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Tutorial

Precision Medicine as a New Frontier in Speech-Language Pathology: How Applying Insights From Behavior Genomics Can Improve Outcomes in Communication Disorders

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ABSTRACT

Purpose: Precision medicine is an emerging intervention paradigm that leverages knowledge of risk factors such as genotypes, lifestyle, and environment toward proactive and personalized interventions. Regarding genetic risk factors, examples of interventions informed by the field of medical genomics are pharmacological interventions tailored to an individual's genotype and anticipatory guidance for children whose hearing impairment is predicted to be progressive. Here, we show how principles of precision medicine and insights from behavior genomics have relevance for novel management strategies of behaviorally expressed disorders, especially disorders of spoken language.
Method: This tutorial presents an overview of precision medicine, medical genomics, and behavior genomics; case examples of improved outcomes; and strategic goals toward enhancing clinical practice.
Results: Speech-language pathologists (SLPs) see individuals with various communication disorders due to genetic variants. Ways of using insights from behavior genomics and implementing principles of precision medicine include recognizing early signs of undiagnosed genetic disorders in an individual's communication patterns, making appropriate referrals to genetics professionals, and incorporating genetic findings into management plans. Patients benefit from a genetics diagnosis by gaining a deeper and more prognostic understanding of their condition, obtaining more precisely targeted interventions, and learning about their recurrence risks.
Conclusions: SLPs can achieve improved outcomes by expanding their purview to include genetics. To drive this new interdisciplinary framework forward, goals should include systematic training in clinical genetics for SLPs, enhanced understanding of genotype–phenotype associations, leveraging insights from animal models, optimizing interprofessional team efforts, and developing novel proactive and personalized interventions.

Speech-language pathologists (SLPs) are trained to diagnose and treat conditions that interfere with interpersonal communication and thus are expressed behaviorally. Many of these conditions have known genetic or chromosomal associations. These include diseases and syndromes affecting communication skills with adult onset, such has

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amyotropic lateral sclerosis, Alzheimer's disease, Huntington's disease, and Parkinson's disease. Similarly, pediatric SLPs see children with communication disorders of known genetic associations, for instance, 22q11.2 deletion syndrome, Angelman syndrome, autism spectrum disorder (ASD), CHARGE syndrome, Down syndrome, fragile X syndrome, Rett syndrome, and rolandic epilepsy. These conditions are relatively rare and severe, and some can be caused by a change in a single gene, for instance, the *HTT* (Huntingtin) gene in Huntington's disease and the *FMR1* (fragile X messenger ribonucleoprotein 1) gene in fragile X syndrome.

Nonsyndromic disorders of spoken and written communication such as speech sound disorder (SSD) including its severe subtype, childhood apraxia of speech (CAS), stuttering, developmental language disorder (DLD), and dyslexia, all represented on many pediatric SLPs' caseloads, are more common and also under genetic influence. However, their exact genetic mechanisms are not as well understood yet as those underlying many syndromic presentations. One reason for this is heterogeneity*[1]—the fact that many different genes have been implicated in different individuals with the same condition. The genetic etiology of nonsyndromic communication disorders is further complicated in that they can arise from interacting effects of multiple genes in the same individual, the same gene can be implicated in more than one type of communication disorder, and environmental factors can play a role as well (Becker et al., 2017; Grandjean & Landrigan, 2014; Guerra & Cacabelos, 2019).

Despite these challenges in characterizing the genetic etiologies of nonsyndromic communication disorders, substantial progress in discovering some genetic causes has been made, even if they do not explain the presence of a condition in the majority of cases. For instance, in some families with familial stuttering, variants* in *GNPTAB* and in the functionally related genes *GNPTG* and *NAGPA* (Kang et al., 2010) were found. More recently, *AP4E1* was implicated in families with familial stuttering (Raza et al., 2015). CAS has been linked to various genetic etiologies including changes in the *FOXP2* (Lai et al., 2001) and *BCL11A* (Bruce & Peter, 2022; Peron et al., 2021; Peter et al., 2014) genes, deletion of several genes on Chromosome 16 (Fedorenko et al., 2016), and duplication of a region on Chromosome 7 (Mervis et al., 2015; Velleman & Mervis, 2011). Several genes of interest have been associated with dyslexia, including *KIAA0319*, *ROBO1* (Mascheretti et al., 2014), *DCDC2* (Marino et al., 2012), *DYX1C1* (Marino et al., 2007), *FOXP2*, and *CNTNAP2* (Peter et al., 2011). Some of the same genes implicated in dyslexia are also relevant for CAS, for instance, *KIAA0319* (Mascheretti et al., 2014; Worthey et al., 2013) and *SETBP1* (Eising et al., 2018; Hildebrand et al., 2020; Perdue et al., 2019). DLD has been associated with various chromosomal regions including Chromosomes 16q23, 10q12, and 13q21 (Bartlett et al., 2002; SLI Consortium, 2002, 2004; Newbury, Warburton, et al., 2009) and the *CMIP*, *ATP2C2* (Newbury, Winchester, et al., 2009), and *BUD13* (Andres et al., 2022) genes. For more extensive overviews, see recent reviews (Becker et al., 2017; Graham et al., 2015; Guerra & Cacabelos, 2019). Note that these findings all underscore the heterogeneous and complex mechanisms underlying common communication disorders.

Whether a genetic condition is rare and syndromic or common and nonsyndromic, it can be inherited and run in families, or it can occur sporadically in a given individual due to genetic changes that are not present in the parents. The latter of these scenarios, also referred to as *de novo**, describes a genetic condition that can be diagnosed in someone without a previous family history of that condition; however, once the condition exists, it can be passed along to future generations. In some cases, the presenting condition may be of a genetic or chromosomal origin that has not yet been recognized as a diagnostic entity in the literature, but it nonetheless affects the patient's communication abilities.

Verbal communication signals are complex and highly susceptible to perturbations, for instance, due to motor control deficits, muscle weakness, and psychological factors. Because the speech signal encapsulates manifestations of the neuromuscular system, it offers diagnostic potential for underlying conditions of genetic origin (Chenausky & Tager-Flusberg, 2022). SLPs are uniquely trained to pick up on these characteristics, which makes it possible to recognize them as the earliest signs of a disorder or syndrome of genetic origin that has not yet been diagnosed in a given patient.

Conventionally, treatment in speech-language pathology is not initiated until a qualifying diagnosis of presenting signs and symptoms has been made, for instance, not until the age of 2–5 years for SSD and DLD and age of 6–8 years for dyslexia. Proactive interventions are rarely available. Another limitation is that treatments are typically evaluated for their efficacy in groups of patients, where the effect sizes represent average improvements. Individually tailored interventions based on specific genetic risk factors are rarely available (Dodd, 2021).

In this tutorial, we propose that translating knowledge and skills from the field of genomics* into the field of speech-language pathology has the potential to improve clinical outcomes. This can be achieved via multiple avenues, including SLPs' enhanced understanding of their

[1]See the Glossary in the Appendix for definitions of technical terms, underlined and marked with an asterisk in the text at first mention.

patients' conditions, earlier and more personalized clinical management, and more comprehensive and effective medical care when SLPs make appropriate referrals based on the clues they observed in the speech and language performance of their patients.

Whether or not SLPs are equipped with relevant knowledge and skills in the area of genetics was the focus of a recent survey of 283 practicing SLPs (Peter, Dougherty, et al., 2019). Also among the respondents were 233 practicing audiologists. We asked the respondents to share their views on how relevant knowledge of genetics was for their field and to rate their own competence in applying principles of genetics in their work setting. The majority of SLPs indicated that they were aware of the relevance of genetics in their clinical specialty (median Likert score = 3.8, where, on a scale of 1–5, 5 indicates the *highest level of agreement* and 1 indicates the *highest level of disagreement*), but they rated their own competence in implementing principles of genetics as low (median Likert score = 1.9). The 2020 certification standards of the American Speech-Language-Hearing Association (ASHA) do not explicitly require any training in genetics; the required training in the biological sciences can be fulfilled by a course in "biology, human anatomy and physiology, neuroanatomy and neurophysiology, human genetics, or veterinary science" (https://www.asha.org/certification/2020-slp-certification-standards/). This is in contrast with the ASHA certification standards for audiologists, requiring that applicants have demonstrated knowledge of "genetics, embryology and development of the auditory and vestibular systems, anatomy and physiology, neuroanatomy and neurophysiology, and pathophysiology of hearing and balance over the life span" (https://www.asha.org/certification/2020-audiology-certification-standards/). It is acknowledged here that the genetic etiologies of hearing impairment are better understood than those of primary disorders of spoken and written language (stuttering, SSD, CAS, DLD, dyslexia), largely because variants in many different and well-described single genes disrupt an affected individual's auditory system in predictable ways, whereas the genetic etiology of common nonsyndromic communication disorders appears to be more complex. Accordingly, in our survey, the audiologists rated the relevance of genetics knowledge in their field with a median Likert score of 4.4 and their own competence with a median Likert score of 2.8, with both ratings being higher than those obtained from the SLPs. In both professional groups, however, the competence ratings lagged behind the relevance ratings, consistent with the perceived need for additional training. In light of these findings, it is not surprising that 84% of the SLPs and 87% of the audiologists indicated the need for additional training in genetics; understanding the genetic causes of disorders was the topic mentioned most frequently.

In what follows, we show how knowledge of genetics/genomics can be leveraged toward improved outcomes in speech-language pathology. We begin with precision medicine and go on to show how its major principles can be translated into the field of speech-language pathology, informed by insights generated by bench scientists.

What Is Precision Medicine?

In his book *The Language of Life: DNA and the Revolution in Personalized Medicine* (Collins, 2010), Francis Collins, MD, PhD, a physician and geneticist who was the director of the National Institutes of Health from 2009 to 2021 and the head of the Human Genome Project*, urges his readers to leverage the power that resides in the knowledge of one's own genome. He writes, "Recent discoveries place us in a position to make several strong statements: (1) for each disease, specific genetic and environmental risk factors exist, and are rapidly being identified; (2) these discoveries are providing powerful new insights into both treatment and prevention; (3) the more you know about all this, the more you can adjust your own lifestyle and medical surveillance to prevent illnesses or catch them in early and treatable stages" (p. 61). Common examples of leveraging this type of knowledge are early and frequent checks for cancers that run in the family and making dietary and exercise changes when cardiovascular disease is a known risk. The book was published 7 years after the completion of the Human Genome Project. Next-generation sequencing, a revolutionary advance in DNA sequencing technology, had introduced an explosive growth in knowledge of human genotype–phenotype associations*. Direct-to-consumer providers began offering genotyping* services on a broad scale, making information about one's own genetic profiles widely available. Two concepts are central to Collins' book: personalized treatment approaches based on a patient's individual genetic risk factors and proactive approaches leveraging known genetic risks toward preventing a disease long before it becomes manifest.

Collins' perspective is that of a physician and geneticist. Diseases discussed in the book include cancer, diabetes, heart disease, cystic fibrosis, phenylketonuria, Marfan syndrome, fragile X syndrome, asthma, stroke, obesity, high blood pressure, and several other medical conditions. Although many genetic causes were known at the time of Collins' book, critical gaps, referred to as "the dark matter of the genome*" or "missing heritability," still existed.

To address these knowledge gaps with a massive research endeavor, the Precision Medicine Initiative, now called All of Us, was officially launched in 2015. Funded by the National Institutes of Health and other research centers, All of Us is based on principles of precision

medicine. According to the Precision Medicine Initiative, as cited in MedlinePlus (2022), precision medicine is "an emerging approach for disease treatment and prevention that takes into account individual variability in genes, environment, and lifestyle for each person." The MedlinePlus article goes on to explain, "This approach will allow doctors and researchers to predict more accurately which treatment and prevention strategies for a particular disease will work in which groups of people. It is in contrast to a one-size-fits-all approach, in which disease treatment and prevention strategies are developed for the average person, with less consideration for the differences between individuals." Thus, precision medicine encapsulates the two concepts of central importance in Collins' (2010) book, prevention and personalization.

All of Us aims to investigate how health and wellness can be optimized by taking into account an individual's environment, lifestyle, and genetic and familial influences toward two major types of clinical translations, namely, prevention and personalized treatment strategies. This work is underway now in a large participant sample designed to include over 1 million participants, intentionally selected to reflect the demographic diversity of people in the United States and to include especially those groups that have previously been underrepresented in research (All of Us Research Program Investigators et al., 2019). Initially, only persons 18 years or older were included, with plans to expand to children later on.

Originally focused on cancer (Collins & Varmus, 2015), the All of Us initiative has expanded to include additional medical conditions, ranked here by their combined prevalence and incidence rates over 10 years per 1 million people (All of Us Research Program Investigators et al., 2019): essential hypertension (592k), diabetes (230k), depression (202k), atrial fibrillation (135k), chronic renal failure (125k), congestive heart failure (114k), asthma (106k), COPD (82k), rheumatoid arthritis (70k), myocardial infarction (66k), thrombosis (48k), epilepsy (45k), breast cancer (42k), stroke (32k), prostate cancer (28k), dementia (23k), lupus (21k), lung cancer (16k), colorectal cancer (16k), abdominal aortic aneurisms (14k), melanoma (10k), and Parkinson's disease (8k).

As of March 2022, DNA data for All of Us participants are available to qualified researchers through the All of Us Workbench (https://workbench.researchallofus.org/), using stringent mechanisms of privacy protection. These data will enable comprehensive analyses of associations between genetic variants and disease on a previously unattainable scale, leveraging both large sample sizes to increase power and robust cloud computing infrastructure.

As new knowledge regarding genotype–phenotype associations rapidly emerges, the potential for clinical translations increases. This includes early identification of individuals at a genetic risk for diseases as well as the development and implementation of individualized and preventive management strategies. To fully leverage this potential, service designers and providers need adequate training in genetics and genomics*. According to recent studies and surveys, this need is recognized but not yet fully met among many medical professions (Campion et al., 2019; Dasgupta et al., 2020) including physicians (Rubanovich et al., 2018), nurses (Calzone et al., 2010), physician assistants (Goldgar et al., 2016), and physical therapists (Curtis et al., 2016), to name a few of the relevant professions.

Medical Genetics/Genomics Versus Behavior Genetics/Genomics

The field of genetics research is broad, encapsulating both medical genetics* and behavior genetics*. Note that these two terms have been modified in recent years to also include the word *genomics*, thus broadening the purview from the study of individual genes to the entirety of all genes and intergenic regions. Through their research endeavors, both medical genetics/genomics and behavioral genetics/genomics deliver knowledge that informs the practice of precision medicine. The essence of medical genetics/genomics is captured in the American College of Medical Genetics and Genomics (ACMG) vision and mission statements: "ACMG will empower its members to be leaders in the integration of genetics and genomics into all of medicine and healthcare, resulting in improved personal and public health. [. . .] to reinforce and expand ACMG's position as the leader and prominent authority in the field of medical genetics and genomics, including clinical research, while educating the medical community on the significant role that genetics and genomics will continue to play in understanding, preventing, treating and curing disease" (https://www.acmg.net/ACMG/About/Vision-and-Mission/ACMG/About_ACMG/Vision_and_Mission.aspx?hkey=f2cf421f-561a-484d-ae71-dee91b46615e).

The journal published by the ACMG is *Genetics in Medicine*, with the following stated purpose: "The journal's mission is to enhance the knowledge, understanding, and practice of medical genetics and genomics through publications in clinical and laboratory genetics and genomics, including ethical, legal, and social issues as well as public health. As genetics and genomics continue to increase in importance and relevance in medical practice, the journal will be an accessible and authoritative resource for the dissemination of medical genetic knowledge to all medical providers through appropriate original research, reviews, commentaries, standards, and guidelines" (https://www.gimjournal.org/content/aims). The use of the terms

"medical practice" and "medical providers" is indicative of the focus on conditions that largely affect a person's physical health and that are managed via medical interventions. Hearing impairment is an example of a condition that benefits from knowledge of the genetic etiology, as the different types of hearing impairment are caused by different genetic etiologies, are characterized by specific disruptions of the auditory system, and can be static (e.g., *GJB2* related) or progressive (e.g., Usher syndrome, Pendred syndrome). This knowledge has clear implications for personalized and proactive clinical management (Alford et al., 2014).

An area that complements medical genetics is *behavior* genetics/genomics. The Behavior Genetics Association (BGA) is an international organization with a long history of twin and family studies investigating behavioral traits. The following is the BGA purpose statement: "The purpose of the Behavior Genetics Association is to promote the scientific study of the interrelationship of genetic mechanisms and behavior, both human and animal; to encourage and aid the education and training of research workers in the field of behavior genetics; and to aid in the dissemination and interpretation to the general public of knowledge concerning the interrelationship of genetics and behavior, and its implications for health and human development and education" (http://bga.org/about/).

The BGA publishes the journal *Behavior Genetics* that, according to its online description (http://bga.org/journal/), "disseminates the most current original research on the inheritance and evolution of behavioral characteristics in humans and other species." Human traits addressed in the journal cover disordered and typical development. The following traits are among those addressed in *Behavior Genetics* articles since 2020 to the time of this writing: neurodevelopmental disorders, ASD, attention-deficit/hyperactivity disorder (ADHD), negative affect, internalizing and externalizing behaviors, substance use disorders, use of coffee/drugs/alcohol/nicotine, learning disabilities, social communication, disorders of spoken and written language, phonological awareness, semantic verbal fluency, depression, anxiety, aggression, psychological effects of the COVID-19 pandemic, eating disorders, fear, cognitive development, cognitive aging, exercise behaviors, sensory processing, response to stress, school achievement, intelligence, physical fitness, sex and gender issues, spatial learning, memory, psychiatric resilience, and sleep patterns. Methodological topics included complex trait analysis, twin studies, polygenic risk scores, gene-by-environment interaction analysis, and population stratification analysis.

Thus, although medical genetics/genomics and behavior genetics/genomics may overlap in some aspects of neurologic and psychiatric phenotypes, as well as in some genetic and genomic methodologies, these two fields generally address two different types of health conditions, medical (physical) versus behavioral (mental), and two different types of service providers, those trained in medical schools versus those trained in professional programs such as clinical psychology, psychotherapy, special education, and counseling. Perhaps most crucial is the difference in the state of clinical translations. The ACMG mission statement emphasizes the role that genetics and genomics play in understanding, preventing, treating, and curing diseases and application of genetics and genomics knowledge in medical practice, whereas the BGA mission statement focuses more on research and education. The BGA mission statement mentions implications for health and human development and education, but not direct application of knowledge of genetics in clinical practice. One indicator of the relatively more advanced status of applied knowledge in medical genetics/genomics, compared to behavior genetics/genomics, is the distribution of traits covered in the Database of Genotypes and Phenotypes (https://www.ncbi.nlm.nih.gov/gap/). Of the 460 study disease/focus terms listed at the time of this writing for which genomic data have been contributed, only approximately 35 fit into the realm of behavioral traits, for example, anxiety, attention-deficit disorder, ADHD, addictive behavior, language development, obsessive–compulsive disorder, posttraumatic stress disorder, and taste perception.

Epigenetics

In both arenas, medical genetics/genomics and behavior genetics/genomics, the current understanding of individual risk toward developing complex disorders now extends beyond the inherited DNA sequences that make up the genome. Epigenetics* refers to the highly complex regulatory code that serves to control gene expression, either by upregulating or downregulating genetic expression or through gene silencing* (Gibney & Nolan, 2010). Epigenetic processes such as DNA methylation*, RNA*-based mechanisms, and changes in chromatin* structure by histone modifications* are key regulators of neuronal development and thus can play an important role in disease risk and development (Kiefer, 2007). Importantly, epigenetic modifications, especially DNA methylation, can be modified by environmental exposures such as stress, toxins, and nutrition (Bollati & Baccarelli, 2010; Jang & Serra, 2014; Stankiewicz et al., 2013). Taking this into account, an individual is unique not only in their genomic landscape but also in their epigenetic landscape that has been shaped by their individual lived experience. Therefore, the future of precision medicine and behavior genetics/genomics should include consideration of the epigenome* alongside with the genome in developing targeted treatment strategies. For example, effective behavioral interventions can be designed and developed based

on epigenetic profiles to inform disorder prevention and treatment (Szyf et al., 2016).

Potential Benefits of Translating Principles of Precision Medicine Into Speech-Language Pathology

It is not uncommon for patients to present with speech and/or language difficulties before their medical and genetic diagnosis. With training (further described below), SLPs can recognize the earliest signs of a known condition of genetic etiology, for example, fragile X syndrome or Turner syndrome, and make an appropriate referral to a genetics professional for consultation, which, in turn, may lead to a genetic diagnostics workup and medical management specific to the condition. In other cases, SLPs may recognize the possibility of a genetic cause that has not yet been associated with a known disease or syndrome. Consider the following case: A child was referred for genetic testing due to a severe speech disorder consistent with CAS; he also presented with fine and gross motor delays, hypotonia, and intellectual delays. No one else in the child's family had any of these conditions, and their cause was unknown. A genetics workup, triggered by the simultaneous presence of these diverse conditions, revealed that the child carried a small deletion on Chromosome 2 that involved the heterozygous* *de novo* loss of one complete copy of one gene, *BCL11A* (BAF chromatin remodeling complex subunit BCL11A). At the time of the genetic diagnosis, this gene had not yet been identified as a gene of interest for CAS. However, the fact that *BCL11A* is situated within a larger region that had been implicated in neurodevelopmental and anatomical anomalies helped to establish the loss of one *BCL11A* copy as the likely cause of the child's diverse symptoms (Peter et al., 2014), and subsequent studies confirmed the role of this gene in CAS (Bruce & Peter, 2022; Peron et al., 2021; Soblet et al., 2018).

Benefits of a genetic diagnosis for the patients and their families include learning the cause of their symptoms, receiving anticipatory guidance based on their prognosis, gaining insights regarding the recurrence risk in the family, having relief from guilt feelings (e.g., "I must have done something wrong to cause this problem"), having better access to insurance coverage depending on the insurance company and state, and receiving appropriate personalized and proactive management of the index condition and the comorbid conditions. An important additional benefit is the opportunity to join advocacy or support groups for families with similar genetic or chromosomal diagnoses, for example, via the organization Unique: Understanding Rare Chromosome and Gene Disorders (https://rarechromo.org).

In what follows, we describe actual case examples from the Speech/Language Genetics Lab at Arizona State University that specializes in investigating the genetic origins of communication disorders and developing novel clinical translations. Because communication disorders are often diagnosed in childhood, most research participants in this lab are children. These cases illustrate the potential benefits of knowledge of genetics in clinical SLP scenarios. Note that, in all cases, families obtained closure in that the question of why their child had a certain condition was answered. All parents learned that the condition had not occurred as a result of their own action, relieving them of potential guilt feelings, and parents also learned that a *de novo* event is unlikely to recur in the same family. In some but not all cases, clinical management of the speech disorder was informed by the genetic diagnosis.

1. A 10-year-old girl was diagnosed with CAS and developmental delay. Medical history included seizures, fine and gross motor delays, and trunk and hand weakness. Neither her parents nor her older sister experienced similar conditions in their development. The confluence of these diverse traits raised the suspicion that they could all be caused by a chromosomal or genetic variant unique to the girl. Exome sequencing and variant analysis revealed a rare deleterious *de novo* variant in the *MECP2* (methyl-CpG–binding protein 2) gene that is associated with Rett syndrome. This diagnosis motivated a re-evaluation of the medical management of her symptoms and provided an opportunity for proactive management of potential osteoporosis, as Rett syndrome can result in later bone loss. The diagnosis further made it possible to consider precise medical management strategies that are specific to patients with Rett syndrome due to *MECP2* variants, as opposed to those with variants in other genes (Vidal et al., 2019).
2. A 7-year-old girl had a diagnosis of CAS and developmental delay (Peter et al., 2017). Her medical history included microcephaly, plagiocephaly, ataxic cerebral palsy, optic nerve dysplagia, and hip dysplagia. A magnetic resonance imaging (MRI) scan at the age of 11 months showed mild enlargement of the ventricles, mild hypoplasia of the splenium of the corpus callosum, hypoplasia of the pons, and abnormal gyral pattern bilaterally in the perirolandic region. None of these conditions were seen in her parents and older sister, and the cause could not be determined until genetic testing was done. DNA analysis revealed a *de novo* heterozygous 1.1million–base pair terminal deletion of Chromosome 6q that encompassed 106 genes. Of interest, one other case reported in the literature (Abu-Amero et al., 2010)

exhibited strikingly similar conditions, including several of the features of the brain MRI, developmental delays, and difficulties with speech, although no details were provided regarding the nature of the speech delay. The genetic diagnosis validated the genotype–phenotype association in this region of Chromosome 6. Parents learned that the diverse traits in their daughter were due to their common cause.

3. A 4-year-old boy with CAS, fine and gross motor delays, developmental coordination disorder, congenital heart anomaly, and skeletal anomalies of the chest and feet was receiving speech, physical, and occupational therapies. Both he and his brother had a diagnosis of ASD. Chromosomal testing revealed a *de novo* heterozygous 184-kb 19p13.3 microdeletion. Comparing his genotype* and phenotype* to those in eight published cases with larger deletions in the same chromosomal region confirmed the genotype–phenotype association and supported these deletions as a microdeletion syndrome. This case served to narrow the chromosomal region of interest for this syndrome (Peter, 2023). The family learned that most of the child's speech, motor, and anatomical conditions, but not the ASD diagnosis, were associated with the microdeletion. Evidence that the child's condition resulted from a genetic cause improved his eligibility for insurance coverage of speech and language services.

4. A 5-year-old boy had diagnoses of CAS, expressive DLD, fine and gross motor delays, and hypotonia. He was receiving SLP services, occupational therapy, and physical therapy, all three targeting, among other things, motor coordination. Chromosomal analysis revealed deletion of six genes on Chromosome 6 (Peter et al., 2017). The boy's father, the father's identical twin brother, and the twin brother's son all shared the deletion and a history of motor, speech, and language delays. The insight that the chromosomal variant caused discoordination across motor systems provided an impetus for interprofessional delivery of services, not only for the patient but also for his cousin.

5. A 1-year-old boy was the youngest of five children in a family in which three of the children had severe nonsyndromic CAS. Histories of severe CAS were also reported for his mother and several other biological relatives. The extended family participated in a research study that investigated the speech and language phenotypes as well as DNA variants shared only by the affected family members. The most likely genetic cause in this family was a variant in the *CDH18* gene (Peter et al., 2016). The boy was too young at the time of the study to be evaluated for presence of CAS, but learning that CAS was likely inherited in the family in an autosomal dominant* pattern motivated his parents to seek earliest professional support from SLPs.

6. A 15-year-old female adolescent presented with a history of severe congenital dysfunction across the speech, fine, and gross motor systems, rendering her unable to learn to speak or walk. When she was 10 years old, she and her parents became candidates for whole genome sequencing, resulting in a genetic diagnosis of a *de novo* mutation in the *DDC* (DOPA decarboxylase) gene that encodes a protein relevant for dopamine production. (For this and other details, see https://www.tgen.org/media/491331/tgentoday_c4rcd.pdf.) Within months of receiving dopamine-related medication, she began to walk and speak for the first time. Her speech sound development between the age of 10 and 15 years followed a similar trajectory to that in typical children aged 1–5 years: Soon after beginning to speak, she accurately produced those consonants typically acquired by very young children, but she took 3 years to accurately produce the /g/, /k/, and /ŋ/ sounds and still struggled with the /r/ and /l/ sounds 5 years after onset of speech. This unique case contributed major insights into the natural acquisition of speech sounds: It showed that the typical sequence of speech sound acquisition does not depend on chronological age but rather on successive mastery of motor skills (Peter, Vose, et al., 2019). However, clearly, the greatest benefit from the genetic analysis was the successful use of a pharmacogenetic intervention that enabled the patient to gain the ability to speak and walk.

Leveraging Behavior Genomics in Clinical Sciences

To implement the key tenets of precision medicine (personalized management, proactive interventions) and insights from behavior genomics in clinical sciences, several subgoals are suggested:

- Increased genetics training in the clinical professions: Clinicians should be equipped not only with an understanding of foundational genetics concepts such as modes of inheritance*, *de novo* occurrence, and the different ways that genetic variants can influence physical and/or behavioral traits but also with pragmatic skills and knowledge in the area of clinical genetics* such as familiarity with the role of genetics professionals on an interprofessional team, how to

recognize signs of a disorder of genetic origin, how to gather an informative family history, how to identify patients who may benefit from a consultation with a genetics professional, how to make an appropriate referral, and how to meaningfully inform their own clinical management based on knowledge of the genetic influence on the condition.

Regarding the referral process, SLPs should be aware of certain restrictions based on their employment setting. Whereas in a hospital setting, genetics services may be available in-house with an established referral process, school-based SLPs are prohibited from making professional referrals. In that environment, they can involve the school nurse as the health officer (Council on School Health, 2008; also see the position statement of the National Association of School Nurses, https://files.eric.ed.gov/fulltext/ED558467.pdf). To refer a patient to a genetics professional such as a genetic counselor, SLPs can summarize their concerns, but it is outside their scope of practice to make recommendations regarding genetic testing or to provide a genetic diagnosis. Genetic counselors help patients understand their conditions and learn what their options for genetic testing are, whether or not genetic testing will positively inform clinical management, and how to interpret the results of genetic testing. Once patients have been given this information, they are free to make an informed decision whether or not to take action, for instance, to pursue genetic testing.

As outlined in this tutorial, training in genetics for SLPs can have a broad impact on clinical management and patient outcomes. However, how to best provide this training has not yet been determined. Potential scenarios for clinicians in training include modified professional qualifications to include coursework in genetics, either by adding a genetics component to content courses on the various forms of disorders or by adding a stand-alone genetics course to the curriculum. For practicing clinicians, continuing education opportunities such as workshops, seminars, and certificates may be effective options.

- Increased training in primary syndromes and diseases that affect communication abilities: To enhance SLPs' ability to recognize earliest manifestations of primary conditions underlying their patients' communication disorders, such as 22q11.2 deletion syndrome, CHARGE syndrome, and fragile X syndrome, systematic training in these primary conditions would be helpful. Such training is not currently required for professional certification. SLPs are already involved in interprofessional management of these kinds of conditions; being able to spot their earliest manifestations would contribute meaningfully to patients' clinical management.

- Increasing the knowledge base of genotype–phenotype associations in the behavioral realm: Toward moving the clinical framework from a deficit-based model to a proactive one and from treatment approaches guided by average efficacy data to more personalized approaches, a better understanding of genotype–phenotype associations is warranted. Behavior genomics research should focus not only on causal genotypes but also on their differential effects, given an individual's genetic background. Studies of protective and disease-modifying genotypes are currently occurring in medical genetics, for instance, in a study of resistance against COVID-19 infection (Roberts et al., 2022). Here, the behavior genomics community can contribute valuable insights by rigorously investigating the genetic substrates of conditions that are not yet well understood, for instance, the genetic contributions to stuttering, SSD, CAS, DLD, and dyslexia. Furthermore, gene-by-environment interactions should be further investigated for all types of communication disorders of genetic origin, whether syndromic or nonsyndromic. As further described below, gene-by-environment interactions involve both the physical and social environments and can introduce layers of complexity to genetic influences on phenotypes.

- Animal models: In medical genetic studies, animal models have been used successfully to investigate the effect of DNA variants on specific traits and also the effect of pharmaceutical interventions. The use of animal models in behavioral genetic studies is less common. Examples of animal models in genes of interest for human behavioral traits related to communication disorders are *FOXP2* studies of vocal behaviors in zebra finch (Heston & White, 2015) and mouse (Fong et al., 2018) models. Also relevant are gene expression studies in the motor centers of zebra finch brains as a function of birdsong activity because the gene expression patterns in the zebra finches provide insights for studying genetic drivers of vocal changes in Parkinson's disease (Medina et al., 2022; Miller et al., 2015). These studies leverage parallels between humans and songbirds in certain acoustic parameters that change predictably with age in both species (Badwal et al., 2019, 2020).

- Increased participation in interprofessional practice (IPP): Because a single genetic change has the potential to impact multiple behavioral domains, using an IPP framework can encourage professional collaboration

with an aim to provide a client-centered plan of support. All cases reviewed above involved multiple disciplines providing services, including physicians, educators, psychologists, SLPs, occupational therapists, physical therapists, and audiologists. These cases highlight a need for IPP teams to consider the best ways to individualize and implement interventions based on an individual's specific genetics. A recent ASHA survey indicated that high workloads and limited time for collaborative activities were factors preventing the implementation of IPP (ASHA, 2019). Thus, medical and educational work settings can serve as suitable environments toward the creation of IPP opportunities as a way to support individuals affected by genetic change.

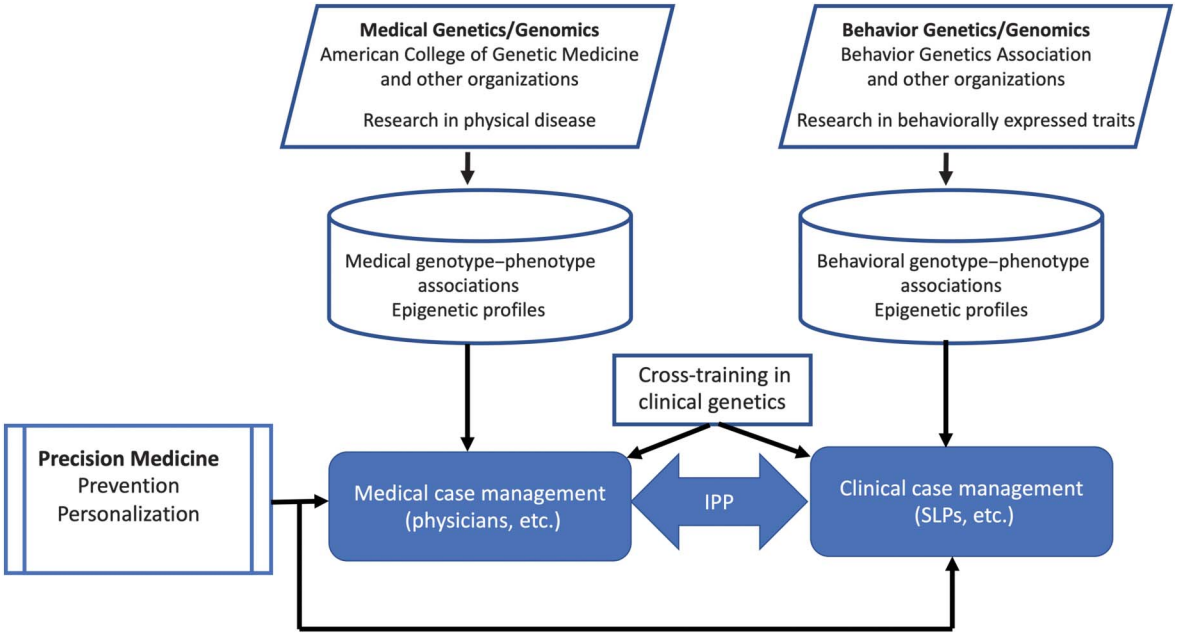
- Development of novel personalized and proactive interventions: An example of such an intervention, currently undergoing clinical trial, is the Babble Boot Camp, developed initially for infants with a newborn diagnosis of classic galactosemia. This inborn error of metabolism is caused by variants in the *GALT* (galactose-1-phosphatase uridylyltransferase) gene via autosomal recessive* inheritance on the short arm of Chromosome 9. Despite strict adherence to a lactose-restricted diet, children with this disease are at a high risk of multiple health impairments but especially severe disorders of speech, language, and the fine and gross motor systems. Babble Boot Camp is a behavioral intervention implemented via parent training that begins as early as children's age of 2 months, ending at children's age of 24 months; thus, importantly, it ends before children are typically old enough for conventional assessment and therapy. Parents learn about developmental milestones and are taught activities and routines designed to increase their child's speech and language perception, babble frequency and sophistication, vocabulary size, syntactic complexity, and social–pragmatic competence. Initial results are consistent with a beneficial and sustained effect of the intervention (Peter, Davis, et al., 2021; Peter, Potter, et al., 2019; Peter et al., 2022) and feasibility in terms of high parent satisfaction and low cost (Finestack et al., 2022). Another way to envision novel therapies informed by a genetic diagnosis is to address not only the surface signs but also the more fundamental and brain-based processing deficit underlying a disorder. For instance, learning disabilities are associated with deficits in sensorimotor gating at the level of the cortex (Perrachione et al., 2016; Peter, McCollum, et al., 2019). Whether or not therapy targeting the underlying deficit is possible and, if so, whether this can positively influence learning outcomes are questions that should be systematically investigated in the future.

In this tutorial, we have provided an overview of the tenets of precision medicine and insights generated by the fields of medical genomics and behavior genomics. Figure 1 illustrates how these components can be implemented in medical and clinical practice, enhanced by cross-training in clinical genetics and IPP.

How Insights From Speech-Language Pathology Can Inform Genomics

As outlined above, patients can benefit in various ways when the practice of speech-language pathology is informed by insights from medical and behavioral genomics, which facilitates novel proactive and personalized approaches. Conversely, insights from speech-language pathology can also inform medical genomics. Verbal communication requires well-functioning neuromuscular infrastructure on many levels. Disruptions in specific subcomponents of the infrastructure can be observed as telltale characteristics in activities of spoken language: in voice production, for example, poor breath control; strained, hoarse, or diplophonic vocalizations; in speech production, for example, evidence of apraxia or dysarthria; in receptive language, for example, impoverished vocabulary or difficulty comprehending complex sentences; in expressive language, for example, unspecific word choice or disorganized syntax; and in social communication, for example, difficulty initiating discourse, staying on topic, or taking turns. As mentioned, because verbal communication is a complex process that involves rapid integration in time and space of cognitive, linguistic, and motoric actions, it is susceptible to perturbations from various sources including incipient diseases and syndromes. Subtle signs in the speech signal can imply neurologic, physiologic, or psychiatric dysfunction at various levels, for example, Broca's area, Wernicke's area, primary motor cortex, cerebellum, cranial nerves, neuromuscular junction, muscle function, and social interaction such as in ASD. Insights from speech-language pathology can inform and enrich the work of medical and behavioral genome scientists in advancing knowledge of genotype–phenotype associations (Chenausky & Tager-Flusberg, 2022), yet in many genetics/genomics publications, the expression patterns in the speech signal are underspecified, for example, delayed speech and language not further characterized (Abu-Amero et al., 2010; Peddibhotla et al., 2013; Peron et al., 2021). Where closer descriptions of the speech and language phenotypes are provided (e.g., "good grammatical structure of language, but had difficulties with semantics and inferencing"; Archer et al., 2005), specifying CAS as the subtype of SSD found in individual cases (Bruce & Peter, 2022; Peter et al., 2014, 2017; Soblet et al., 2018), the genotype–phenotype association is more interpretable in light of other developmental, cognitive, and motor findings.

Figure 1. Schematic of the roles of medical genetics, behavior genetics, precision medicine, and cross-training in clinical genetics. IPP = interprofessional practice; SLPs = speech-language pathologists.



This cross-training in speech-language pathology is relevant not only for genome scientists in the research arena but also for medical service providers in clinical practice. Potential benefits include a heightened awareness of serious delays or disorders that may be an early indicator of a genetic condition and that warrant a referral to an SLP, deeper insights into the nature of a patient's condition, and more precise treatment selections. This type of cross-training is not yet part of the medical school curriculum. In the future, it could be made available via doctoral-level SLPs with training in genetics/genomics who join medical school faculties to integrate core clinical insights from their field into medical science and practice. These SLPs could also contribute valuable insights to the literature by actively conducting research in the genetic causes of communication disorders.

Misconceptions, Unanswered Questions, Caveats, and Limitations

The field of behavior genomics contains several areas in need of clarification. One potential misconception is the idea that if a behavioral condition is influenced by genetic factors, it can only be addressed by genetic measures such as gene editing*, not by behavioral interventions. As described in a recent review (Larsen et al., 2022), in a school context, views of genetic essentialism can have many negative consequences, including social distances from peers and teachers as well as low teacher expectation. With the same reasoning, individuals whose condition is known to be under genetic control might not be motivated to engage in therapy, assuming that the genetic cause leads to permanent and immutable behavior patterns. These misperceptions should be addressed by pointing out that, regardless of cause, behaviorally expressed conditions can be addressed successfully using behavioral techniques (e.g., speech/language therapy, reading intervention, psychotherapy, and family-based interventions).

More generally, it would be a mistake to claim that certain behavioral traits result directly from certain genotypes. Not all genetic variants have full penetrance*; thus, their presence does not determine the trait. An example of nonpenetrance is an obligate carrier* in a family with familial CAS in which a woman's father and children were affected but she was not, although she presumably carried the risk genotype (Peter et al., 2016). In addition, a given genotype can be associated with variable phenotypes among carriers. An example of this variable expressivity is a family consisting of a mother and two sons with a familial 22q11.2 deletion where, despite the identical deletion region, the phenotypes differed substantially in that only the mother and the younger child had congenital heart disease and only the two children but not the mother had submucous clefts (Peter, Scherer, et al., 2021).

Many behaviorally expressed conditions have a complex genotype–phenotype relationship, which makes it challenging to create proactive and personalized interventions based on genotype–phenotype associations alone. First, as illustrated in the case examples above and also

described in various reviews (Becker et al., 2017; Graham & Fisher, 2015; Guerra & Cacabelos, 2019), behaviorally expressed disorders can have many different genetic or chromosomal causes in different individuals. This heterogeneity complicates early identification of children at risk, as many different genetic possibilities must be considered. A related challenge is the fact that behaviorally expressed disorders can result from either single DNA changes of large effect or many DNA changes, each of smaller effect. This scenario is at play in ASD (Bourgeron, 2016; Gaugler et al., 2014) and also in other behaviorally expressed traits, such as dyslexia (Becker et al., 2017). However, even in a complex and heterogeneous condition such as ASD, research into genotype–phenotype relationships is beginning to shed light on the types of behaviors that are more likely to be associated with common variants versus rare *de novo* variants, which may aid precision medicine efforts in ASD. For example, one recent large study (N = 12,893) found common variants to be associated with two ASD subtype presentations: (a) insistence on sameness and (b) self-injurious behavior (Warrier et al., 2022). Moreover, another recent large study (N = 12,270) found both an abundance of common ASD variants (i.e., high ASD polygenic risk scores*) and *de novo* loss-of-function variants* to be associated with greater social difficulties (Antaki et al., 2022). Collectively, information such as this may aid treatment planning and prognostic indications for families with ASD.

As mentioned previously, DNA variants are not the only factors that influence behaviorally expressed traits, and thus, the assumption that all clinical traits have a genetic cause is misleading. Environmental toxins, especially when the early developing central nervous system is exposed to them, can contribute to neurobehavioral traits. For instance, maternal smoking is a risk factor for dyslexia (Becker et al., 2017), and early childhood exposure to lead, methylmercury, inorganic arsenic, polychlorinated biphenyls, ethanol, manganese, excessive fluoride concentration, solvents, pesticides, and fungicides can all have detrimental effects on neurodevelopment, depending on dosage (Grandjean & Landrigan, 2014). In addition, household toxicant use was associated with negative effects on children's language and cognition, particularly during the second year of life (Jiang et al., 2020). Early identification of individual children at risk for behaviorally expressed disorders based on environmental exposure to toxins is a challenge, given the broad spectrum of possible toxins and the lack of universal monitoring systems. Gene-by-environment interactions can further complicate the quantification of risk factors. For instance, one of the genes of interest for dyslexia, *DYX1C*1, influences memory function to a greater extent in the presence of maternal smoking during prenatal development (Mascheretti et al., 2013).

Environmental factors influencing behavioral outcomes are not restricted to the physical environment; the social and emotional environment can play a role as well. For instance, in most individuals who carry a variant in the *MAOA* gene, violent behavior appears to be strongly influenced by environmental risk factors, especially negative childhood experiences. The exact roles of the genetic variant and the negative childhood experiences are not yet fully understood, which contributes to the controversies regarding using a genotype as a legal defense (Beaver et al., 2014; Gonzalez-Tapia & Obsuth, 2015).

Not all behavioral traits associated with genetic variants pose the necessity for an intervention (Plomin et al., 2016). The decision whether to intervene should be made on an individual basis and by the individuals most directly involved.

Conclusions

Principles of precision medicine offer great opportunities for translation into clinical and behavioral sciences, informed by knowledge generated by genome scientists. Here, we have outlined some ways in which patients with behaviorally expressed conditions can benefit from a genetic diagnosis. Toward driving this new approach to clinical practice forward, it is essential that SLPs receive appropriate training in clinical genetics/genomics. Paired with circumspect awareness of caveats and creative approaches to challenges, clinical practice informed by genetics/genomics has the potential of inducing paradigm shifts from conventional postdiagnostic, remediative management strategies to proactive and personalized ones.

Web Resources

All of Us: https://allofus.nih.gov/

American College of Medical Genetics and Genomics: https://www.acmg.net/

Behavior Genetics Association: http://bga.org/

Database of Genotypes and Phenotypes: https://www.ncbi.nlm.nih.gov/gap/

Unique: Understanding Rare Chromosome and Gene Disorders: https://rarechromo.org/

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Appendix

Glossary

Autosomal dominant: a condition resulting from one genetic variant, inherited from one parent.
Autosomal recessive: a condition resulting from two genetic variants, inherited from both parents.
Behavior genetics: implementing principles from genetics in the study and/or management of behaviorally expressed conditions, for instance, aggression or developmental language disorder. Sometimes used interchangeably with "behavior genomics."
Behavior genomics: implementing principles from genomics in the study and/or management of behaviorally expressed conditions, for instance, aggression or developmental language disorder. Sometimes used interchangeably with "behavior genetics."
Chromatin: the material that makes up chromosomes in organisms that are not bacteria.
Clinical genetics: principles of genetics applied in clinical practice. This includes the study of genetic causes, dialogue with patients, and implementing insights from genetics in clinical management.
De novo: a genetic change that was not inherited from a parent; rather, it arose sporadically.
Epigenetics: the study of gene functions altered by environmental influences without a chance in the DNA sequence.
Epigenome: the chemical changes that affect how the genome functions.
Expressivity: the different ways a genetic or chromosomal variant can cause observable traits. Example: Carriers of an extra copy of Chromosome 21 may present with some, but not all, of a number of associated traits, e.g., congenital heart disease, short hands, or strabismus.
Gene editing: changing the DNA sequence of a gene, thus changing the way the gene is expressed. This is done in living cells, using enzymes.
Gene silencing: reducing or preventing a gene's production of its protein product.
Genetics: the study of individual genes. Sometimes used interchangeably with the term *genomics*.
Genome: an individual's entire set of genetic material.
Genomics: the study of the entire DNA sequence, all genes it contains, and all regions between the genes. Sometimes used interchangeably with the term *genetics*.
Genotype: an individual's DNA profile at a given gene position.
Genotype–phenotype association: the effects of a genetic change on an observable trait.
Genotyping: determining an individual's DNA profile at chromosomal regions of interest.
Heterogeneity: Individuals with a similar condition carry different genetic mechanisms that caused their condition.
Heterozygous: Nearly all chromosomes and the genes situated on them are present in pairs that are similar but not necessarily identical. A DNA change only affecting one of the two copies is a heterozygous change.
Histone modification: one way in which gene expression is modified, not by a change in the DNA sequence but by changes in a protein that is a building block of DNA.
Human Genome Project: a large-scale, international effort to sequence the entire human DNA for the first time; conducted between 1990 and 2003 (https://www.genome.gov/human-genome-project).
Loss-of-function variant: a change in the DNA sequence of a gene that interferes with the gene's functional properties.
Medical genetics: implementing principles from genetics in the practice of medicine, for instance, in the management of cancer or epilepsy. Note that the newer term "genomics" is often used in this context to emphasize a more comprehensive purview of the entire genome sequence, not just individual genes.
Methylation: a chemical process where a small molecule, a methyl group, is attached to another molecule such as DNA. Methylation does not change the DNA sequence, but it can alter the way in which a gene functions.
Mode of inheritance: the pattern in which a trait is inherited from one or both parents. Examples: Autosomal dominant inheritance results in a trait due to a variant inherited from just one parent. Autosomal recessive inheritance results in a trait due to variants inherited from both parents. X-linked inheritance results in a trait that is caused by a variant on the X chromosome.
Obligate carrier: an individual who does not show the physical manifestation of a trait but is assumed to have the causal genetic variant based on the family history. This includes the parents of a child who has a recessive condition.
Penetrance: the probability of showing a trait in the presence of a genetic variant. Example: Approximately 65% of women who carry the *BRCA1* risk variant receive a breast cancer diagnosis by the age of 70 years; thus, this variant has an expression rate of approximately 65%.
Phenotype: observable characteristics that resulted from a genetic factor.
Polygenic risk score: a weighted score based on multiple genetic variants that together predict an individual's risk of having a certain condition, compared to a different individual with a different set of variants.
RNA: ribonucleic acid, a molecule that plays a role in the expression of genes.
Translational genetics: applying knowledge from research in genetics/genomics in clinical settings, with the goal of improving outcomes.
Variant: a change in an individual's DNA sequence that differs from that found in the reference population. Formerly referred to as mutation.