch, & Records, 1981). In addition, family-based studies have identified a number of highly significant genetic linkage loci, suggesting the existence of causative genes at specific chromosomal locations (Domingues et al., 2014; Raza, Amjad, Riazuddin, & Drayna, 2012; Raza et al., 2013; Raza, Riazuddin, & Drayna, 2010; Riaz et al., 2005; Shugart et al., 2004; Suresh et al., 2006; Wittke-Thompson et al., 2007). Finally, gene-finding studies have identified mutations in the *GNPTAB*, *GNPTG*, *NAGPA*, and *AP4E1* genes associated with this disorder (Kang et al., 2010; Raza, Domingues, et al., 2015, Raza, Mattera, et al., 2015).

These four genes are closely related functionally, and the products of these genes interact *in vivo* as well as *in vitro* (Kang et al., 2010; Raza, Mattera, et al., 2015). All are involved in the process of intracellular trafficking, and deficits in this cellular function are now recognized as causative of a wide range of neurological disorders (Neefjes & van der Kant, 2014). Engineering mutations found in human stuttering into the genome of mice results in animals that are largely normal except they present deficits in the flow of their ultrasonic vocalizations, similar to the deficits in the flow of vocalizations present in humans who stutter and carry mutations in these genes (Barnes et al., 2016). These findings suggest that the control of vocalization is an innate, conserved biological process, and that genetic deficits in this control could affect therapies designed to correct such deficits.

Although the genes identified to date appear to be causative in only a fraction of cases of stuttering (Frigerio-Domingues & Drayna, 2017), the number of such cases is sufficient to allow some initial inquiries about stuttering in this group of individuals. Here, we examined the outcomes of intensive stuttering therapy using a programmatic, standardized fluency-shaping approach in individuals who carry such mutations and compared them to therapy outcomes in an age-, gender-, and ethnicity-matched group of controls without such mutations who underwent the same therapy program.

Stuttering therapy has employed an array of approaches and methods (Bloodstein & Ratner, 2008). A number of these approaches have fallen into one of two general categories, stuttering management and fluency shaping. Broadly speaking, stuttering management has sought to modify cognitive factors and the anxiety often present in this disorder, while fluency shaping has focused on teaching stuttering individuals to speak more fluently (Blomgren, 2010). More recently, combined or integrated methods have sought to include elements from both of these approaches (Guitar, 2014). In this study we focused on one therapy approach, analyzing results from an intensive fluency shaping therapy program that has been applied in a relatively large subject sample ($>$ 6000 clients over a period of more than 30 years) at the Hollins Communications Research Institute (HCRI) (Webster, 1980).

2. Materials and methods

Subjects with persistent developmental stuttering were enrolled with written informed consent under IRB-approved protocol 97-DC-0057 of the National Institutes of Health. Subjects ranged in age from 16 to 55, and all reported a family history of stuttering. Therapy for all subjects was based on a fluency shaping approach (Blomgren, 2010; Prins & Ingham, 2009) and was performed in a standardized, intensive program taking place over 12 successive days at the Hollins Communications Research Institute, Roanoke, VA (Webster, 1980). In this program, individuals use computer- and therapist-assisted methods to learn to focus on speech fluency targets to reduce overt stuttering. 80% of subjects were male and all displayed persistent developmental stuttering. While subjects' previous therapy experiences differed, all were participating in the HCRI program for the first time.

Mutation carrier status was determined using dideoxy-Sanger sequencing of all exons and adjacent intronic sequences of *GNPTAB*, *GNPTG*, *NAGPA*, and *AP4E1* as previously described (Kang et al., 2010; Raza, Domingues, et al., 2015; Raza, Mattera, et al., 2015). In the 416 subjects screened, 153 individuals were found to carry a mutation in one of these genes. Among these individuals, 51 (carrying the mutations detailed in Supplement 1) had speech diagnostic records and could be matched with 51 non-mutation carriers by age, gender, and self-reported racial/ethnic background ($N = 102$). Among these subjects, complete speech diagnostic records allowing analysis by speech-language pathologists were available for 50 mutation carriers and 47 non-mutation carriers ($N = 97$).

Pre- and post-therapy fluency was measured in two ways. The first involved ratings of fluency made by speech-language pathologists who scored videotaped speech samples from each subject. These speech samples contained a small amount of directed speech (subjects stating their name and the date) and a standardized reading passage (Kang et al., 2010; Webster, 1979) (Appendix A). Total stuttering disfluencies, measured as the percentage of words with stuttering disfluencies (DWS), were scored blind to subject mutation status. These video recordings (except for five samples for which video records were not available, which were excluded from subsequent DWS statistical analyses) were scored by Z.G. and independently by A.Z. at the NIDCD, with a total of 97 subjects scored. Personal reactions to different speaking situations for each subject were measured using the Perceptions of Stuttering Inventory (PSI), in which subjects self-reported stuttering symptoms and ancillary behaviors possibly related to stuttering (Woolf, 1967). The use of the PSI for this measure was chosen to provide consistency across all subjects, who received therapy across a period spanning more than 40 years. Therapy outcome was measured by the difference (Δ) in fluency before and immediately following the standard intensive fluency program. Statistical tests for differences between pre- and post-therapy were performed using the independent (unpaired) *t*-test for means and, for mutation carriers and non-carriers were performed paired *t*-test for means.

Table 1
Inter-rater diagnostic reliability. DWS score correlations – Pearson's r, $p < 0.0001$ for all correlations.

Speech-language pathologists	Non-mutation carriers ($N = 50$)		Mutation carriers ($N = 47$)	
	Pre-therapy	Post-therapy	Pre-therapy	Post-therapy
Z.G. vs. A.Z.	$r = 0.9616$	$r = 0.9748$	$r = 0.975$	$r = 0.9712$

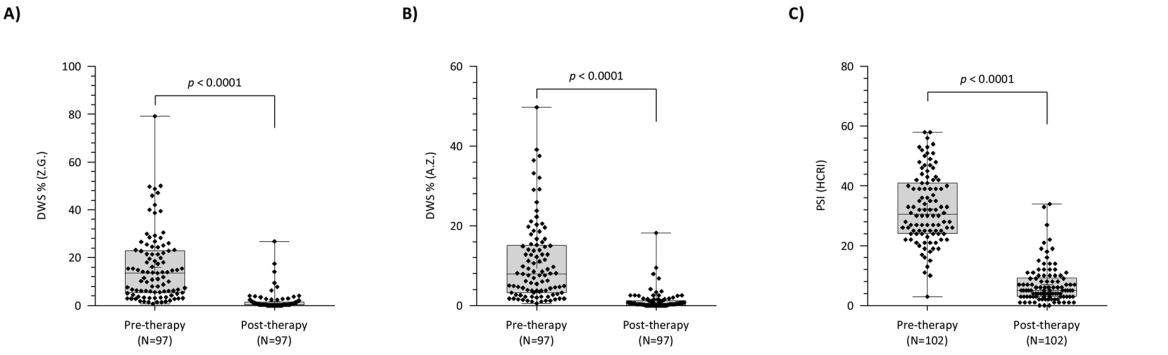
3. Results

Fluency ratings were made by quantifying percent disfluencies scored from videotaped speech samples that contained both directed speech and reading of a standard diagnostic text. Although the scores for individual subjects showed some variation between the two speech language pathologist raters (Z.G. and A.Z.), they were highly correlated (Pearson's $r = 0.971–0.975$, $p < 0.0001$) (Table 1). We also tested inter-rater reliability (IRR) on pre- and post-therapy DWS scores using Fleiss's Kappa reliability of agreement test (Lantz & Nebenzahl, 1996). The scores from the two trained speech-language pathologists (A.Z. and Z.G.) were normalized and converted to binary and nominal values, where a resulting value of 1.0 indicates perfect inter-rater agreement and 0.0 indicates no agreement. IRR in pre- and post-therapy scores displayed 97% and 93% agreement, respectively, demonstrating high consistency between raters. Based on the high correlation between raters, we used the mean of the two DWS scores for each subject for subsequent analyses.

Post-therapy video speech recordings were made one day following the completion of the therapy program, with subjects instructed to use strategies learned during therapy. Pre-therapy and post-therapy reading passages used the same text (either text A or text B, Appendix), read to the same therapist. Pre-therapy dysfluency scores were significantly higher than those immediately post-therapy in both mutation carriers and non-mutation carriers, indicating a strong effect of therapy overall, as measured by both percent dysfluent words (DWS, paired t-test, $p < 0.0001$, Fig. 1A and B) and self-reported stuttering perceptions (PSI, paired t-test, $p < 0.0001$, Fig. 1C). While the pre-therapy scores varied for both DWS (range 0.5–79.17) and PSI (range 3.0–58.0), post-therapy scores were low (DWS range 0.0–26.83; PSI range 0.0–34.0) indicating that fluency immediately following this therapy program was generally high, both as externally measured by independent ratings done by speech-language professionals and by subject self-report.

Therapy efficacy measured by DWS was somewhat less in subjects who carried a mutation in a known stuttering gene compared to those without a mutation, although this difference did not achieve statistical significance (independent t-test, $p = 0.1172$, Fig. 2A). Despite this failure to reach statistical significance, the direction of the difference observed was consistent with possibly poorer therapy outcomes in mutations carriers by this measure.

The change in stuttering symptoms measured by PSI, which includes self-perceived fluency as well as self-reported struggle, avoidance and expectancy associated with speaking, showed a significant difference between mutation carriers and non-mutation carriers. Subjects with a mutation achieved less resolution of symptoms following this therapy program. This was true with both the

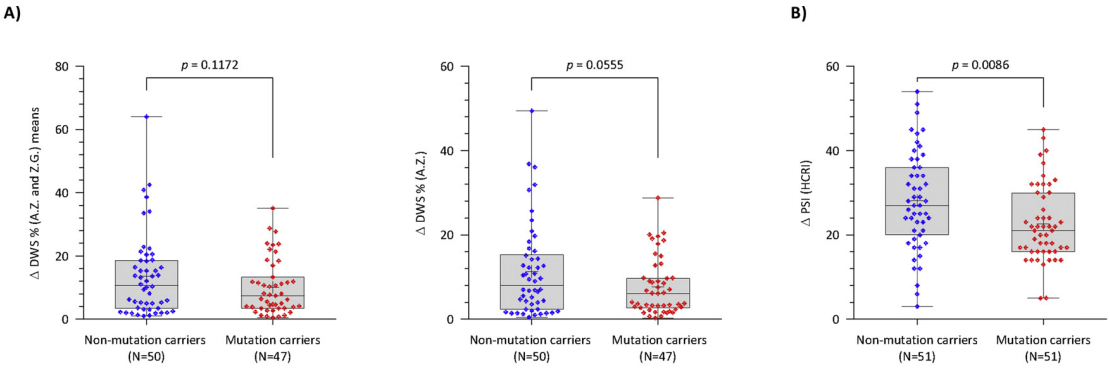


Statistic	Pre-therapy	Post-therapy
Minimum	0.71	0
Median	13.59	0.39
Maximum	79.17	26.83
Mean	15.9	1.64
SD	14.21	3.699
SEM	2.185	1.552

Statistic	Pre-therapy	Post-therapy
Minimum	0.5	0
Median	7.9	0.5
Maximum	49.7	18.2
Mean	10.76	1.182
SD	9.944	2.335
SEM	1.546	0.9898

Statistic	Pre-therapy	Post-therapy
Minimum	3	0
Median	30.5	5
Maximum	58	34
Mean	32.38	7.02
SD	11.63	6.41
SEM	1.633	1.261

Fig. 1. Fluency diagnostic measures for all subjects combined. Box & Whisker plots show mean and standard deviation (SD) of fluency scores, with numerical statistics listed below for each group. SEM – standard error of the mean, DWS – dysfluent word score, PSI – Perception of Stuttering Inventory. (A) Z.G. evaluation using DWS%, paired t-test, $p < 0.0001$. (B) A.Z. evaluation using DWS%, paired t-test, $p < 0.0001$. (C) Self-reported stuttering perception (PSI), paired t-test, $p < 0.0001$.



Statistic	Non-mutation carriers (N=50)	Mutation carriers (N=47)
Minimum	1.03	0.52
Median	10.72	7.46
Maximum	64.1	35.09
Mean	13.65	10.07
SD	13.05	8.659
SEM	1.845	1.263

Statistic	Non-mutation carriers (N=50)	Mutation carriers (N=47)
Minimum	0.5	0.3
Median	8.05	6.1
Maximum	49.4	28.8
Mean	11.32	7.713
SD	10.93	6.786
SEM	1.546	0.9898

Statistic	Non-mutation carriers (N=51)	Mutation carriers (N=51)
Minimum	3	5
Median	27	21
Maximum	54	45
Mean	28.12	22.59
SD	11.66	9.003
SEM	1.633	1.261

Fig. 2. Change in fluency following therapy. Box & Whisker plots show mean and standard deviation (SD) of fluency scores, with numerical statistics listed below for each group. SEM – standard error of the mean, DWS – dysfluent word score, PSI – Perception of Stuttering Inventory. Mutation carriers in red, Non-mutation carriers in blue. (A) Speech-language pathologists – mean of A.Z. and Z.G. DWS % Δ values, independent *t*-test, $p = 0.1172$ and (B) Speech-language pathologists A.Z. DWS % Δ values, independent *t*-test, $p = 0.0555$ (C) HCRI self-reported stuttering perception (PSI), independent *t*-test, $p = 0.0086$ (51 × 51) and, (D) $p = 0.0091$ (50 × 47).

full set of 51 non-mutation and 51 mutation carriers (independent *t*-test, $p = 0.0086$, Fig. 2B), as well as the subset of 50 mutation carriers and 47 non-mutation carriers that could be measured with DWS (data not shown, independent *t*-test, $p = 0.0091$). The presence of a mutation was associated with a reduction in the effect of therapy on PSI scores with a relative risk of 1.75 and an odds ratio (OR) of 2.92, $p = 0.0157$ (Fisher's exact test) (Table 2).

4. Discussion

Factors that influence stuttering therapy outcomes have been extensively studied (Baxter et al., 2016a; Cook et al., 2013; Euler, Lange, Schroeder, & Neumann, 2014; Ingham & Andrews, 1973; Iverach, Jones, et al., 2009; Iverach, O'Brian, et al., 2009). These studies have noted a variety of factors that can affect outcomes, but the breadth of stuttering therapy methods, differences in the subject populations studied, and differences in efficacy measures has limited the generalizability of the conclusions from any individual study. In addition, the investigation of genetic factors in stuttering and in stuttering therapy outcomes has suffered from a lack of specific identified genetic variants associated with this disorder, which has previously hampered the ability to test for an association of such variants with therapy outcomes. With four genes now identified, we have made a limited initial inquiry into this question, using a group of subjects who underwent a specific and standardized intensive fluency shaping therapy program.

We tested short-term therapy outcomes by measuring the difference in fluency before and immediately after therapy using video recordings of subject's directed speech and reading of a standard diagnostic passage. Two independent raters scored each subject's recording pre- and post-therapy, with raters blinded to mutation status. We also tested therapy outcomes using the PSI, in which individuals self-report their struggle, avoidance and expectancy behavior associated with speaking. All subjects were blinded to their own mutation status.

Our results indicate that carrying a mutation in one of the known stuttering genes can affect therapy outcomes, with mutation carriers achieving less resolution of self-reported stuttering symptoms, and possibly less resolution of stuttering disfluencies as measured by speech-language pathologists. Regarding effect size, we found an OR of 2.922 for PSI scores, and the between-group

Table 2
Therapy efficacy effect sizes. Relative risk (RR), odds ratios (OR) and significance, Fisher's exact test.

Parameter	Speech-language pathologist	*N*, Mutation carriers		*N*, Non-mutation carriers	RR	OR	*p*-Value
Δ DWS %	Z.G.	47	vs.	50	1.518	2.176	0.0956
	A.Z.	47	vs.	50	1.454	2.008	0.1429
	A.Z. and Z.G. mean	47	vs.	50	1.613	2.414	0.0592
Δ PSI	–	51	vs.	51	1.749	2.922	0.0157

difference in therapy outcome for self-reported stuttering symptoms measured by *t*-test was highly significant ($p = 0.0086–0.0091$) (Fig. 2C and D). Our results did not support a statistically significant difference in outcomes when fluency was measured by external raters. However, these showed a trend toward significance in the same direction, that is, with mutation carriers achieving less therapy success when measured by Percent Words Stuttered scores as well. While our subject sample contained both males, females and individuals of different ethnicities, it predominantly consisted of males of European ancestry, and the number of other subjects did not provide sufficient statistical power to examine possible effects in males versus females, or in European versus non-European subgroups. Likewise, our subjects carried mutations any one of four different genes, and our analysis pooled these subjects based on the shared biological function of these genes, which encode unique, specific, and closely related cellular functions in intracellular trafficking. Our sample size had insufficient power to detect therapy effects in sub-groups carrying a mutation in any of these genes individually. Our results suggest additional future studies that might resolve this definitively.

One important caveat of our study is the nature of the speech samples that were available for analysis. The speech samples predominantly consisted of reading a standard passage, and contained limited spontaneous speech, which was directed. Fluency can often differ between reading and conversation, and thus our conclusions might best apply to fluency while reading aloud. Another concern could be adaptation, because repeated practice of a reading passage can improve fluency. In our study, the passage was read twice, once each to the generate the pre- and post-therapy DWS scores. The two readings were separated by 12 days. In the intervening time, there was no practice reading and no therapy activity that involved oral reading. Because fluency improvements due to adaptation to an oral reading passage typically involve multiple repetitions (Max, Caruso, & Vandevenne, 1997; Venkatagiri, Nataraja, & Deepthi, 2013) we believe adaptation is unlikely to provide a significant contribution to the fluency differences we observed.

Our findings may have been influenced by the intensive fluency shaping therapy approach used in this study, which was associated with large fluency improvements immediately following therapy. Measuring therapy outcome in this way may not fully capture long-term outcomes or other relevant factors, but our findings either significantly support or are suggestive of the view that therapy achieves poorer outcomes in individuals who carry a stuttering gene mutation. This may be because the expression of genetic mutations is lifelong and can lead to disorders that do not improve with time. The fluency shaping therapy approach is strongly motor oriented, so it is perhaps not surprising that the non-motor components of stuttering, including anxiety and self-perception of stuttering as measured by the PSI, appear to be more resistant to this particular therapy approach, both in general and in mutation carriers.

We also note that stuttering treatment outcomes are influenced by many factors, of which genetics is only one (Andrews & Craig, 1988; Baxter et al., 2016b; Block et al., 2006; Blomgren, 2010). The fact that we observed significant effects of genetic factors in therapy outcomes suggests that genetics, along with other individual characteristics, play an important role in persistent stuttering therapy and therapy outcomes. This indicates that while the genetic factors in stuttering are not yet fully enumerated, they may develop greater clinical relevance in stuttering treatment plans as more such factors are identified.

A strength of our study is the standardized and consistent therapy program provided to all subjects, which served to minimize possible effect of therapy differences between subjects. A potential weakness of our study is that all subjects enrolled reported a family history of stuttering. Our subjects were evaluated for mutations only in the four genes which have been demonstrated to be associated with stuttering to date. Mutations in other genes are also likely to be associated with stuttering, and our non-mutation carrier group could well have contained individuals with mutations in other genes. Thus, our conclusions regarding therapy outcomes currently apply only to individuals who carry a mutation in the *GNPTAB*, *GNPTG*, *NAGPA*, or *AP4E1* genes. Our conclusions may apply differently or not at all to stuttering subjects who carry mutations in other genes. However, we note that if mutations in unknown genes were present in our non-mutation carrier group and if these mutations also gave rise to poorer therapy outcomes, this would tend to weaken, rather than erroneously strengthen, the between-group differences we found. The fact that we found a statistically significant difference thus adds confidence to our conclusion that mutations in one of the four genes tested are associated with a poorer therapy outcome as measured by PSI, and may be associated with a poorer outcome as measured by PWS.

We also note that the subjects enrolled in this study were individuals with persistent stuttering age 16 and over. Our findings may or may not apply to younger individuals, and they do not provide information regarding individuals who display spontaneous recovery from stuttering. Overall, however, knowledge of specific genetic factors in individuals who stutter may be informative for speech language pathology interventions in this disorder. As additional genetic factors in stuttering become known, a conversation among stakeholders regarding incorporating genetic testing in the development of individuals' stuttering therapy plans may become warranted.

Conflicts of interest

R.W. is an employee of the The Hollins Communications Research Institute, a 501(c) (3) not for profit organization. All authors declare no conflicts of interest.

Author contributions

C.D., E.S., and J.G. performed DNA sequencing and analyses, Z.G. and A.Z. performed speech diagnoses, C.D. performed the statistical analyses, C.B. and R.W. supervised the speech diagnostic methods, R.W. and D.D. enrolled research subjects, and D.D. supervised the study and wrote the manuscript with contributions from all authors.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.jcomdis.2019.03.007.

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