# UNDERSTANDING THE SHARED MOLECULAR BACKGROUND OF AUTISM SPECTRUM DISORDERS AND MUSIC PERCEPTION

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**MASTER OF TECHNOLOGY**

**IN**

**BIOINFORMATICS**

*Submitted by*

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**(2K17/BIO/03)**

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## DECLARATION

I, **Elizabeth M. Mathew**, Roll No. **2K17/BIO/03**, student of **M.Tech Bioinformatics**, hereby declare that the Project Dissertation titled "**UNDERSTANDING THE SHARED MOLECULAR BACKGROUND OF AUTISM SPECTRUM DISORDERS AND MUSIC PERCEPTION**" which is submitted by in partial fulfilment for the requirement of the award of degree of Master of Technology, is original and not copied from any source without proper citation. This work has not previously been submitted in part or full for any Degree or Diploma to this University or elsewhere.

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## CERTIFICATE

I, hereby certify that the Project Dissertation titled "**UNDERSTANDING THE SHARED MOLECULAR BACKGROUND OF AUTISM SPECTRUM DISORDERS AND MUSIC PERCEPTION**" which is submitted by **Elizabeth M. Mathew**, Roll No. **2K17/BIO/03**, student of **M.Tech Bioinformatics**, in partial fulfilment for the requirement of the award of degree of Master of Technology, is a record of a project work carried out by the student under my supervision. To the best of my knowledge this work has not been submitted in part or full for any Degree or Diploma to this University or elsewhere.

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**Elizabeth M. Mathew**

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# ABSTRACT

Music is universal. Understanding Music perception forms a foundation for understanding the functioning of the brain. A lot of literature studies have demonstrated that music perception can alter the human brain structure and function and induce physiological changes through neurochemical modulation. More recently different kinds of studies have been done in understanding the molecular background of Music Perception. People with Autism Spectrum Disorders suffer from various disorders. Numerous studies have shown the effects of Music on people with Autism spectrum disorders. But there's no particular study which shows the shared molecular background between these two phenotypes. The Gene set for Music perception was obtained from a study done in understanding the effect of listening to music on the human transcriptome. The ASD gene set was obtained from the SFARI – Autism Database (https://gene.sfari.org). The set approach was used to find out the common genes among these two phenotypes. Three genes SLC6A8, JMJD1C, HDAC4 were found to be common in these two phenotypes.

Rank scores were derived from the number and nature of overlapping genes, gene-disease association, tissue specificity and gene functions subdivided into categories (e.g., diseases, tissues or functional pathways). 3 genes were common in these two phenotypes and mapped to a total of 20 biological pathways including Sumoylation by RanBP2 Regulated transcriptional Repression (Score-9.23), Notch signalling pathway (Score=7.69).Brain tissues included Midbrain tegmentum, Striatum, Medulla Oblongata, Cerebral Cortex and 6 other tissues. Functional analysis of the overlapping genes showed a medium-match for major mental diseases which included cerebral creatine deficiency syndrome 1 (score=2.83), Slc6a8-related creatine transporter deficiency (Score=2.33), intellectual disability (score=1.04), autism spectrum disorder (score=0.89) and 4 other medium-match mental diseases. Overlapping genes impacted phenotypes such as decreased circulating creatine level, increased blinking frequency, hyperactivity, abnormal, short term object recognition memory and 29 other phenotypes.

This thesis puts a step forward in understanding the shared molecular background between autism and music perception using bioinformatics approaches. The GeneAnalytics, a simple bioinformatics tool was used for understanding the shared molecular background of music perception and autism.

**Keywords:** Music perception, Autism Spectrum Disorders, Phenotypes, Pathway

# 1. INTRODUCTION

Over the last two decades, substantial effort has been put into delineating the neurobiology of music perception and performance owing to two reasons:

1. Music perception and performance are complex cognitive functions and thus studying their neurobiology provides an opportunity to understand the function of the normal brain.

2. Investigation of the biological basis of music perception and performance may elucidate the evolutionary functional origins of music and it's biological value.

Like language, music is universal to all human cultures. The technological advances in functional neuroimaging methods allowed the cognitive neuroscience field to perform systematic and sustainable studies to understand the biological basis of music perception and performance. Scientific evidence over the past decade has amply demonstrated that music performance and perception modulates specific regions of the brain and alters its structure and function (Zatorre *et al*., 2013; Koelsch, 2011; Chanda *et al., 2013;* Koelsch, 2014; Levitin *et al., 2009*).

The development of genomic and bioinformatics approaches (Lander, 2011) have made it possible to study the genetic and biological basis of human cognitive traits. These methods can be applied to study human traits based on their molecular properties rather than anatomic regions. The greatest benefit of genomic methods is that they enable the studies on biological phenomena using an unbiased and hypothesis-free approach, without any knowledge of the biological background of the phenotype. In addition, a more detailed analysis at the molecular level is possible. There is evidence that not everyone who practices music becomes a professional musician (Ericsson *et al.*, 1993) which suggests that music perception and performance in addition to exposure to music (education and training), requires certain innate qualities like predisposing genetic variants. Music is also a strong environmental trigger that affects emotions (Zentner *et al.*, 2008*;* A. J. & Zatorr, 2001; Salimpoor, 2011).

In last decades, a growing body of evidence in the use of musical intervention in the clinical setting have been seen, concerning singing, music listening,

musical improvisation, and other musical activities, as long as more structured music therapy (MT) treatments. Given that music engages a variety of brain areas involved in emotion, motivation, cognition and motor function, musical interventions have been used to increase socialization and cognitive, emotional, and neuromotor functioning (Hillecke *et al.*, 2005; Schlaug *et al.*, 2009*;* Koelsch *et al.*, 2009*;* Koelsch, 2010; Raglio *et al.*, 2013*;* Chanda *et al.*, 2013).

Although the discussion on what the limits of MT are still going on, different approaches to musical intervention are actually available referring to three principal domains: relational approaches, rehabilitative approaches and music listening.

In context with neurological disorders, MT may promote functional recovery and also improve social and psychological outcomes such as socialization, motivation, mood, and depression (Maratos, 2008). Research in this field shows that most of the musical interventions are presently used in therapy.
The most common interventions are based on a combination of rehabilitative and relational techniques. Also, listening to music seems to be a common practice in neurological rehabilitation.

Due to the possible side effects of pharmacological treatment of depressive syndrome following neurological disease,music and MT may represent a valid support in reducing depressive symptoms, improving mood and adherence to treatment while contributing to the functional recovery at the same time.

This thesis attempts to use bioinformatics approaches to understand the molecular background of Autism Spectrum Disorders and Music Perception.

# 2. LITERATURE REVIEW

## 2.1.Evolution of Music

Music is universal across all human societies. Nearly 40,000-year-old flutes have been discovered recently in archaeological excavations (Conard *et al.,* 2009*).* For a musical instrument to exist thousands of years ago, music must have existed in its advanced form already several years before that (Zatorre *et al*., 2013).The rationale for the existence of music has been multifold. Music has been seen as a means of communication, and as a source that regulates emotions and facilitates cultural enhancement (Hauser *et al.,* 2003*;* Mithen, 2007; Wallin *et al.,* 2001*).* Interestingly, the auditory center (the part of the brain that processes sounds) of present-day humans function similarly to that of earliest primates that existed millions of years ago (Langner *et al.,* 2003*).* Likewise, genes related to hearing or deafness have evolved convergently in bats and bottlenose dolphins (mammals that use sound to locate objects) (Parker et al., 2013). A similar convergence in amino acid sequence evolution has been reported among vocal-learning birds and mammals (Zhang et al., 2014). Recently convergent gene expression specializations have been identified in both vocal-learning birds and humans in the brain regions that are necessary for sound perception and speech production (Pfenning et al., 2014). Thus, the genes that exhibited convergent expression specializations between songbirds and humans represent genes belonging to the auditory perception pathway. These data point out at a possible hypothesis of evolutionary conservation in the biological processes of sound perception between different species.

## 2.2.Innateness of Music Perception

The ability to perceive music is substantially characterized by innateness. No specific training is required to listen or appreciate music. Recent studies on human newborns have established that infants possess abilities to detect beats (Winkler *et al.,* 2009*),* extract pitch independent of timbre (Háden *et al.,* 2009*),* process pitch intervals (Stefanics *et al.,* 2009*),* detect changes in tonal key (Perani et al., 2010), distinguish consonance vs. dissonance, and distinguish minor and major chords (Virtala *et al.,* 2013*).* Above all, these pieces of evidence impart the innateness of music perceptive abilities that already appear during the early stages of

development in newborns. Contradictory hypotheses state that professional expertise in music performance can be attained through intense training for more than 10,000 hours (Ericsson *et al.*, 1993*)*. The innateness of musical abilities that comes naturally can be considered as nature, whereas the acquisition of further abilities to perceive other components of the musical structure can be seen as nurture.

### 2.3.Neuroscientific Studies

A large abundance of neuroscientific investigations over the last two decades has provided novel insights into the effect of music perception on neurological disorders. This section reviews the landmark neuroscientific studies that provide relevant background information for this thesis.

### 2.4.Perception of Musical Structure

Music is a multi-dimensional structure comprising of eight main attributes namely pitch, rhythm, timbre, tempo, meter, contour, loudness and spatial location (Levitin, 1999; Pierce, 1983). Different combinations of these eight attributes give rise to different types of music and thus each human culture has a different type of music. Initially, it has been thought that music processing is predominantly a right-hemisphere activity (Bever *et al.*, 1974*)*, although later it has been proved that music processing involves all the regions of the brain (Peretz *et al.*, 2003*; Platel et al*., 1997; Sergent, 1993; Tramo, 2001) Different attributes of music structure like pitch, rhythm, and loudness are processed in different regions of the brain and the perceived signals conjoin at a later stage to give a holistic picture of the music structure (Ayotte *et al.*, 2000*;* Di Pietro *et al.*, 2004*;* Peretz *et al.*, 1998*;* Peretz *et al.*, 1990*;* Piccirilli *et al.*, 2000; Vignolo, 2003). The musical activity associated with different regions of the human brain is shown in the following table.

| BRAIN REGION | ASSOCIATED MUSICAL ACTIVITY |
|---|---|
| Amygdala | Emotional reactions to music |
| Auditory cortex | The first stages of listening to music;<br>The perception and analysis of tones |
| Cerebellum | Movement, foot tapping, dancing and playing and instrument;<br>Emotional reactions to music. |
| Corpus callosum | Connects left and right hemispheres |
| Hippocampus | Memory for music, musical experiences and contexts |
| Motor cortex | Movement, foot tapping, dancing and playing an instrument; |
| Nucleus accumbens | Emotional reactions to music |
| Prefrontal cortex | Creation of expectations;<br>Violation and satisfaction of expectations |
| Sensory cortex | Tactile feedback from playing an instrument and dancing |

**Table 1:** Musical activity associated with different regions of the human brain (Levitin et al., 2009)

### 2.5.Music listening and perception

Biologically important functions like eating, love, and sex modulates the mesolimbic striatal reward system, which leads to a reinforcement behaviour to obtain repetitive pleasure (Hernandez *et al.,* 1998; Pfaus *et al.,* 1995; Hansen *et al.,* 1993*;* Small *et al.,* 2003*;* Aron *et al.,* 2005*;* Komisaruk *et al.,* 2005). Likewise, listening to music has also been shown to cause intensely pleasurable responses by modulating brain regions like ventral striatum, midbrain, amygdala, orbitofrontal cortex, and ventral medial prefrontal cortex. These brain regions are known to be associated with emotion, reward, and motivation. Certain regions of the brain that are responsible for the locomotory behaviours are also activated during music listening. Further, listening to music has been hypothesized to facilitate neurogenesis by inducing the

regeneration and repair of cerebral nerves, which is mediated by the release of steroid hormones (Fukui *et al.,* 2008).

The verbal memory and focused attention have improved significantly in stroke patients after listening to music when compared to those patients who did not listen to music. The music-induced reward is further elucidated by the release of dopamine in the mesolimbic striatum when experiencing peak emotional arousal (pleasure) during music listening. The reward value of musical stimuli has been shown to be associated with the activity in mesolimbic striatal regions including the nucleus accumbens, which is known to be responsible for making predictions and anticipation.

Moreover, the functional connectivity between the nucleus accumbens and the superior temporal gyrus (the region that stores prior information of sounds) has increased with increase in reward value, suggesting that the reward associated with listening to music may partly depend on the prior musical experience of individuals (Salimpoor *et al*., 2013). The degree of rewarding aspects of listening to music has been shown to depend on the degree of emotional arousal associated with listening (Salimpoor *et al.,* 2009) and the degree of emotional arousal and pleasure obtained through listening to music depends on the familiarity to an extent (Van den Bosch *et al.,* 2013*).*

### 2.6.Music education and Training

Music education and training are known to cause functional and anatomical changes in the human brain. Because of this reason, the brains of professional musicians have been suggested to be an excellent model to study neuroplasticity in humans (Münte *et al.,* 2002). Indeed, music training has been extensively studied as a model for brain plasticity (Herholz *et al.,* 2012*).* The gray matter volume has been found to differ in auditory, motor, and visual-spatial regions of professional musicians' brains when compared to non-musicians (Gaser *et al.,* 2003). The associative learning involved in music performance strengthens the connections between auditory and motor regions of the brain and the repeated modulation of this neural network through musical training may explain the music performance-induced sensorimotor and cognitive enhancements (Wan *et al.,* 2010).

Training in music is known to enhance human cognitive abilities. Musical training at a young age has enhanced the long-term visual-spatial, verbal and mathematical performance (Schlaug *et al.,* 2005*).* Likewise, a school-based instrumental training program has significantly enhanced the verbal memory of school children (Roden *et al.,* 2012). Musical experience has been shown to shape the human brainstem encoding of linguistic pitch patterns more robustly and faithfully when compared to non-musicians, showing a possible link between professional musicians' higher language-learning ability (Wong *et al., 2012).* In orchestral musicians, musical training altered the structure of Broca's area, which is responsible for sight-reading skills and motor-sequence organization, both of which are essential for performing music (Sluming *et al.,* 2007).

### 2.7.Music Therapy and Autism

The American Music Therapy Association (2002) reports that music therapy enhances one's quality of life and can assist with the development of relationships.

According to the American Music Therapy Association (2002):

"Music therapy is the clinical and evidence-based use of music interventions to accomplish individualized goals within a therapeutic relationship by a credentialed professional who has completed an approved music therapy program…the prescribed use of music by a qualified person to effect positive changes in the psychological, physical, cognitive, or social functioning of individuals with health or educational problems. Music therapy is considered a powerful and non-threatening medium and because of its unique outcomes is possible." (AMTA, 2002)

Music therapy is used in a variety of non-threatening mediums and with many different approaches. The American Music Therapy Association (2002) also reports that there are many different ways to use music with a therapeutic approach. Music therapists can be used to treat patients with Alzheimer's, people who are terminally ill, children and adults with a variety of special needs, individuals on chemical dependency, at-risk youth living in disadvantaged areas, teachers on the verge of burn-out, children with autism and many others. Music therapy reaches a broad range of people with a variety of needs all over the world.

Music therapy is performed by trained professionals and is most commonly used for individuals with special needs. The focus of music therapy is using a music approach towards development of goals in the areas of motor skills, social development, self-awareness, and cognitive development (Patterson, 2003). According to Patterson (2003), the role of a music therapist in the school setting is to assess a child's needs and teach to academic and social skills in areas of deficit both with and without music. one purpose of using music in therapy is to use songs to teach a skill (Zoller, 1991).

In his 1987 study, Hicks (as cited in Zoller, 1991) discovered that when he taught using rap music, children who were 3 and 4 years old learned more names of unfamiliar body parts as opposed to those who instructed without the rap music. There was a similar study in 1981 conducted by Get Ready Inc., which explored the use of rap music as a motivational tool to learning the eight parts of speech with fourth-grade students. The results showed a considerable increase in recognition with the group that received the rap music approach (Zoller, 1991).

A music therapist is trained to implement strategies that will help to strengthen certain skills through participation in musical experiences (Patterson, 2003). The goal is to help all skills learned to generalize into everyday situations. The purpose of a music therapist in a school district is to use music to achieve non-musical goals in a classroom setting. Music therapists structure lessons around music or rhythm to teach skills such as math, reading, social skills, communication, and other areas of need. Music therapy is being used for a variety of children in the school systems, but research shows that it is particularly useful in addressing the specific needs of children on the autism spectrum (Thaut, 1998; Nordoff & Roberts, 1977). Gourney (1998) described the role of music therapists who work with teachers and other therapists, is to plan and implement treatment tailored to a specific child's needs according to the Individual Education Program (IEP). Music therapy, as a service provided according to an IEP, is recommended when it has a certain level of motivation and/or benefit towards a child's educational program (Patterson, 2003). This therapy service falls under the IEP category of related services.

Related services are services that may include corrective, developmental, or support services, such as music, art, and dance therapy (Patterson, 2003). The US Department of Education(1999) reports if these services are necessary in assisting a child with special needs to benefit from special education in order to be given free and appropriate public education (FAPE), then the service is considered a related service. Parents have had a difficult time getting school districts to provide music therapy as a related service. In response, Dr. Kenneth Warlick (2000), director of the office of Special Education Programs for the Department of Education, states: "If the IEP determines that music therapy is an appropriate related service for a child, the team's determination must be reflected in the child's IEP, and the service must be provided at public expense and at no cost to the parents."

Music therapy is an emerging therapy being implemented with children on the autism spectrum (Dempsey & Forman, 2001; Duffy & Fuller, 2000; Shore, 2003; Thaut, 2000). Studies have focused on the benefits of music therapy with school-age children diagnosed with pervasive development disorder (PDD) and, more specifically, autism.

Significant behavior improvements have been reported when children are treated with interventions using a music therapy approach. Some of the improvements observed in behavior have been the development of communication skills and social skills with children diagnosed with autism (Brownel, 2003).

### 2.8.Communication and Autism

Hoshizaki (as cited in Zoller, 1991) defined communication as combinations of rhythm, melody, speech, and gestures. Like math, he suggested, music is a universal language. Nash (1974) described rhythm and melody as "innate forces at birth, placing them at the core of human expression and development".

For children, music can be a more natural medium to learn through. This is especially true as it relates to learning speech and language skills. Music is also fun and enjoyable,

which can help maintain students' interest while they are learning a variety of skills (Zoller, 1991). According to Zoller, by using music with children, one is exposing them to a multi-sensory experience that enhances many skills and has an impact on their development of speech and language skills. Communication seems to be the most difficult area for children with autism. Children with autism demonstrate an obvious difficulty with expressive language, and this has multiple implications in the school setting. Kanner (1943) identified some of the difficulties children with autism demonstrate with language as muteness, delayed echolalia (repetitiveness of words or phrases), pronoun reversals, word substitution, and literalness. The most obvious communication deficit proves to be spontaneous speech.

Children with autism can learn the rote language and what educators define as a functional language, but they have an extremely difficult time relating to situational or conversational language. Pronovost (1961) noted that children with autism who do not respond appropriately to verbal communication or social speech respond to the language used through music.Thaut (1998)found that children with autism perform better at basic skills when introduced to music than without. Researchers have noted the benefit of using music to teach children with autism and have begun to investi gateusing music to specifically help modify behavior(Patterson,2003; Chadwick, Nash & Wimpory,1995). Music is considered by many as a universal language, which helps facilitate relationships, learning, self-expression, and communication—all the areas of deficit for children with autism.

"Children with autism have a need for structure and organization in their lives" (Grandin & Scariano,1986). Music is inherently structured and predictable. According to their study (and from the researcher's observations), children with autism seem drawn to music, which may be due to its repetitive and rhythmic nature. Music in a classroom can engage students with autism, as well as provide them with an environment in which they can learn specific skills. According to Darrow and Armstrong (1999), music in a classroom creates a non-threatening environment for students with autism and their peers, which can help to promote initiation of communication. A musical environment is an environment in which social and academic integration can occur naturally.

As respected experts in the area of music therapy, Nordoff and Roberts (1971) note that music could be a tool for reaching not only children with autism but also any children with language delays. They have also suggested that there are specific guidelines in the areas of intonation, range, rhythm, and tempo. Songs should be used in a way that they mirror the intonations of speech patterns because children with autism respondverbally to repetition and rhythm, songs with repeating lyrics are generally bes t to use for the purpose of teaching communication skills. Nordoff and Roberts (1971) also state that the best way to use music to teach communication is to stress syllables with a strong beat and keep the tempo slow enough to make sure the children can readily understand the words being used. Songs with repeated lyrics allow children to comprehend the message and have more practice with language.

Communication and social interaction are very closely related. Engaging in and listening to music can become an enjoyable social event. Music therapists can design lessons to create interaction among children in small group settings. Songs are used to help children initiate interaction, to illicit eye contact, allow for choice making, and follow instructions. Strategies used in a music therapy session are to use songs and/or music to help students to with verbal imitation, initiation of language, increase vocalizations and length of utterances, and learn new vocabulary, followed by fading music to spoken language (Coast music therapy, 2006).

A variety of approaches has been used to elicit communication skills from children during music therapy sessions. Songs can be created to focus on eye contact and social greetings. other approaches use music to modify behavior and model appropriate behavior for children with autism. According to Thaut (1998), there have only been a few studies that have focused on the particular aspects of musical performance in children with autism.

Educational experts have completed studies with individuals diagnosed with autism using a musical teaching or music therapy approach. Shore (2003) found that while working with students with autism without any functional communication, they had a

variety of vocabulary in their heads that was learned from songs. When he worked with particular students with autism he found they responded to him more often and with appropriate conversational language when he would sing to them. Another benefit he found to using a music therapy approach was it helped to control behaviours in the classroom, as well. Music in his program helped to keep children focused and on-task. He concluded, after his study, that music helps to provide alternative means of communication for children with autism as well as help organize thoughts and assist with improving self-esteem (Shore, 2003). Clarkson (1994) has had many years of experience working in the music therapy field, and specifically, in creative music therapy and conducted a study with a 24-year old young man diagnosed with autism. The individual was always attracted to music and began his music therapy with Clarkson in 1988. Initially, she used music to gain contact and interaction with the student, and eventually, she used music along with facilitated communication, to help him develop better communication skills. Facilitated communication is an approach to teaching in which a facilitator holds the child's hand or wrist, while the child uses a computer or typewriter to type for the purpose of communicating (Clarkson, 1994).

By 1992, Clarkson reported that in three years' time, the student's behaviour had improved. He made eye contact during sessions and was able to use facilitated communication to type sentences in order to communicate with others. According to Clarkson (1994), "Music can be a valuable tool not only for reaching students with autism but for also working with any children delayed in language". Chadwick, Nash, & Wimpory (1995) conducted an evaluative case study with a two-year follow-up on the benefits of musical interaction therapy (MIT) with children diagnosed with autism. Musical interaction therapy is different than the describe music therapy but has similar aims and goals for children with autism. MIT synchronizes live music for an adult to child interactions. MIT aims to allow children with autism to predict the actions of their partner based on the music used. MIT uses non-verbal activities and attempts to solicit social interactions and interpersonal contact, whereas music therapy is used primarily with children with autism to help facilitate social interactions, communication, and develop academic skills.

The subject used for the study conducted by Chadwick, Nash, & Wimpory (1995) was a three-year-old girl with a diagnosis of autism under the DSM-III-R diagnostic criteria for autism. Her diagnosis of autism was in the severe range, and she was almost completely non-verbal. The musician and the mother of the child worked together to create spontaneous music to the child's daily actions. "one example is when the child would walk around the room, the musician would play the piano and sing something like 'walking around the room, we walk around the room' and the mother would also sing and walk around the room". They would also create play scenarios and play music to match the actions, labelling any social interactions with songs. The researchers videotaped the sessions and observed the number of eye contacts per minute, the frequency of child-initiated interactions, and time passed without social interactions. The results of this study are encouraging. The child had a mean baseline of six minutes of time passed without social interaction before the music was introduced and following the MIT; the child always gave social acknowledgement and most occurred within a minute of the MIT beginning. The other data also supports an increase in eye contact and in child-initiated interactions. The two-year followup also showed the improvements were sustained, and the girl was considerably more tolerant to social interactions (Chadwick, Nash & Wimpory, 1995).

Research suggests there are benefits to using a music therapy approach in a program with children diagnosed with autism. Some of the benefits from studies have shown development and improvement of basic communication skills. Additional research and studies have explored other benefits, but as it relates to children with autism, the music therapy approach has not been studied in depth. It has not explored the benefits to communication using a music therapy approach with children diagnosed with severe autism. Further research is needed to determine the benefits, or lack thereof, to using a music therapy approach with the population of children diagnosed with moderate/severe autism.

## 2.9.GeneAnalytics

HIGH THROUGHPUT GENOMICS TECHNOLOGIES, such as next-generation DNA/RNA sequencing or microarray analyses, are frequently used in biomedical research, as well as in diagnostic and therapeutic product development. These generate large quantities of Big Data that require advanced bioinformatics analysis and interpretation. The key step towards translating these results into meaningful scientific discoveries is a deduction of biological and clinical contexts from the generated data. In this realm, several methods and tools have been developed to interpret large sets of genes or proteins, using information available in biological databases. Prominent among these are gene set enrichment tools.

In conventional examples, the Gene ontology database is used for the functional study of large scale genomics or transcriptomics data. Multiple applications such as GeneCodis, GoEAST, Gorilla, and Blast2Go (Conesa et al., 2005; Eden et al., 2009; Nogales-Cadenas et al., 2009; Zheng and Wang, 2008) can analyze and visualize statistical enrichment of Go terms in a given gene set. other tools rely on popular data sources such as Kyoto Encyclopedia of Genes and Genomes (KEGG), TransPath, online Mendelian Inheritance in Man (oMIM), and GeneCards to identify enriched pathways, diseases, and phenotypes (Backes et al., 2007; Huang da et al., 2009b; Safran et al., 2010; Sherman et al., 2007; Stelzer et al., 2009; Zhang et al., 2005). These analysis tools differ in several respects, including statistical methodology, supported organisms and gene identifiers, coverage of functional categories, source databases, and user interface. The common result is the identification of known functional biological descriptors that are significantly enriched within the experimentally-derived gene list.

Enrichment of biological descriptors for a given set of genes introduces three immediate challenges: The first is determining the statistical significance of enrichment of each descriptor.

There are several approaches to calculate the statistics for a descriptor shared among genes, such as Gene Set Enrichment Analysis [GSEA (Maezawa and Yoshimura, 1991)] and Fisher's exact test [Database for Annotation, Visualization and Integrated Discovery—DAVID

(Dennis et al., 2003)]. Tools like the DAVID functional annotation tool, initially cluster the descriptor belonging to similar categories and then present a score for an enriched group of terms.

It is a nontrivial task to integrate and model information derived from various origin s. In an example, disease information could be derived from data sources such as oMIM (Hamosh et al., 2005), SwissProt/UniProt (Wu et al., 2006), and orphanet (Maiella et al., 2013), and pathway information—from Reactome (Jupe et al., 2014; Matthews et al., 2009) and/or KEGG (Kanehisa et al., 2010). Therefore many analysis tools present separate enrichment results for each data source, while others perform consolidated analysis on source types.

A third challenge is optimal data presentation. Tools such as DAVID group enriched terms by biological categories in an attempt to provide a general sense of the biological processes involved in the experimental results. other tools, such as MSigDB (GSEA) (Liberzon et al., 2011) and GeneDecks Set Distiller (Stelzer et al., 2009), interlace biological descriptors of various kinds, based on their statistical enrichment strength, thus emphasizing the individual significance of each in the context of the general enriched descriptor list. It would be optimal to give both a birds-eye view of grouped descriptors for a given set of genes, as well as display the descriptors in detail.

Multiple data sources are generally employed for both broad and in-depth depictions of enrichment. A related challenge is to develop a straightforward and easy-to-use application, with intuitive output results, rendering the tool accessible to inexperienced users, with little or no bioinformatics background.

GeneAnalytics™ (geneanalytics.genecards.org), designed to distill enriched descriptors for a given gene set, while optimally addressing the aforementioned challenges. It is empowered by the GeneCards Suite, embodied as LifeMap's integrated knowledgebase, which automatically mines data from more than 120 data sources. GeneAnalytics' broad descriptor categories enable users to focus on areas of interest, each rich with annotation and supporting evidence. GeneAnalytics analyses provide gene associations

with tissues and cells types from LifeMap Discovery (LMD, discovery.lifemapsc.com), diseases from MalaCards, (www.malacards.org), as well as Go terms, pathways, and phenotypes, and drug/compounds from GeneCards (www.genecards.org), (Fig. 1). Navigation within such comprehensive information, as well as further scrutiny, is facilitated by GeneAnalytics categorization and filtration tools.

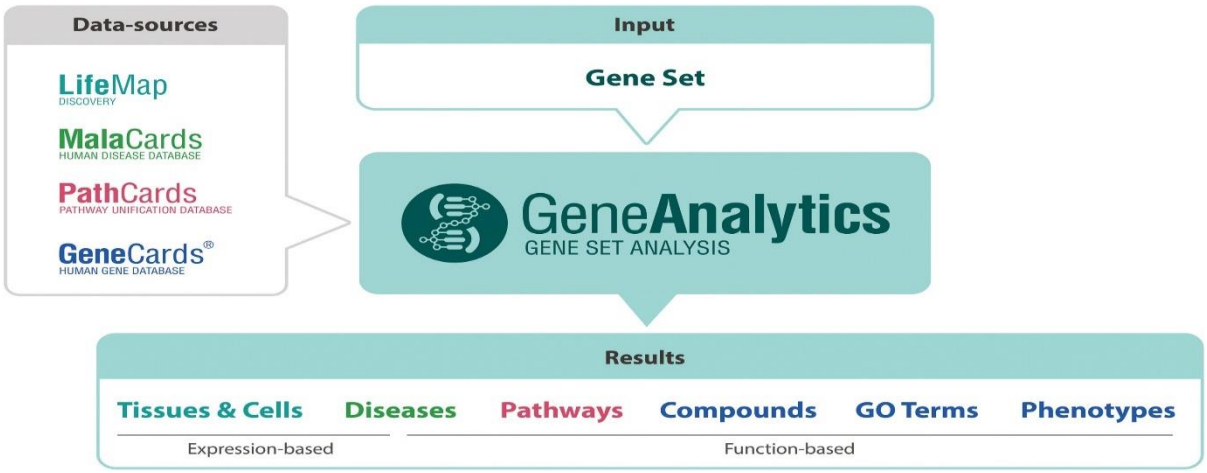


**Fig.1. *GeneAnalytics structure.*** *GeneAnalytics is powered by GeneCards, LifeMap Discovery, MalaCards, and PathCards, that integrate data from more than a hundred sources. These databases contain annotated gene lists for tissues and cells, diseases, pathways,compounds, and GO terms. GeneAnalytics compares the user's gene set to these compendia in search of the best matches. The output contains the best matched gene lists, scored and subdivided into their biological categories such as diseases or pathways. In the figure, each output category and its respective data source are marked with the same color.*

### 2.9.1. GeneAnalytics Input

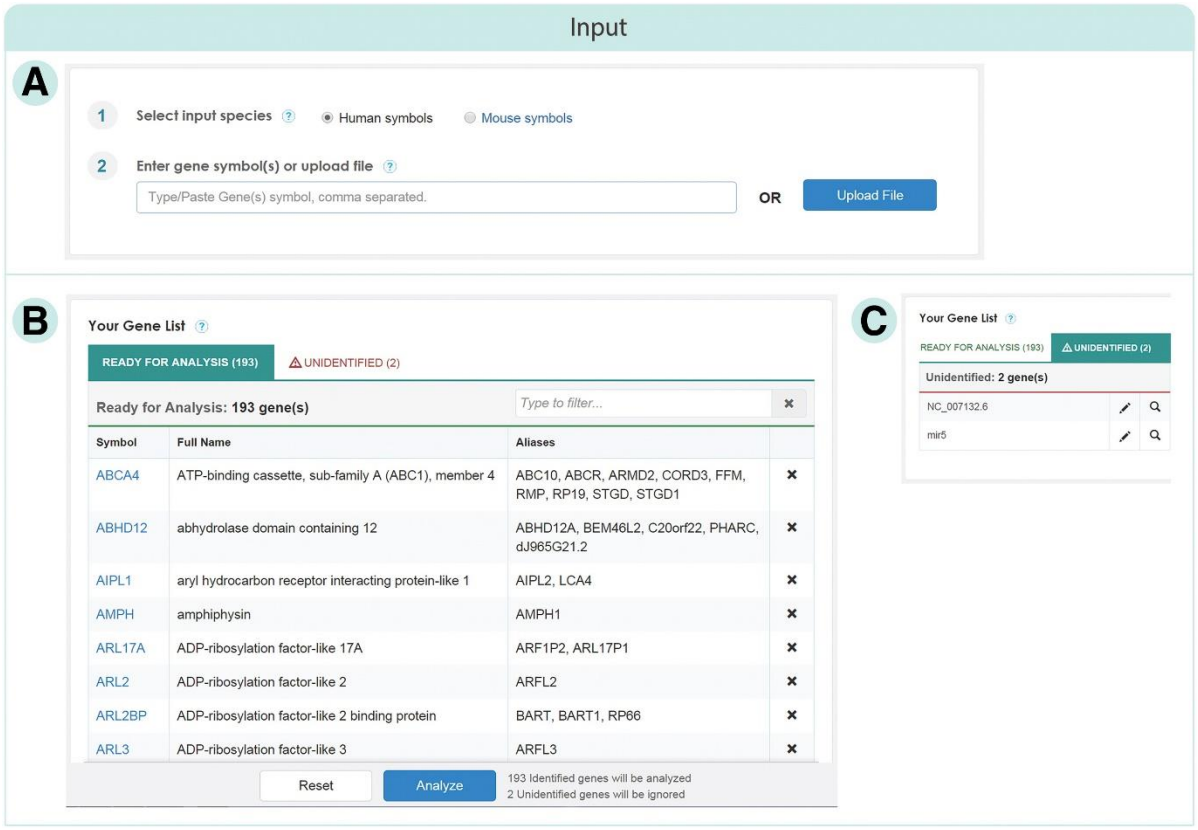


**Fig.2.** ***The gene set input.*** ***(A)*** *The input page is used to insert and identify the query gene list. 1) The identification process requires species indication in order to identify the gene symbols and their orthologs. GeneAnalytics identifies only official human and mouse gene symbols. 2) The genes can be inserted by typing/pasting gene symbols in the input window or by uploading a file containing the gene list. Typing a gene name in the search box initiates an autocomplete tool that includes only official gene symbols. The identification process yields two lists:* ***(B)*** *"Ready for analysis" gene list, which includes identified gene symbols, their full name, and all available aliases/synonyms, and* ***(C)*** *"Unidentified genes" list, which includes genes that were not recognized as official human or mouse gene symbols. These gene names can be manually corrected by running a search in GeneCards or by using the autocomplete option.*

For the “unidentified genes” list, GeneAnalytics assists in manual symbol identification by directly linking to the gene search in GeneCards. To provide all relevant results for each gene symbol, GeneAnalytics unifies orthologs and paralogs into ‘ortholog groups’ based on the information available in HomoloGene (www.ncbi.nlm.nih.gov/homologene), with minor adaptations.

Upon completion of the input stage, GeneAnalytics analysis produces results that are divided into the following categories: Tissues and Cells, Diseases, Pathways, GO terms, Phenotypes, and Compounds. Genes are associated with these categories either by their expression (“expression-based analysis”) or by their function (“function-based analysis”) (Table 2). All sections have a “drill down” capacity for performing subqueries, allowing users to focus only on genes from their original gene set, filtered by those that match the selected entity.

| Analysis Based on | Entity | Data source | Total number of entities with associated genes | Total number of genes related to entities |
|---|---|---|---|---|
| **Expression** | Normal tissues and cells | LifeMap Discovery | 3,346 | 17,512 |
| | Diseased tissues and cells | LifeMap Discovery (via MalaCards) | 96 | 6,963 |
| **Function** | Disease | MalaCards | 12,085 | 22,280 |
| | Pathways | PathCards | 1073 SuperPaths (unification of 3215 pathways) | 11,479 |
| | Go—biological process | GeneCards | 9,436 | 14,907 |
| | Go—molecular function | GeneCards | 3,509 | 15,624 |
| | Go—molecular function | | 3,509 | 15,624 |
| | Compounds | | 19,961 (unification of 44,942 compounds) | 8,434 |

**Table 2:** GeneAnalytics data sources and statistics

#### 2.9.1.1.Tissues and cells

All gene expression data, including those that are manually collected, annotated, and integrated into LMD, are used to rank the GeneAnalytics matching results.

The gene expression data available in LMD are obtained from three types of sources:

- Scientific peer-reviewed manuscripts and books (Edgar et al., 2013).
- High Throughput (HT) gene expression comparisons available in the Gene Expression omnibus (GEo) (Edgar et al., 2002). These are subject to variouss tandardization and analyses methods. For this, we developed and fine-tuned an algorithm for extracting differentially expressed genes from GEo matrix files. Applying a uniform algorithm to the gene data increased the comparability of the resulting differentially expressed gene list. For experiments that do not have normalized data deposited in a public repository, the different expressed gene lists, incorporated into the LMD database, are derived from the relevant article.
- Large Scale Data Sets (LSDS): those obtained from wide-scope experiments that

  encompass multiple samples and require suitable standardization and analyse smethods. This refers to data that obtained by *in situ* hybridization (ISH, immunostaining (IS), microarray, or RNA sequencing data sets. These data, retrieved from big-data repositories such as Mouse Genome Informatics (MGI) (Smith et al., 2014), Eurexpress (Geffers et al.,2012) or BioGPS (Wu et al., 2013), are filtered and analyzed in-house or obtained in analyzed form from projects that developed unique large-scale analysis methods such as Homer or Barcode.

The complete list of data sources is provided on the LMD webpage (discovery.lifemapsc.com/gene-expression-signals#ht-gene-expression). In LMD, each anatomical entity has a unique card that contains a list of associated expressed genes. organ and tissue cards include lists of genes expressed in whole tissue samples (e.g., RNA extracted from tissue homogenates). Genes reported to be expressed in a specific cell type (*in*

*vivo* or *in vitro*) or in an anatomical compartment are listed in the relevant cards, which contain extensive manually curated information from the literature.

The High Throughput gene expression comparisons are described within 'experiment cards.' The top differentially expressed genes derived from these comparisons are link into the highest resolution entity card possible (organs, anatomical compartments, or cells). Each card details the comparisons used in the experiment, listing the test and control samples comprising each comparison and supplying additional information for the experiment. The top differentially expressed genes as well as links to LifeMap entities (tissues, compartments, etc.) may be viewed in the comparison card associated with an experiment card.

Similarly, the lists of differentially expressed genes derived from Large Scale Data Sets are linked into entity card, unless such a card is not available (for exampl when the entity does not exist for a given release), in which case they are presented in Large Scale Data Sets cards.

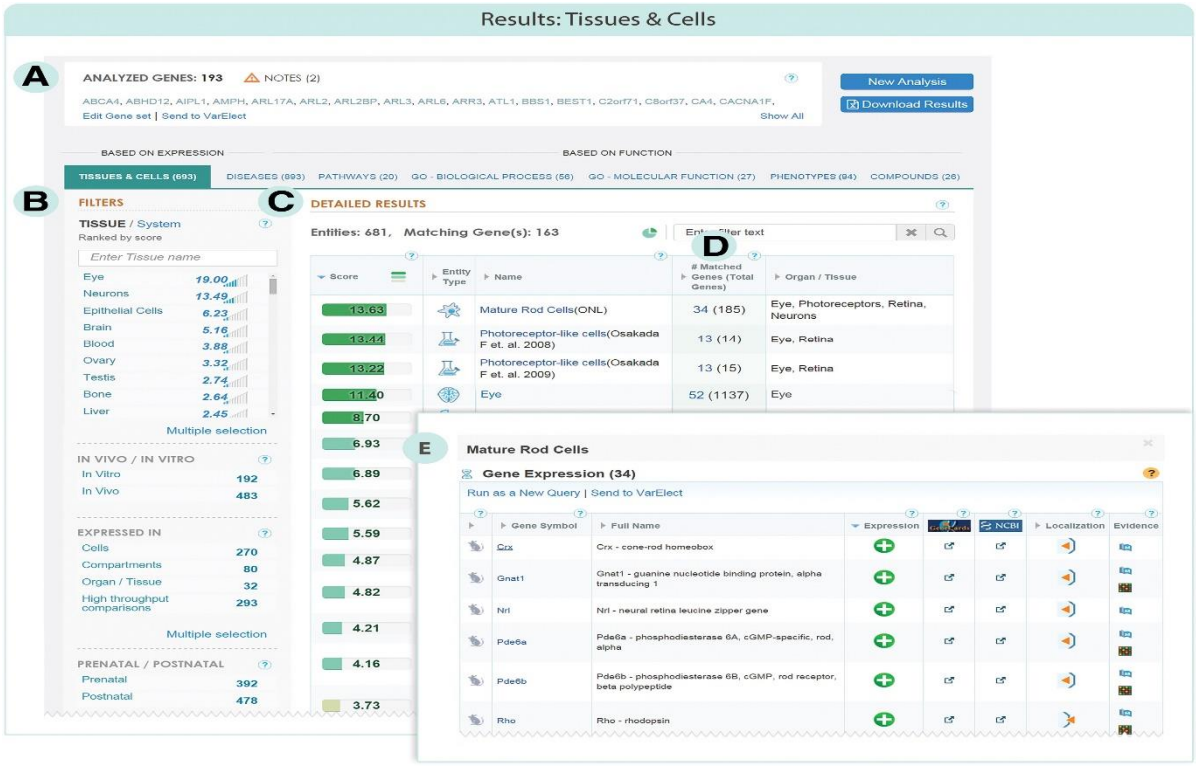


**Fig.3.** ***Tissues and Cells results***. ***(A)*** *The Analyzed genes are the queried genes that were identified and included in the analysis. The "Notes" indicate genes in the query that were found to be abundant or defined as housekeeping genes in human. These genes get lower scores in the Tissue and Cells matching analysis.* ***(B)*** *The filters panel allows for filtering genes specifically expressed in Tissue/system, In vivo/In vitro 'Expressed in' (cells, anatomical compartments, organs, tissues, andor high throughput comparisons and large-scale dataset samples), Prenatal/Postnatal.* ***(C)*** *The detailed results table presents all entities in which at least one of the analyzed genes is expre ssed, along with links to their cards in LMD.* ***(D)*** *A link to the list of the matched genes and additional information for them (for example, "Mature Rod Cells").*
***(E)*** *The list of matched genes linked to the specific entity in LMD (connected to "M ature Rod Cells").*

The Tissues and Cells GeneAnalytics results contain useful filters that enable focus o nspecific subsets of the results (Fig. 3B). Each entity is classified into tissue(s) and/ orsystem(s) in LMD, enabling results aggregation and filtration. This is done using hi ghanatomical hierarchy elements, tissues, and systems. For example, the *in vivo*

cell Dopaminergic Progenitor Cells belongs to the anatomical compartment Substantia Nigra pars Compacta, which belongs to the tissue Brain, which is included in the system Nervous System.

The filtering into tissues or systems is associated with scores that reflect their quality to the query gene set (Fig. 3C). The Tissues and Cells results can also be used to filter *In vivo*/*In vitro* or Pre-natal/Post-natal entities. Further, GeneAnalytics allows user interaction for display of additional information.

For example, for each entry in the Tissues and Cells table, we provide the type of entity, the expression type (expressed, selective marker, etc.), the number of genes matched to that entity (including the number of total genes expressed in the entity) and localization (within a popup).

When scoring after tissue/system filtering, during this aggregative filtering, a gene that appears in more than one entity will be represented only once at the tissue/system level and will get the maximal score attributed to it in any of its associated entities. once all of the genes are assembled for the tissue/system, the score is computed in the same manner as for every entity.

The matching algorithm for this category aims to identify anatomical entities most strongly associated with the query gene set. The algorithm is composed of two major stages:

- Computation of a score for each gene associated with an entity. These pre-computed scores represent the importance of this gene in the specific entity as compared to its distribution in the entire entity landscape.
- Computation of the matching score, which is the similarity score between the user's query gene set and the genes associated with each of the entities, taking into account the differences in the expression information, both quantitative and qualitative, available for each entity.

The above is based on the fact that each gene associated with an entity is assigned one or more of the following specificity annotations: specific, enriched, selective, expressed, abundant, and/or low confidence (Edgar et al., 2013). The annotations are

derived from the literature and/or from bioinformatic calculations. The calculations consider the source from which the gene–entity association was established and the distribution of the gene expression in LMD. Criteria include how rare is the gene in the database, how specific it is to a certain cell type or tissue, and whether there is extensive evidence for the expression of the gene in the tissue.

In addition, the gene score considers the entity type in which the expression is observed. Genes listed in organ/tissue, anatomical compartment or cell cards are ranked higher than genes with the same specificity annotations, which are listed in Large Scale Data Sets entities that are not linked to any of the above (tissue, compartments, etc.).

After defining the gene scores, the gene set of each entity and the query gene set can be viewed as gene expression vectors. The entity gene–set vector holds defined scores for each of its genes and zero for all other genes, while the query gene–set vector is a binary vector that holds the value 1 for each of the query's genes and 0 for all othe rexisting genes. The affinity between the query gene set and each of the entities is measured by the scalar product of the two vectors (i.e., the sum of the scores of the entity genes matched to the query gene set).

The entity scores are divided into three levels, representing the strength of the results (high, medium, or low), which is indicated by the color of the score bar. This categorization is performed by a two-step procedure that runs automatically before each release.

The first step is determining the threshold for medium and high scores for a group of query gene sets with varying sizes. The second step uses a linear regression between the various query sizes and their computed medium/high scores in order to create an equation from which the thresholds in the first step can be computed easily for any query gene size.

The first step of the automatic procedure uses a set of 50 test cases. From each tes tcase, six gene lists of different sizes are generated (5 to 300 genes). The matching algorithm applied on these gene lists produces a range of typical scores for each query size. In order to obtain the high and medium threshold automatically, a preliminary analysis was performed on many control microarray experiments. Each experiment

represents a known cell/compartment/tissue and therefore was expected to produce high scores for the highly relevant entities, medium scores for entities with modest relevance, and lower scores for weakly related entities.

By analyzing the distribution curves for all control sets, we established the percentiles of entities that produce medium and high scores. These determined percentiles enable dthe high and medium boundaries in the aforementioned first step to be compute dautomatically. In the second step, a linear regression is applied to the various quer ysize and their high or medium scores from which an equation for computing these boundaries in the general case is generated.

### 2.9.1.2.Diseases

Gene–disease relations in GeneAnalytics are divided into the following categories, indicated in the GeneAnalytics results (Fig. 4):

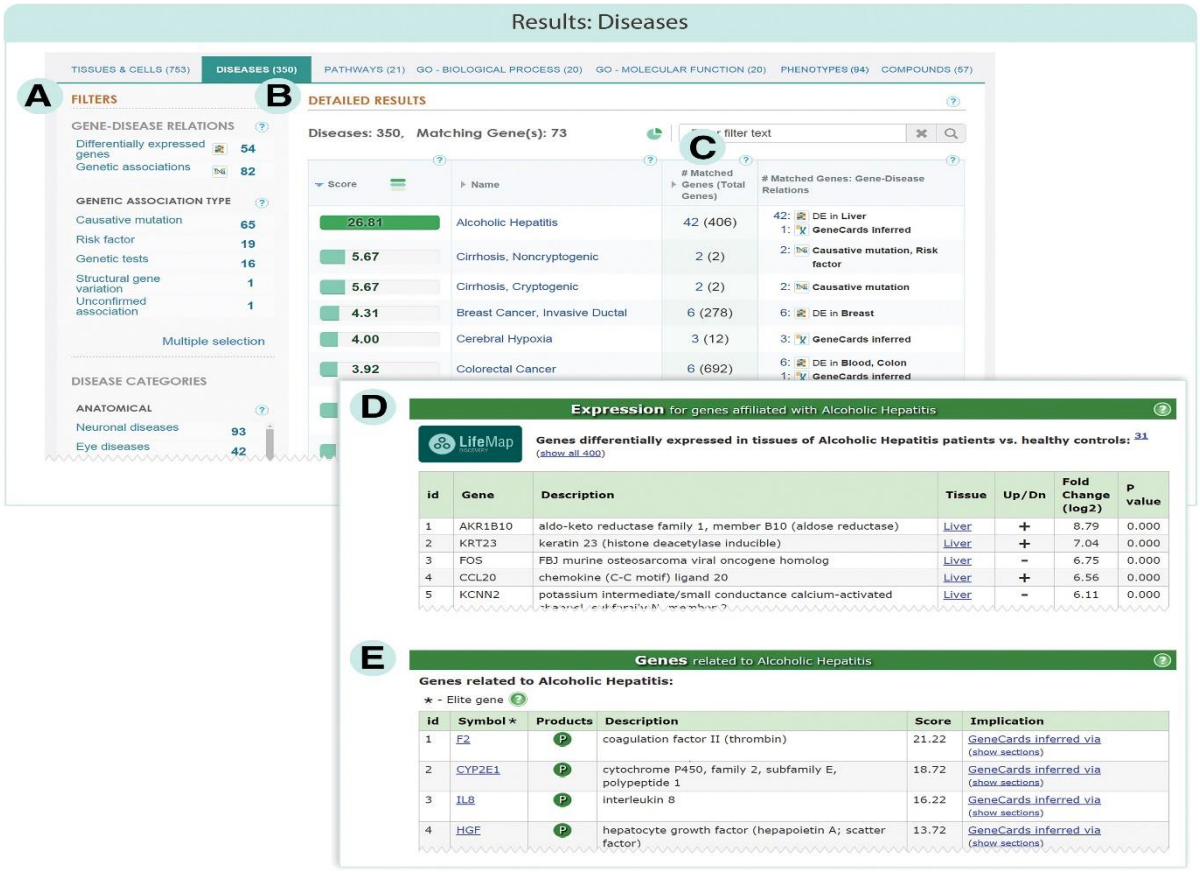


**Fig.4.** ***GeneAnalytics Disease results.*** ***(A)*** *The disease filter enables filtration of results by gene–disease associations and disease categories obtained from the MalaCards database.* ***(B)*** *The detailed results table presents diseases matched to the queried gene set. Each disease is linked to its card in MalaCards.* ***(C)*** *Clicking on the number of matched genes opens a list of the matched genes and associated information.* ***(D)*** *Differentially expressed genes ('expression'), and* ***(E)*** *disease-related genes in their respective sections in a disease card in MalaCards. Both sections serve as evidence for each matched disease in the GeneAnalytics disease category.*

- Gene associations along with their confidence classifications as derived from MalaCards data sources. Since each data source has its own annotation terminology, Table 3 categorizes all of the possible disease–gene associations in descending order according to their source-associated confidence, which is later transformed into a GeneAnalytics score.
- Genes that are significantly up- or downregulated in disease tissues in comparison to their healthy counterparts.
- GeneCards inferred genes (i.e., genes with the disease name mentioned anywhere in the relevant GeneCards webcard, e.g., in the publication section). This is a somewhat weaker association, which often does not imply causality.

| **Association category** | **Source** |
|---|---|
| Causative mutation | ClinVar, oMIM, orphanet |
| Risk factor | ClinVar, oMIM, orphanet |
| Resistant factor | ClinVar, oMIM |
| Genetic tests | GeneTests |
| Drug response | ClinVar |
| Structural gene variation | oMIM, orphanet |
| Unconfirmed association | oMIM, orphanet |

**Table 3:** Disease-Gene Associations from Manually curated Genetic sources

The disease matching score is calculated in three steps:

- Each gene associated with each disease receives a score based on the gene–disease relations described in the disease data modeling section.
- Genes with a genetic association to the disease receive a score according to the association category. A gene linked with multiple filter categories is then assigned the strongest association score among them.
- Differentially expressed genes are binned and scored based on their rank in the list of differentially expressed genes in the diseased vs. normal tissue analysis.
- Genes with "GeneCards inferred" relations receive scores based on the number of sections in GeneCards in which the disease appears.
- Each gene may have more than one type of relationship with the disease; the final gene score a disease receives is the highest among all of the possible scores mentioned in point and above.
- The gene–disease matching score is calculated based on scores of each of the matched genes, the number of matched genes, and the total number of genes associated with the disease in MalaCards (used for normalization). The scoring function is identical to the one used in the Tissues and Cells category.
- The disease results category in GeneAnalytics include several filters that enable the user to focus on the results of interest (Fig. 4).
- Gene–disease relations. This enables the user to filter for gene–disease relation types, including differentially expressed genes and the specific types of genetic associations.

  Selection of 'differentially expressed genes' (DE) or 'genetic association', will only show diseases for which their matched gene set includes at least one differentially expressed or genetically associated gene, respectively.

This filtration caters to users who are interested in diagnostic disease markers, in the case of differentially expressed gene, or those with genetically associate dvariants for specific diseases. Importantly, the matching score for each diseas ecategory is recalculated following filtration, so the scoring algorithm conside rsonly entities that contain at least one gene matching the requested filter term s.

- Disease categories. This filter enables the users to focus on specific disease categories, as defined by MalaCardsc categorizations.c MalaCards categorizes diseases into anatomical (e.g., eye, ear, liver, blood) and global (rare, fetal, genetic, cancer, and infectious) diseases.

  The categorization is based on either the International Statistical Classification of Diseases and Related Health Problem 10th Revision (ICD-10) (organization, 1992) or on the MalaCards classification algorithm that utilizes category-specific keywords contained in the disease names and annotations, as well as textual heuristics. For example, if the disease name includes the words 'tumor ' or 'malignant,' it is classified as a cancer disease (Rappaport et al., 2014). Further, a disease can be associated with more than one category.

**2.9.1.3.Pathways**

In GeneAnalytics, matched SuperPaths appear with their matching score and link to the relevant webcard in PathCards, as well as the list of matched genes and a total number of genes associated with each SuperPath. The user can then expand each matched SuperPath to view the list of its clustered pathway with links to their origin individual pathway sources and to the relevant genes in the user's query (Fig. 5).

The scoring algorithm in the pathways category is based on the algorithm used by GeneDecks Set Distiller tool (Stelzer et al.,2009). Briefly, all genes in each SuperPath are given a similar weight in the analysis, and the matching score is based on the cumulative binomial distribution, which is used to test the null hypothesis that

the queried genes are not over-represented within any SuperPath. As in all sections, the score is represented by a colored score bar and classified by its quality.

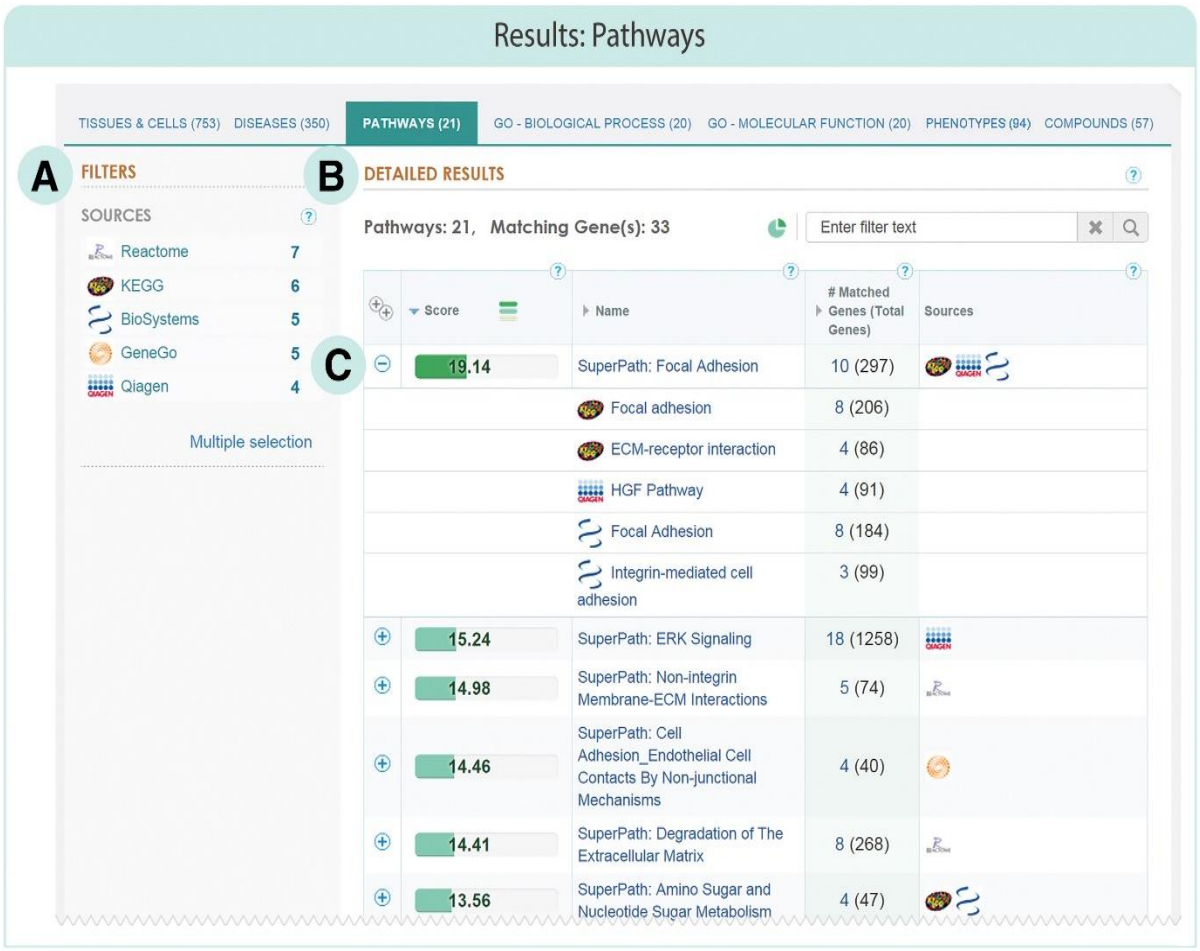


**Fig.5.** ***GeneAnalytics Pathways results***. ***(A)*** *The pathway filter panel enables filtration of results according to their data sources.* ***(B)*** *The detailed results table includes all of the matched SuperPath, presented in descending score and with link to the related card in PathCards.* ***(C)*** *Each SuperPath includes one or more pathways from different sources. Clicking on the plus sign exposes the names of the separate pathways that comprise the SuperPath, with links to the pathway page in the original data source.*

#### 2.9.1.4.Gene Ontology (GO) terms and phenotypes

The matching algorithm for both Go terms and phenotypes is based on the binomial distribution and is identical to that used in the pathways category.

#### 2.9.1.5.Drugs and Compounds

The GeneAnalytics compounds category takes advantage of multiple source that cover more than 83,000 compounds, almost 45,000 of which are associated with genes.
GeneAnalytics uses unification process which reduces the number of compounds with associated genes by more than half, from ~45,000 to ~20,000 compounds.
This robust process saves time in reviewing identical compounds presented under various names by different data sources and enables massive aggregation of genes per compound and is featured in GeneCards.

The compound unification process seeks out similar compounds described in different data sources, and is based on the following rules:

- Unification of compounds with exact identical names (case/dash- insensitive).
- Unification of compounds with identical identifiers, more specifically both a Chemical Abstracts Service (CAS) number (unique numerical identifier assigned to chemical substances) and a PubChem ID (PubChem is an NCBI database providing information on the biological activities of small molecules). Note tha not all compounds have these identifiers, nor do all databases provide these id for their compounds.
- Unification of compounds with either an identical CAS or PubChem ID and identical synonyms. Only compounds with at least one identical identifier and one identical synonym are unified.
- Metabolite unification based on metabolite family and gene sharing: severa metabolite families contain thousands of compounds with almost identical nam emany of which are associated with an identical list of genes. In GeneAnalytic s,prevalent metabolite family subgroups belonging to Triglycerides, Diglyceride

s,Phosphatidylcholines, Phosphatidylethanolamines, have been unified based identical lists of associated genes.

Unified compounds are shown with links to all supporting data sources, providin ginformation and its relevance to the evaluated genes, while the original compou name is shown near its data source. The matching algorithm is based on the binomia distribution and is identical to that used in the pathways category.

The compound category in GeneAnalytics provides the opportunity to explore relation between compounds and gene sets, to define potential drugs and their mechanisms of action and to facilitate drug target discovery.

### 2.9.2. GeneAnalytics Output

#### 2.9.2.1.Tissues and Cells

GeneAnalytics provides novel and meaningful contextualization of various input gene sets.

These include NGS-derived mutated genes, as well as differentially expressed genes identified by a microarray experiment, RNA sequencing, *in situ* hybridization or real-time PCR. In addition, lists of genes encoding protein targets of a specific drug or proteins known to be a part of a specific molecular pathway or biological process ar recommended for this analysis.

The Tissues and Cells results category in GeneAnalytics leverages the extensive and high quality gene expression data available in LMD. Results include the following *in vivo* cells, *in vitro* cells, anatomical compartments, organs, and tissues ("anatomical entities"), whose reported gene expression profiles match the query gene set (Fig. 3). This category provides matching to cases in which given normal (healthy, wild type, untreated) tissues and cells show differential expression relative to control tissues. It excludes genes differentially expressed in diseased tissues and cells, as compared to healthy tissues, which are available in the disease category.

This distinction is essential for result interpretation and eliminates incorrect associatio of aberrant gene expression profiles with normal tissues and cells. Importantly,

members of a highlighted gene subset appear in both of the above scenario, they will be shown in parallel in the two relevant categories.

#### 2.9.2.2.Diseases

The diseases category of the GeneAnalytics results (Fig. 4) harnesses the broadly integrated information available in MalaCards (Rappaport et al., 2013; 2014). MalaCards mines and merges over 60 data sources and provides a comprehensive list of diseases, unified by various annotations, such as names, acronyms, and oMIM ids. Each disease entry has a webcard containing wide-ranging disease information. This including related diseases, genes with relevant disease-implicating annotations, genetic tests, variations with pathogenic significance, expression information and more.

#### 2.9.2.3.Pathways

The pathway category in GeneAnalytics is empowered by the information available in PathCards, the biological pathways database (Belinky et al., 2015). PathCards unifies 12 pathway sources into SuperPath, generating an explicit list of the included pathwa yas well as their associated genes. This unification is important because it integrate pathway information from various sources, thereby introducing novel gene–gene associations within the unified pathways.

The PathCards algorithm enable the unification of over 3000 pathways, obtained from all of its data sources, into a set of approximately 1000 pathway clusters called "SuperPaths" (Table 2 for statistics). Each SuperPath encompasses up to 70 pathways and is presented in a webcard that includes an aggregated gene list and also links relevant pathway sources. The PathCards algorithm (Belinky et al., 2015) estimates pathway similarity by overlapping gene content, with the assumption that the gene content defines the pathway identity.

Thus, unifying pathways by names and/or hierarchal clustering,which significantly vary between different pathway sources, is simplified. The chosen SuperPath name is that

of the most ‘connected’ pathway in the cluster, namely the pathway with the highest gene similarity to the other pathways in the SuperPath.

#### 2.9.2.4 Gene ontology (GO) terms and phenotypes

Gene ontology analysis in GeneAnalytics exploits the information available in the Go project (www.geneontology.org) and integrated into GeneCards (Safran et al., 2010). Go provides an ontology of defined terms representing gene product properties. This project uses set of structured and controlled vocabularies for the annotation of gene and gene products in an effort to standardize their attribute representation across species(Gene ontology, 2010). Go consists of three hierarchically structured ontology that describe gene products in terms of their associated biological processes, cellular components, and molecular functions.

Since its inception, many tools have been developed to explore, filter, and search the Go database (Conesa et al., 2005; Eden et al., 2009; NogalesCadenas et al., 2009; Zheng and Wang, 2008). one of the most common applicationsof the Go vocabulary is enrichment analysis (i.e., the identification of Go terms thatare significantly overrep resented in a given set of genes). Go terms can be either tissues or cells in embryo and in adult, pathways, diseases, or other functions. As such, Go enrichment analysis in GeneAnalytic provides supporting information about the functional roles of the query gene set.

Phenotype analysis in GeneAnalytics utilizes the Mouse Genome Informatics (MGI—www.informatics.jax.org) data that are presented in GeneCards. MGI phenotypes descri be the outcome of either naturally occurring or induced mouse mutations.
These aberrations are genetically characterized and portrayed with high resolution in a hierarchical phenotype tree (similar to the Go term tree). The observed outcome of genetic abnormalities in mice is a powerful instrument for inferring of the function al influence of genes, therefore identifying enriched mouse phenotypes may give insig htas to the biological processes involved in various experimental conditions.

Enriched Go terms results are divided into two categories, corresponding to two of the three ontologies, ‘biological processes’ and ‘molecular function’. A third categor

ydisplays mouse phenotype enrichment results. The terms in each category are ranke by their matching score, and appear with a direct link to relevant webcard in either the AmiGo browser (www.geneontology.org) or MGI website (www.informatics.jax.org Also shown are the list of the matched genes from within the input gene set and the total number of genes associated with each enriched Go term.

#### 2.9.2.5.Drugs and Compounds

The Compounds analysis in GeneAnalytics derives its information from GeneCards, which associates genes with biochemical compounds and drugs. This information extracted from several data sources, which contain extensive biochemical and pharmac ological information about drugs, small molecules and metabolites, their mechanisms action, and their targets. Gene–compound associations are determined either by direct binding between the compound and the gene product(e.g., enzyme, carrier, transporter) or by demonstration of a functional relationship(e.g., pharmacogenomics,genetic varian tand drug pathways affecting drug activity).

The wide range of compounds in the Compound category naturally includes many inthe realms of glycomics, metabolomics, and lipidomics. Consequently, GeneAnalytics has the capacity to portray various gene set enriched in such compounds, hence point to relationships between genomics and other omics domains. Such relations would include cases in which carbohydrates, metabolites, or lipids serve as ligands for the receptors, substrates, or regulators for enzymes, as well as posttranslational modifiers of proteins. In such cases, compounds such as Nacetylglucosamine, dopamine, or phosphatidylserine could readily be targets for enrichment in inputted gene sets.

# 3. MATERIALS AND METHODS

A recently published list of genes found to be clinically relevant and known to play a role in ASD and music perception for molecular profiling and pathway analysis of genes common to these two conditions withw similar features was used.

- GeneAnalytics (http://geneanalytics. genecards.org/) computer program and gene databases are part of the GeneCards Suite developed by LifeMap Sciences (http://www.lifemapsc.com/products/genecards-suite-premium-tools/) and were used

  to map the resultant list of common genes to characterize molecular pathway s,biological processes, molecular functions, phenotypes, tissues and cells, diseas esand compounds affected by overlapping genes.

- GeneAnalytics is powered by GeneCards, LifeMap Discovery, MalaCards, and PathCards, which combine >100 archived data sources. The databases contain gene lists for tissues and cells, diseases, phenotypes pathways and compounds curated from published literature reports to develop the best-matched list of genes, scored and subdivided into their biological categories such as diseaseor pathways.

- These applications integrated with GeneCards human gene database, Malacards human disease database, PathCards, human biological pathways database, Life Map Discovery tissues and cells database in order to provide an extensive data from human genes, proteins, cells, biological pathways, disease and their relationship with integration for research and discovery purposes.

- Disease matching scores were derived based upon the number of overlapping genes found and the nature of the gene-disease associations. Tissues and cells were scored using a matching algorithm that weigh tissue specificity, abundant and function of the gene. Related pathways were grouped into Superpathway sto improve inferences and pathway enrichment, reduce redundancy and ran kgenes within a biological mechanism via multiplicity of constituent pathway swith the methodology and algorithm generated by the GeneAnalytics computer -based program.

- The top 5 results from each category i.e. Diseases, Tissue & Cell types, Pathways, Biological Process and Phenotypes were taken into consideration.

# 4. RESULTS

There were 792 genes for ASD initially published in the literature while 45 genes were listed for music perception out of which, 3 genes were found to be common to them. (Table 4).

Functional analysis of these 3 genes showed a medium match for Cerebral Creatine Deficiency Syndrome 1 (1 gene, score = 2.83) and for autism spectrum disorder (1 gene, score = 0.90). Two types of brain tissues were found to have high match scores when profiled for tissue and cell types (Table 5b).

The Sumoylation by RanBP2 (regulates transcriptional repression) achieved the highest medium-match score for 1 gene (score = 9.23), followed by Notch Signalling Pathway (sino) involving 1 gene (score = 7.69) and Signalling events mediated by HDAC Class II (1 gene, score = 7.61) (Table 9).

| **Gene Symbol** | **Gene Name** |
|---|---|
| SLC6A8 | Solute Carrier Family 6 Member 8 |
| JMJD1C | Jumoji Domain Containing 1C |
| HDAC4 | Histone Deacetylase 4 |

**Table 4:** Genes shared by ASD and Music perception that are clinically relevant

| Disease | Genes (Highmatch Score) | No. of Genes in the disease | Score |
|---|---|---|---|
| Prehypertrophic Chondrocytes (SGP) | SLC6A8 | 1 | 2.83 |
| Prehypertrophic Chondrocytes (ZgGP) | HDAC4 | 1 | 2.67 |
| Immature Endochondral osteoblasts (Vrt) | HDAC4 | 1 | 2.33 |
| Immature Endochondral osteoblasts (Rib) | SLC6A8 | 1 | 2.33 |

**Table 5a:** Disease mapping to display conditions that significantly match the 3 overlapping genes for ASD and Music perception

| Tissues & Cells | Genes Matched to Tissue & Cell Type (Highmatch Score) | No. of Genes in Tissue & Cell Type | Score |
|---|---|---|---|
| Prehypertrophic Chondrocytes (SGP) | HDAC4 | 15 | 1.14 |
| Prehypertrophic Chondrocytes (ZgGP) | HDAC4 | 16 | 1.14 |
| Prehypertrophic Chondrocytes (Rib) | HDAC4 | 22 | 1.08 |
| Immature Endochondral osteoblasts (Vrt) | HDAC4 | 35 | 1.02 |

**Table 5b:** Tissue and cell mapping that shows high match scoring tissues

| **Superpathways** | **Genes Matched** | **No. of genes in superpathways** | **Score** |
|---|---|---|---|
| Sumoylation by RanBP2 regulates transcriptional repression | HDAC4 | 11 | 9.23 |
| Notch Signalling Pathway(sino) | HDAC4 | 11 | 7.69 |
| Signalling events mediated by HDAC Class II | HDAC4 | 32 | 7.61 |
| Signalling events mediated by HDAC Class III | HDAC4 | 34 | 7.41 |
| Jak/STAT Signalling Pathway Intracellular Regulation | HDAC4 | 39 | 7.37 |

**Table 6**: Superpathway mapping for the 3 overlapping genes to list 5 highest scoring superpathways

Neural Crest Differentiation and Transcriptional Misregulation in Cancer were also among the superpathways identified. There was only one gene (*HDAC4*) common to all 17 superpathways.

In the examination of gene ontology pathways, medium-match scores were found for a few molecular functions such as: Creatine Transport with one gene (*SLC6A8*), score = 12.69; Regulation of Striated Muscle Cell Differentiation with one gene (*HDAC4*), score = 11.69 and Creatine Transmembrane Transport with one gene (*SLC6A8*), score = 11.11. A total of 38 GO-biological processes were identified to have medium-match involving 1 gene each (Table 7).

| GO-Biological Processes | Genes matched to GO- Biological Processes | No. of genes in GO-Biological Processes | Score |
|---|---|---|---|
| Creatine Transport | SLC6A8 | 1 | 12.69 |
| Regulation of Striated Muscle Cell Differentiation | HDAC4 | 2 | 11.69 |
| Creatine Transmembrane Transport | SLC6A8 | 2 | 11.69 |
| Regulation of Skeletal Muscle Fibre Development | HDAC4 | 3 | 11.11 |
| Regulation of Cardiac Muscle Contraction by Calcium Ion Signalling | HDAC4 | 7 | 9.88 |

**Table 7:** Gene ontology (GO) biological processes with high match scores mapped to the 3 overlapping genes for ASD and Music perception

During phenotype mapping to the 3 overlapping genes, 33 phenotypes were found involving 1 gene each (Table 8). The medium-matched phenotypes were Decreased circulating creatine level (one gene, score = 12.69), Decreased creatine level (one gene, score = 11.69), Increased blinking frequency (one gene, score = 11.11) and Hyperactivity (two genes, score = 10.81).

| **Phenotypes** | **Genes Matched to Phenotypes** | **No. of Genes** | **Score** |
|---|---|---|---|
| Decreased circulating creatine level | SLC6A8 | 1 | 12.69 |
| Decreased creatine level | SLC6A8 | 2 | 11.69 |
| Increased blinking frequency | HDAC4 | 3 | 11.11 |
| Hyperactivity | HDAC4, SLC6A8 | 272 | 10.81 |

**Table 8:** Phenotypes with high match scores mapped to the 3 overlapping genes for ASD and Music perception

# 5. DISCUSSION

In order to obtain authentic data regarding the shared molecular background of ASD and music perception, gene lists for the same were retrieved from reported literature and also through SFARI- Gene Autism Database. The gene list was retrieved in order to investigate and find the shared genes between the two entities that are being researched upon i.e. ASD and music perception. The gene list for ASD contained a total of 792 genes which had been experimentally observed to have been expressed differently in patients suffering from ASD. The list of genes which are expressed differently in music perception comprised of 45 genes. The genes were listed in the literature and in the database only after thorough experimental investigation of their expression in people suffering from ASD. This was then followed by the usage of set approach to obtain the list of shared genes between ASD and music perception. This resulted in the identification of three genes namely, SLC6A8 (Solute Carrier Family 6 Member 8), JMJD1C (Jumoji Domain Containing 1C) and HDAC4 (Histone Deacetylase 4) (Table 4). It has been observed that the upregulation of these three genes occurs in music perception which has led to the conclusion that therapy through music can lead to possible formulations for the treatment of ASD.

The molecular and genetic architecture of music perception, as well as, ASD were analysed using the three identified candidate genes which were found to be common. This was performed in order to assess shared biological factors and phenotypical contributions of the three identified genes. GeneAnalytics software was used to perform analysis on five different aspects in order to understand the role of the three genes on each level in the human body. The five aspect used to analyse the roles of the particular genes were as follows; Diseases, Tissues and Cells, Superpathways, Go- Biological processes and Phenotypes.

Table 5a displays the list of related diseases which occur as a direct response to the altered expression of the particular gene mentioned. The scores obtained were used to determine the gene that was responsible for the onset of that particular disease or disorder. The altered expression of SLC6A8 has been found to be responsible for prehypertrophic chondrocytes (SGP) found in the cartilaginous cells. It was found to be the only causative gene for the above mentioned anomaly. Another form of the pre-hypertrophic chrondocytes (ZgGP) was found

to occur due to the altered expression of HDAC4 gene. In this case, HDAC4 was found to be the only gene from the genes obtained which was responsible for the occurrence of the disease. Another anomaly found to occur with the altered expression of HDAC4 was immature endochondral osteoblasts (Vrt). HDAC4 was found to be the only responsible gene for the observance of this disease type. Immature endochondral osteoblasts (Rib) were found to occur on the altered expression of SLC6A8 in the body. Again, only SLC6A8 was found to be responsible for the occurrence of this disease.

Table 5b displays the list of tissues and cells which were found to most probably contain the genes. The scores obtained were used to determine the location of the three genes in the body. HDAC4 was found to be present in the prehypertrophic chondrocytes (SGP). It was found to present along with 15 other genes that might be present along with it in the aforementioned cell type. The score obtained after GeneAnalyticS mapping was 1.14. HDAC4 was found to be present even in the prehypertrophic chondrocytes (ZgGP). A total of 16 other genes were predicted to be present along with this gene in the cells. A score of 1.14 was obtained from the GeneAnalytics software which was used to map the tissues and cells which matched the presence of the three overlapping genes in them. HDAC4 was found to be present in prehypertrophic chondrocytes (Rib). A total of 22 genes has been identified which may be present in the cells along with HDAC4. The score obtained was 1.08. HDAC4 was to be present in immature endochondral osteoblasts (Vrt). 35 genes were found to be present in the cells along with HDAC4. The score obtained from the software was 1.02.

Table 6 depicts the results obtained when mapping of superpathways was performed to check for the involvement of the particular genes in the pathways in the body. Interestingly, the genetic architecture of the overlapping genes converged on brain structures (e.g., Midbrain tegmentum, Striatum etc.), transcriptional repression, and notch signalling. The top 5 scores were chosen to represent the roles played by the genes in certain pathways. HDAC4 was observed to play a role in the sumoylation by RanBP2 which is important for regulation of transcriptional repression. A combined total of 11 genes were found to possess similar properties as HDAC4. A score of 9.23 as obtained from the GeneAnalytics software. This was followed by the observation of the role of HDAC4 in the Notch Signalling Pathway (sino). HDAC4 was found to be one among the 11 others which are known to participate in the notch

signalling pathway. A score of 7.69 was obtained after analysis using the software. HDAC4 was found to be involved in the Signalling events mediated by HDAC Class II. It is one among the 32 other genes involved in such pathways. A score of 7.61 was obtained from the software. HDAC4 was again found to participating in the Signalling events mediated by HDAC Class III. A set of 34 genes, including HDAC4, are present which participate in the pathways in the same manner as HDAC4. A score of 7.41 was obtained from the software. The next molecular pathway which was found to possess the participation of HDAC4 was Jak/STAT Signalling Pathway Intracellular Regulation. The score obtained from the software was 7.37. A total of 39 genes is known to have similar roles in the above said pathway.

Table 7 emphasizes on the mapping of gene ontology biological processes in the human body. Go-molecular processes were mapped to Creatine: sodium symporter activity, transcription factor binding and a few others as well. SLC6A8 was found to be involved in creatine transport as the sole propagator of the function in the body. HDAC4 was observed to have a role in Regulation of Striated Muscle Cell Differentiation. The number of genes which have been reported to have similar functions as HDAC4 were two. This was then followed by the observation which stated a role of SLC6A8 in the Creatine Transmembrane Transport. A total of two genes (including SLC6A8) are known to have similar functions. The HDAC4 gene was found to be involved in the Regulation of Skeletal Muscle Fibre Development. The gene belongs to a set of three other genes which have similar functions i.e. involvement in the regulatory process mentioned above. HDAC4 was found to have an influence on the Regulation of Cardiac Muscle Contraction by Calcium Ion Signalling in the human body. A total of 7 genes (including HDAC4) were found to possess similar properties and functions as HDAC4. The scores obtained are shown in Table 4.

Table 8 depicts the effects on certain phenotypes due to the altered expression of the identified common genes in music perception and ASD. The phenotypes are certain features which are expressed in the cells, tissues or other body parts. The expression of specific phenotypes during such conditions as ASD can be treated or worked upon in order to obtain a solution for the above said issue through music perception. As mentioned earlier, the three genes identified have specific roles in the body related to ASD as well as music perception. This indicates that the roles played by the identified common genes in upregulating or downregulating certain

functions in the body can be manipulated in order to treat ASD through music and also through other treatment methodologies. The table here depicts the 4 such phenotypes which can be observed on the alteration of the expression of the identified genes in the body. Thus, the following effects can also be treated music as these genes are also responsible for music perception.

SLC6A8 is a major contributor to creatine deficiency which is one of the many causes of ASD. SLC6A8 is responsible for the decreased circulating creatine levels in the body as obtained from the software analysis. only SLC6A8 has property to induce such a phenotypical effect to the creatine levels in the body. Decreased creatine levels in the body was also obtained as a result of the altered expression of SLC6A8 in the body. Two genes, including SLC6A8, have been known to possess similar properties as SLC6A8 wherein they possess the capacity to cause a decrease in the creatine levels in the body. The increased frequency of blinking has been linked to the altered expression of HDAC4 in the body. A set of 3 genes have been known to cause the same phenotypical effect as HDAC4. Hyperactivity is a phenotype which is quite common to the altered expression of a large number of genes. HDAC4 and SLC6A8 are among the 272 genes which can induce such a phenotypical effect as hyperactivity. JMJD1C is involved in mydriasis (dilated pupils) and tonic seizures as well.

The genes are known to possess such characteristics which are related to the onset of autism and this can be prevented and/or treated with the help of targeted treatment of the three overlapping genes (JMJD1C, SLC6A8 and HDAC4) with music. The tables aptly display the gene analysis performed on each of the above mentioned genes and displays the roles they play in all the five categories they have been analysed. This can be utilized further in order to facilitate mechanistic understanding and potential development of new treatment approaches.

The main for understanding the shared molecular background is to be able to develop new treatment approaches so as to help people with ASD. Another aim would be to understand the molecular background of how music affects autism. This study does not claim any causality yet, but already gives a glimpse into what can be expected from doing further experiments.

This analysis is limited by the current status of research and availability of published literature reports on candidate genes as well as the reliability of the curated databases and integrated

pathway analyses produced by the GeneAnalytics algorithms. Advances in genomic technology and bioinformatics will continue to identify and characterization new candidate genes, but not all identified genes will be equally important or certain to be causative.

# 6. CONCLUSION

By leveraging the strengths of Bioinformatics approaches, this thesis enters an unexplored territory so far: the molecular determinants and mechanisms underlying ASD and Music Perception. To date, neuroscientific literature has provided substantial evidence concerning the neuroanatomical and physiological changes associated with music perception. But this study presented a set of candidate genes that could have a role in ASD and Music perception.

While the findings cannot be generalized, these findings could guide further research in the molecular genetics of ASD and Music Perception. In general, listening and practicing music gives an intense feeling of happiness. The genes involved in mediating such euphoria-like feeling could also cause the opposite state of feelings like depression and mood disorders when affected by genomic variation or gene-environment interaction. Therefore, studies like these may also serve a purpose to identify novel candidate genes for various neurological disorders. After all, such studies may enhance our everyday life because of the immense social relevance.

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