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Music in DNA: From Williams Syndrome to Musical Genes

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Abstract

Williams syndrome (WS) is a genetic disorder caused by a heterozygous contiguous gene deletion on chromosome 7q11.23. Clinical features of the disease include low IQ and deficit in some cognitive domains, and the presence of relatively strong abilities in social drive, face processing, language, and musical skills. The presence of a strong predisposition to the development of musicality in individuals affected by WS leads us to suppose that some genes deleted in this syndrome are somehow involved in the evolution of this ability, and that these genes could act in normal conditions as "suppressors of music ability". To test this hypothesis, we carried out an "*in silico*" analysis by using the Ingenuity Pathway Analysis (IPA) software to identify the interaction between genes mapped in the WS critical region and genes previously related to musical ability by literature data. This approach allowed us to identify 3 networks of interaction, involving AVPR1A, NCF1, UNC5C and LAT2 in the first network, STX1A and SLC6A4 in the second one and only WS related genes in the last one. Among these associations, the one involving STX1A and SLC6A4 suggested a possible mechanism of interaction was based on the influence played by STX1A deletion on the serotonin levels through a decrease of SLC6A4 activity.

Keywords

Williams Syndrome, Music Ability, Serotonin

1. Introduction

Music is one of the most mysterious aspects of human nature (Charles Darwin—The Origin of Species; 1859).

Music represents a universally diffused practice, endowed of ubiquity in time and culture. For this reason, it

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comes immediate to wonder which function music has in people's life. Some authors attribute the importance of music to social factors, as cohesion and group cooperation [1]; others consider music as a valid tool to express feelings, being able to arouse deep and meaningful emotions [2]. Darwin proposed in 1871 that singing was used to attract the opposite sex [3]. Furthermore, music provides a tool to study numerous aspects of neuroscience from motor-skill learning to emotion [4].

Despite naturalness and diffusion of music, musical executive competence is characterized by strong differences among individuals, which can be located on a continuum where it is possible to find competences ranging from very scarce to excellent with the majority of people located in the middle with modest production skills. The existence of individual differences in musical competence has driven the interest of researchers to clarify the basis of this variability, especially as concerning the different role played by biological and experiential factors. A biological basis in the development of music ability is supported by the existence of specific behavioural features, like absolute pitch (AP) and congenital amusia, for which a genetic influence has clearly been individualized [5]-[7]. AP is the ability to identify or produce isolated musical tones [8]. This condition can be considered as a complex trait, depending on both genetic factors and exposure to musical training during childhood [5]. On the other hand, congenital amusia, also known as "tone-deafness", is a deficit of music perception that, in absence of deafness or any other cognitive disorder, determines the inability to correctly reproduce sounds. The hereditary component of the congenital amusia has been demonstrated within 9 amusic families, where 39% of first-degree relatives had the same disorder, against 3% only in control families [9].

A very peculiar condition strongly suggesting the presence of genes related to the individual musical ability is represented by the great musical abilities existing in individuals affected by Williams syndrome (WS). WS (OMIM 194050) is a multisystem genomic disorder affecting 1/7500 -1/10,000 live births caused by a heterozygous contiguous gene deletion on chromosome 7q11.23 [10]. The common deletion region ranges in size from 1.5 to 1.8 Mb between the polymorphic markers D7S1816 and D7S489B and encompasses approximately 28 genes, including Elastin (ELN), LIM1 kinase (LIMK1), Frizzled (FZD9, previously called FZD3), and Syntaxin1A (STX1A) [11] [12]. A clear genotype-phenotype correlation has been established in WS only for the ELN gene, which is responsible for the vascular and connective tissue abnormalities [13].

Individuals with WS are characterized by low IQ, ranging from 40 to 100 (mean = 61, SD = 11), and deficit in some cognitive domains including conceptual reasoning, problem solving, and spatial cognition [14]. However, the most interesting aspect of WS cognitive profile is the presence of relatively strong abilities in four specific domains: social drive [15], face processing, language [16], and musical skills [17] [18]. Individuals with WS show unique communication strengths and impairments that are challenging to treat in community, educational, and vocational settings. Many issues regarding characteristics of auditory sensitivity in WS remain to be resolved [19].

Studies about this rare syndrome have suggested various candidate genes for the intellectual disability, like GTF2I [20]. Since WS has a clearly defined genetic etiology, playing for sure a role in the determination of the characteristic cognitive and behavioral profile, investigators have used this syndrome as a model to elucidate gene-brain-behavior relationships [21]-[24]. In this view, the existence of a strong predisposition to the development of musicality in individuals affected by WS leads us to suppose that some genes deleted in this syndrome are somehow involved in the evolution of this ability. The general hypothesis of this study is that genes deleted in WS act in normal conditions, in healthy people, as "suppressors of music ability". Assuming this hypothesis is correct, the consequence should be that musical behaviour is expressed naturally and at a superior level in individuals where these genes are inactive.

To verify this hypothesis, we carried out a study to identify the interaction between genes mapped in the WS critical region and genes previously related to musical ability by literature data.

2. Methods

The present study has been organized in three steps. In the first part of the study, we analyzed the functions played by genes mapped within the WS critical region in order to verify their possible roles in the development of musical competence. To this aim, we carried out a review of the most recent literature by means of Pubmed, using "William syndrome" "genes" "critical region" and "deletion" as key words.

In the second step of the study, we performed a search of literature data in order to identify other genes, outside the WS critical region, which have been previously suggested as involved in the development of musical

ability. Also in this case a literature review was carried out by Pubmed, using "genes" and "music" as specific key words.

Finally, we carried out an "*in silico*" analysis in order to highlight the presence of functional correlation among genes mapped in the critical region for the WS and those evidenced in literature as involved in musical competences. For this part of the study, we used the Ingenuity Pathways Analysis (IPA) software, allowing classifying genes detected in the first two steps of the study on the basis of their biological functions and detecting the functional networks connecting genes among them.

3. Results

3.1. Genes Mapped within WS Critical Region

Literature data evidence that the following genes are removed by the deletion on 7q11.23: ELN, LIMK1, GTF2I, STX1A, BAZ1A, CYLN2, GTF2IRD1, NCF1, RFC2, FZD9, FKBP6, TBL2, BCL7B, CLDN4, EIF4H, LAT2, WBSCR11, STAG3L, PMS2L, GATS-L, WBSCR19, GTF2IRD2, POM121, NSUN5, TRIM50, FKBP6, FZD9, BAZ1B, BCL7B, TBL2, MLXIPL, VPS37D, DNAJC30, WBSCR22, WBSCR26, ABHD11, CLDN3 and CLDN4, EIF4H, LAT2, RFC2, CLIP2, WBSCR23.

Although no one of these genes has been so far suggested as a candidate for musical abilities, all these genes are expressed in the nervous system, and thus all of them have been considered in the present study as potentially involved in the regulation of other genes mapped outside the WS critical region and directly affecting the development of musical abilities.

Furthermore, some evidences have argued that a haploinsufficiency of the ELN gene may also be involved in the peripheral impairments mediating hyperacusis. Since the elastase enzyme destroys the stereocilia tip links [25], a deficiency of this protein could lead to a desynchronized movement of the stereocilia, resulting in hearing loss and delayed cochlear nerve activation [26]. This would, in turn, adversely affect the acoustic reflex and lead to hyperacusis [27].

3.2. Genes Connected with Musical Abilities

A few studies have been performed about genetic component in musical skills.

Considering the possibility that music was an innate ability, Pulli *et al*. [28] investigated biological basis of music perception, using statistical and molecular genetic approaches and behavioural tests, through 15 Finnish multigenerational families (in total 234 family members). Linkage analyses showed a significant evidence in 4q22 with an interesting candidate gene, namely UNC5C, Netrin receptor. UNC5C interacts with netrins in axon guidance and neuronal migration during central nervous system development. Netrins are essential for inner ear semicircular duct formation, suggesting a role in development of structural-musical ability. Furthermore, netrins appear some way related with ROBO1, candidate gene for dyslexia [29], suggesting a possible common molecular background between musical and linguistic abilities.

One more candidate gene that appears to play a role in "structural-musical abilities" is TRPA1, a member of the transient receptor potential (TRP) family of ion channels, mainly expressed by cells of the inner ear [30]. This gene is located on chromosome 8q12 - 8q13, very close to the region involved in AP.

Unlike UNC5C and TRPA1, related to physical and structural characteristics that "allow to listen the music", other two polymorphic genes have been directly associated to social aspects of musical abilities: the arginine vasopressin 1a receptor (AVPR1a) and the serotonin transporter (SLC6A4) related by literature to several social, emotional and behavioral traits, including musical abilities, musical aptitude and musical memories [31] [32].

AVPR1a gene has been shown to affect many emotional and social traits. Microsatellite repeat regions (RS1 and RS3) located in the human AVPR1a gene promoter have been associated with autism spectrum disorders [33]-[35], prepulse inhibition [36], altruism in a dictator game [37], pair bonding and aggression in males [38] [39], parenting [40] and love [41].

SLC6A4 promoter region polymorphism (5-HTTLPR) is one of the most important genes in emotion regulation and social cognition. It contains a regulatory variation (Short Variant, S, and Long Variant, L) that have been associated with anxiety-related traits and susceptibility for depression [42]. Furthermore, the long 5-HTTLPR allele has two variants (*i.e*., LA and LG). In the first of two extra 20 - 23 bp repeats in the L allele, a common single nucleotide polymorphism occurs at the sixth nucleotide (adenine to guanine; A to G) [43]. The LG

variant and the S allele appear to be very similar in terms of transcriptional activity; therefore, only the LA variant is high expressing with regard to transcriptional activity [44].

AVPR1A and SLC6A4 have been directly correlated both to social cognition and musical abilities in different studies. Bachner-Melman *et al*. [31], in their interesting research, have shown that the AVPR1a in association with the SLC6A4 seems to affect individual's aptitude, propensity, and need for dancing, which is integrally related to music. The authors had examined performing dancers, elite athletes, and nonathletes/nondancers observing significant differences in allele frequencies for both genes when dancers were compared to athletes as well as to nondancers/nonathletes. Furthermore, these two genes were also associated with scores on the Tellegen Absorption Scale (a questionnaire that correlates positively with spirituality and altered states of consciousness since spirituality personality facets important in the dance phenotype) and Reward Dependence (measure aspects of social communication) of Tridimensional Personality Questionnaire, suggesting that the association between these genes and dance is mediated by personality factors reflecting the social communication of the dancing phenotype [31].

In order to investigate genetic contribution of musical abilities, Granot *et al*. [32] analyzed the relation between AVPR1a and SLC6A4 and music memory using a specific battery MBEA (Montreal Battery of Evaluation of Amusia) and genetic analyses for involved regions. Results showed that polymorphisms related to AVPR1a and SLC6A4 were associated with short term memory for music although they were not specific for music processing.

Moreover, Donaldson *et al*. [45] argued that association with the AVPR1A receptor gene that mediated the effects of highly conserved AVP suggested that listening to music was related to the pathways affecting attachment behaviour and social communication. In fact, several behavioural features in listening (perceiving) music are closely related to attachment: Lullabies are song to infants to increase their attachment to a parent, and singing or playing music together may add group cohesion [9]. Thus lullabies could be one example of important environmental factor that can interact with other factors (genetics, biological and socio-cultural) in order to develop some social features as attachment and/or musicality disposition or sensitivity.

3.3. Correlation between Deleted Genes in WS and Musical Genes

Results of the second step of our study evidenced four candidate genes for musical abilities: (UNC5C, TRP1A, AVPR1a and SLC6A4), all considered in the third step of our investigation, aimed to explore the presence of a relation between genes related to music by literature data and deleted genes in WS.

3.4. IPA Functional Analysis of Genes Related to Williams Syndrome and Musical Abilities Genes

After the identification of genes selectively involved to Williams syndrome and musical abilities, we employed Ingenuity Pathway Analysis (IPA) to further investigate key biological functions and networks linked to these genes. IPA analysis revealed that the main functions involved were: Cardiovascular Disease, Developmental Disorder, Endocrine System Disorders, Hereditary Disorder, Organismal Injury and Abnormalities, Renal and Urological Disease, Behavior showing a p-value ranging from 1.91E−08 to 4.45E−02 (**Table 1**). The identified functions are displayed as bar chart in **Figure 1**. Among these, some genes enclosed within behavior class function are specifically related to the formation of neural circuits and could mediate WS musical abilities.

3.5. Networks Associated with Genes Related to Williams Syndrome and Musical Abilities Genes

We employed IPA to study how the selected genes were interacting in specific networks. IPA predicts functional networks based on known protein-protein and functional interactions. IPA infers and ranks networks by a score, expressed as a numerical value, which is a probabilistic fit between the amount of focus genes that are potentially eligible for a network composition and present on a given gene list, the size of the network, as well as all the molecules present in the Ingenuity Knowledge Base that can be part of such a network.

IPA analysis of the selected genes generated 3 networks with a score of 27, 24 and 21.

In the first top network (**Figure 2**, **Table 2**), we found ten WS related genes (ABHD11, CLIP2, EIF4H, LAT2, NSUN5, M121/POM121C, TBL2, TRIM50, VPS37D, WBSCR27) and two musical abilities genes (TRPA1,

Table 1. Main functions played by WS genes.

Cardiovascular Disease	1.91E−08 - 4.11E−02	ELN, MLXIPL, NCF1, EIF4H, SLC6A4, BAZ1B, LIMK1
Developmental Disorder	1.91E−08 - 4.11E−02	ELN, MLXIPL, NCF1, PMS2, SLC6A4, LIMK1
Endocrine System Disorders	1.91E−08 - 4.45E−02	ELN, MLXIPL, PMS2, BAZ1B, CLDN3, LIMK1
Hereditary Disorder	1.91E−08 - 3.77E−02	ELN, MLXIPL, NCF1, SLC6A4, PMS2, AVPR1A, LIMK1
Organismal Injury and Abnormalities	1.91E−08 - 4.11E−02	ELN, NCF1, MLXIPL, LAT2, PMS2, TRPA1, SLC6A4, LIMK1
Renal and Urological Disease	1.91E−08 - 1.9E−02	ELN, MLXIPL, SLC6A4, LIMK1
Behavior	1.16E−06 - 4.45E−02	NCF1, **SLC6A4**, TRPA1, FZD9, STX1A, GTF2IRD1, **AVPR1A,** LIMK1

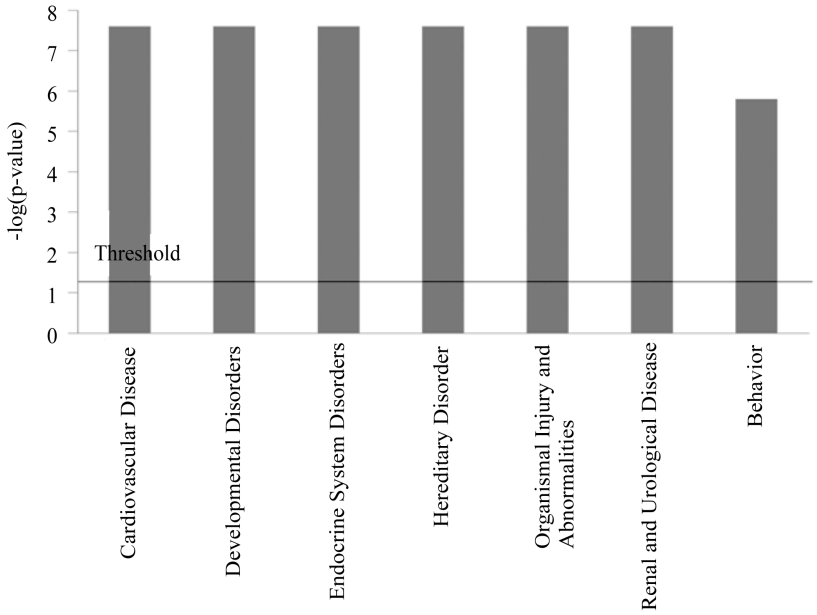

Figure 1. Bar chart showing the main functions played by WS and musical abilities related genes. The high-level functional categories that are involved in this analysis are displayed along the x-axis. The y-axis displays the −log significance. Taller bars are more significant than shorter bars. Functions are listed from most significant to least and the orange horizontal line denotes the cutoff for significance (p-value of 0.05).

UNC5C). The analysis of this network evidenced an indirect relationship among Williams and music related genes (AVPR1A to NCF1 and UNC5C to LAT2) but, as mentioned, these were non significant for our purpose.

The second network (**Figure 3**, **Table 3**) is composed by 9 Williams related genes (ELN, FZD9, GTF2I, GTF2IRD1, NCF1, PMS2, RFC2, STAG3, STX1A) and two musical abilities genes (SLC6A4, AVPR1A).

Interestingly, as depicted, we observed a direct correlation between STX1A and SLC6A4 (5-HTT), a Williams and music related genes, respectively. This direct correlation is supported by four Source Ingenuity Expert Findings [46]-[49] and can suggest a role of STX1A in development of musical abilities.

The third network includes only ten Williams related genes (BAZ1B, BCL7B, CLDN3, CLDN4, DNAJC30, FKBP6, GTF2IRD2, LIMK1, MLXIPL, WBSCR22) and no music related genes, and it doesn't reveal any interesting gene-gene relationship (**Figure 4**, **Table 4**).

3.6. Functional Correlation between STX1A and SLC6A4

SLC6A4, the serotonin transporter gene, is involved in the formation of neural circuits. Factors regulating the expression of serotonin transporter could have a role in cortical development. Syntaxin 1A (STX1A) can be one

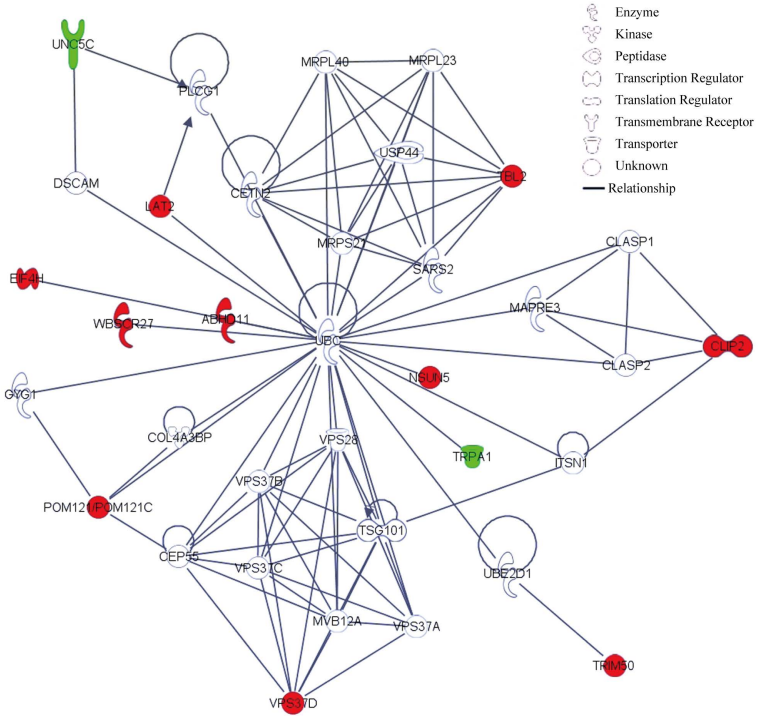

Figure 2. First top network generated by IPA showing indirect interactions between WS and music related genes. Gray indicates WS related genes; light gray indicates music related genes. Genes inferred by IPA are represented in white. Arrows indicate that a molecule acts on another while lines indicate that a molecule binds to another.

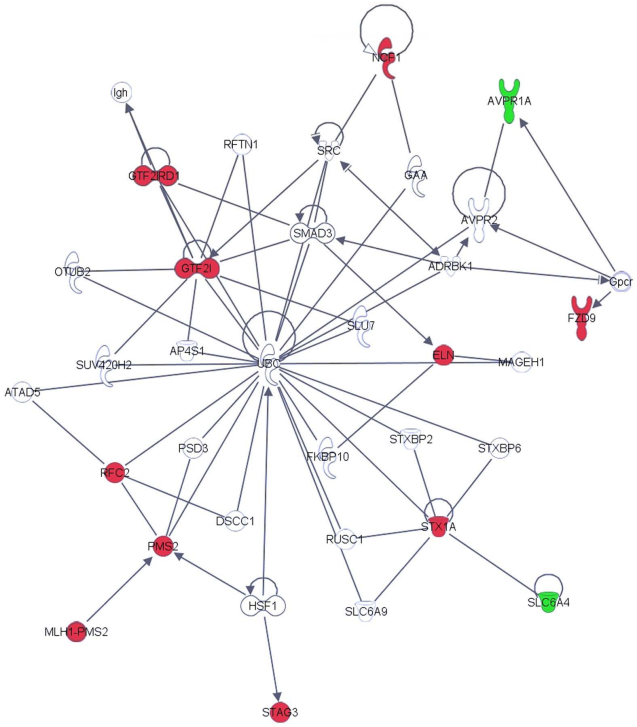

Figure 3. Second top network generated by IPA showing direct and indirect interactions between WS and music related genes. The network shows the direct interaction between STX1A and SLC6A4 genes. Gray indicates WS related genes; light gray indicates music related genes. Genes inferred by IPA are represented in white. Arrows indicate that a molecule acts on another while lines indicate that a molecule binds to another.

Table 2. Genes involved in the network 1. In bold genes associated to WS or musical abilities.

Symbol	Entrez Gene Name	Entrez Gene	Location
ABHD11	abhydrolase domain containing 11	83451	Cytoplasm
CEP55	centrosomal protein 55kDa		Cytoplasm
CETN2	centrin, EF-hand protein, 2		Nucleus
CLASP1	cytoplasmic linker associated protein 1		Cytoplasm
CLASP2	cytoplasmic linker associated protein 2		Cytoplasm
CLIP2	CAP-GLY domain containing linker protein 2	7461	Cytoplasm
COL4A3BP	collagen, type IV, alpha 3 (Goodpasture antigen) binding protein		Cytoplasm
DSCAM	Down syndrome cell adhesion molecule		Plasma Membrane
EIF4H	eukaryotic translation initiation factor 4H	7458	Cytoplasm
GYG1	glycogenin 1		Cytoplasm
ITSN1	intersectin 1 (SH3 domain protein)		Cytoplasm
LAT2	linker for activation of T cells family, member 2	7462	Plasma Membrane
MAPRE3	microtubule-associated protein, RP/EB family, member 3		Cytoplasm
MRPL23	mitochondrial ribosomal protein L23		Cytoplasm
MRPL40	mitochondrial ribosomal protein L40		Cytoplasm
MRPS21	mitochondrial ribosomal protein S21		Cytoplasm
MVB12A	multivesicular body subunit 12A		Cytoplasm
NSUN5	NOP2/Sun domain family, member 5	55695	Unknown
PLCG1	phospholipase C, gamma 1		Cytoplasm
POM121/POM121C	POM121 transmembranenucleoporin	9883	Nucleus
SARS2	seryl-tRNAsynthetase 2, mitochondrial		Cytoplasm
TBL2	transducin (beta)-like 2	26608	Plasma Membrane
TRIM50	tripartite motif containing 50	135892	Unknown
TRPA1	transient receptor potential cation channel, subfamily A, member 1	8989	Plasma Membrane
TSG101	tumor susceptibility gene 101		Cytoplasm
UBC	ubiquitin C		Cytoplasm
UBE2D1	ubiquitin-conjugating enzyme E2D 1		Cytoplasm
UNC5C	unc-5 homolog C (C. elegans)	8633	Plasma Membrane
USP44	ubiquitin specific peptidase 44		Nucleus
VPS28	vacuolar protein sorting 28 homolog (S. cerevisiae)		Cytoplasm
VPS37A	vacuolar protein sorting 37 homolog A (S. cerevisiae)		Cytoplasm
VPS37B	vacuolar protein sorting 37 homolog B (S. cerevisiae)		Cytoplasm
VPS37C	vacuolar protein sorting 37 homolog C (S. cerevisiae)		Cytoplasm
VPS37D	vacuolar protein sorting 37 homolog D (S. cerevisiae)	155382	Cytoplasm
WBSCR27	Williams Beuren syndrome chromosome region 27	155368	Unknown

Table 3. Genes involved in the network 2. In bold genes associated to WS or musical abilities.

Symbol	Entrez Gene Name	Entrez Gene	Location
ADRBK1	adrenergic, beta, receptor kinase 1		Cytoplasm
AP4S1	adaptor-related protein complex 4, sigma 1 subunit		Cytoplasm
ATAD5	ATPase family, AAA domain containing 5		Extracellular Space
AVPR1A	arginine vasopressin receptor 1A	552	Plasma Membrane
AVPR2	arginine vasopressin receptor 2		Plasma Membrane
DSCC1	defective in sister chromatid cohesion 1 homolog (S. cerevisiae)		Nucleus
ELN	elastin	2006	Extracellular Space
FKBP10	FK506 binding protein 10, 65 kDa		Cytoplasm
FZD9	frizzled family receptor 9	8326	Plasma Membrane
GAA	glucosidase, alpha; acid		Cytoplasm
Gpcr			Unknown
GTF2I	general transcription factor IIi	2969	Nucleus
GTF2IRD1	GTF2I repeat domain containing 1	9569	Nucleus
HSF1	heat shock transcription factor 1		Nucleus
Igh	immunoglobulin heavy chain complex		Unknown
MAGEH1	melanoma antigen family H, 1		Cytoplasm
MLH1-PMS2			Nucleus
NCF1	neutrophil cytosolic factor 1	653361	Cytoplasm
OTUB2	OTU domain, ubiquitin aldehyde binding 2		Unknown
PMS2	PMS2 postmeiotic segregation increased 2 (S. cerevisiae)	5395	Nucleus
PSD3	pleckstrin and Sec7 domain containing 3		Cytoplasm
RFC2	replication factor C (activator 1) 2, 40kDa	5982	Nucleus
RFTN1	raftlin, lipid raft linker 1		Plasma Membrane
RUSC1	RUN and SH3 domain containing 1		Cytoplasm
SLC6A4	solute carrier family 6 (neurotransmitter transporter, serotonin), member 4	6532	Plasma Membrane
SLC6A9	solute carrier family 6 (neurotransmitter transporter, glycine), member 9		Plasma Membrane
SLU7	SLU7 splicing factor homolog (S. cerevisiae)		Nucleus
SMAD3	SMAD family member 3		Nucleus
SRC	v-src sarcoma (Schmidt-Ruppin A-2) viral oncogene homolog (avian)		Cytoplasm
STAG3	stromal antigen 3	10734	Nucleus
STX1A	syntaxin 1A (brain)	6804	Cytoplasm
STXBP2	syntaxin binding protein 2		Plasma Membrane
STXBP6	syntaxin binding protein 6 (amisyn)		Cytoplasm
SUV420H2	suppressor of variegation 4-20 homolog 2 (Drosophila)		Nucleus
UBC	ubiquitin C		Cytoplasm

Table 4. Genes involved in the network 3. In bold genes associated to WS.

Symbol	Entrez Gene Name	Entrez Gene	Location
ACACB	acetyl-CoA carboxylase beta		Cytoplasm
ACLY	ATP citrate lyase		Cytoplasm
ATAD5	ATPase family, AAA domain containing 5		Extracellular Space
BAZ1A	bromodomain adjacent to zinc finger domain, 1A		Nucleus
BAZ1B	bromodomain adjacent to zinc finger domain, 1B	9031	Nucleus
BAZ2A	bromodomain adjacent to zinc finger domain, 2A		Nucleus
BCL7A	B-cell CLL/lymphoma 7A		Unknown
BCL7B	B-cell CLL/lymphoma 7B	9275	Unknown
CDC42BPA	CDC42 binding protein kinase alpha (DMPK-like)		Cytoplasm
Cldn			Plasma Membrane
CLDN1	claudin 1		Plasma Membrane
CLDN3	claudin 3	1365	Plasma Membrane
CLDN4	claudin 4	1364	Plasma Membrane
CLDN5	claudin 5		Plasma Membrane
CLDN8	claudin 8		Plasma Membrane
DNAJC30	DnaJ (Hsp40) homolog, subfamily C, member 30	84277	Cytoplasm
ELAVL1	ELAV (embryonic lethal, abnormal vision, Drosophila)-like 1 (Hu antigen R)		Cytoplasm
FGF21	fibroblast growth factor 21		Extracellular Space
FKBP6	FK506 binding protein 6, 36kDa	8468	Nucleus
GTF2IRD2	GTF2I repeat domain containing 2	84163	Unknown
HNF4A	hepatocyte nuclear factor 4, alpha		Nucleus
LIMK1	LIM domain kinase 1	3984	Cytoplasm
MID1IP1	MID1 interacting protein 1		Cytoplasm
MLXIPL	MLX interacting protein-like	51085	Nucleus
MYO1A	myosin IA		Cytoplasm
NME7	NME/NM23 family member 7		Cytoplasm
PHF10	PHD finger protein 10		Nucleus
PHF21A	PHD finger protein 21A		Nucleus
SMARCA4	SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily a, member 4		Nucleus
SS18	synovial sarcoma translocation, chromosome 18		Nucleus
SUMO2	SMT3 suppressor of mif two 3 homolog 2 (S. cerevisiae)		Nucleus
TJP1	tight junction protein 1		Plasma Membrane
TP53	tumor protein p53		Nucleus
VHL	vonHippel-Lindau tumor suppressor, E3 ubiquitin protein ligase		Nucleus
WBSCR22	Williams Beuren syndrome chromosome region 22	114049	Nucleus

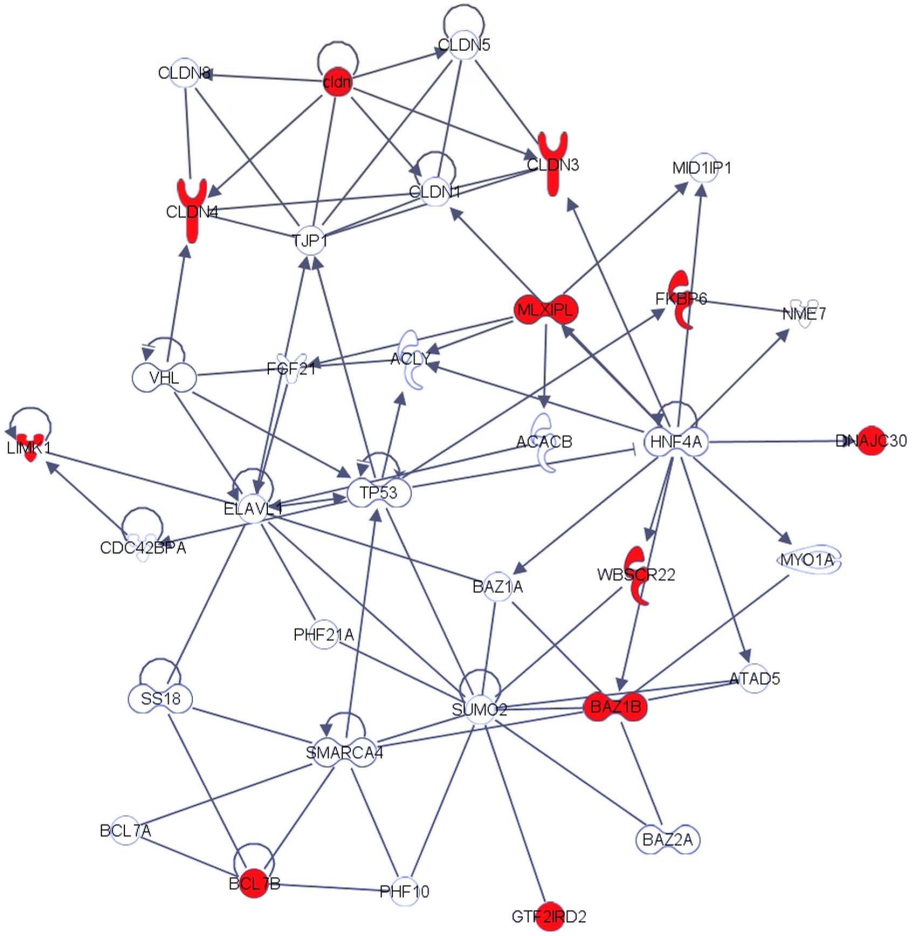

Figure 4. Third top network generated by IPA showing the interactions among WS genes. Gray indicates WS related genes. Genes inferred by IPA are represented in white. Arrows indicate that a molecule acts on another while lines indicate that a molecule binds to another.

of these factors, being involved in synaptic transmission. Particularly, a physic interaction between SERT and STX1A could be responsible for modulation of serotonin reuptake. SERT function is reduced by the deletion of STX1A in WS, suggesting a different development of specific cognitive skills such as music abilities.

4. Discussion

Since 1990, technological development has largely modified our approach to biological and medical information. For instance, genome-wide association studies (GWASs) have revolutionized the field of human quantitative genetics and genome sequencing and gene expression data were used to identify gene modifications and modulations related to specific phenotypes. However, these experimental efforts to measure the functions of genes, especially those of unknown function, which are very challenging and very expensive in terms of time, effort, and money. Nowadays the use of appropriate hardware and software makes it possible to simulate static or dynamic, even complex, physiological or cellular processes to unravel the molecular pathways which are modulated by diverse set of genes in the hope of discovering information that would prompt future studies.

Analysis *in silico*, made through computer programs, represents an important new research method that allows the examination of a large amount of data not possible in a different way, if not with great human and economical efforts. For this reason we used this method to verify the initial hypothesis of this work, especially using IPA software to verify the possibility that some deleted gene in Williams syndrome acted, in normal conditions, as suppressor of other genes that were able to influence the development of musical skills.

Many studies have investigated genotype-phenotype correlation in WS individuals, but a clear, direct link has

been established only for the elastin gene (ELN) responsible for the SVAS [50] [51]. Moreover, mouse models have suggested other genotype-phenotype correlations, such as those between craniofacial abnormalities and GTF2I and GTF2IRD1 genes [52], tooth anomalies and visuo-spatial deficit, associated to GTF2I, GTF2IRD1 and GTF2IRD2 genes [53], as well as deficits in motor coordination, associated with CLIP2 gene [54]. Likewise, the function of the carbohydrate response element-binding protein (MLXIPL, a.k.a. ChREBP or WBSCR14) in the regulation of the expression of enzymes involved in glucose and lipid metabolism [55] [56] suggests that haploinsufficiency of this gene is associated with the higher relative body fat, silent diabetes and/or impaired glucose tolerance found in WS adult individuals [57]. The molecular substrates underlying the other clinical features of 7q11.23 CNVs, including the neurocognitive phenotypes, are still debated [58].

For this reason, it can be interesting to consider the observed direct correlation between STX1A and SLC6A4, the serotonin transporter gene. Neocortex receives serotoninergic innervations at the beginning of the development, suggesting an important role of serotonin in the formation of neural circuits [59] [60].

Levels of serotonin during the development influence the neural morphology [61] and density of synaptic contacts [62]. Levels of serotonin are important also in modulation of synaptic plasticity [63] [64], neural activity [65] and neural maturation [66]. Experimental manipulation in serotonin levels during the first post-natal development can produce characteristic behavioural syndromes [67] [68] and long term cognitive damages [69]-[71]. Furthermore, changes in normal serotonergic signalling reveal a crucial role of serotonin system in the formation of sensitive maps of somatosensorial [72] [73] and visual [74] [75] systems. Then, SERT regulation in neocortex 5HT levels can have serious physiological, anatomical and behavioural effects. Reduction of STX1A results in decreased function and expression of SERT. Reduction of STX1A is related to a decrease of SERT function. STX1A acts like a positive regulator of synaptic signalling [48].

5. Conclusions

Since in normal conditions, STX1A influence serotonin levels, the results of research suggest that the lack of STX1A could cause alterations of 5HT levels justifying a different development of specific cognitive skills.

Specific cognitive abilities are involved in listening, processing and producing music, so musicality can be considered as a particular form of cognitive profile.

For this reason, it cannot be excluded the involvement of serotonin not only in the development of basic cognitive abilities but also in musical abilities.

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