Williams Syndrome: The Costs and Benefits of Chromosomal Deletion

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Summary

Williams Syndrome (WS) is a complex neurodevelopmental disorder characterized by vascular and heart disease, mental retardation, characteristic facial features, and characteristic personality. WS, which is usually sporadic, affects approximately 1 in 20,000 live births and is caused by a particular deletion of about 1.5 Mb of chromosome 7q11.23. My lab has shed light on the anatomical and cognitive basis for WS. While WS patients have cognitive gifts, such as notable linguistic abilities, they also have deficits, such as visuospatial deficits. WS patients also show significant anatomical differences, with a reduced perimeter of the corpus collosum and amygdalar nuclei. The major current goal in the field is to connect the genetic basis to these anatomical and cognitive differences. About 28 genes are deleted in WS; four such genes are Elastin, Lim kinase, WSTF and GTF21.. An elastin deletion results in supravalvular aortic sclerosis (SVAS), which is common in WS patients. Lim kinase absence affects actin polymerization and lamellipodia formation and may regulate abnormal synaptic development. WSTF deletion results in misregulation of chromatin remodeling and this may have profound consequences during development. GTF absence explains the facial and skull abnormalities in WS. The impact of other gene deletions is poorly understood; thus, future work continues to focus on the relationship between genetics, the brain and cognition in relation to WS syndrome.

Introduction

A rare, generally sporadic neurodevelopmental disorder was first described by Williams *et al* in 1961. Williams and colleagues described a group of individuals with growth deficiencies, supravalvular aortic stenosis, and atypical facial features[1]. Beuren *et al* then described individuals with similar characteristics as well an amicable personality and some dental irregularities[1]. Collectively, these characteristics describe individuals with Williams-Beuren Syndrome (Williams Syndrome).

Along with the characteristics described by Williams and Beuren, individuals with this rare disorder have mild to moderate mental retardation, sensitivity to sound, exhibit hypersociability, and commonly have infantile hypercalcaemia, gastrointestinal problems, hypertension, and ADHD[1-3]. In addition to these features, Williams Syndrome patients also display significant anatomical differences[3]. While WS patients exhibit significant strengths in short-term memory and language, they also exhibit deficiencies, especially in visuospatial cognition. We have done several studies to investigate the neuroanatomical features of the syndrome. We have also examined its behavioral and developmental aspects, and their respective contributions to WS.

Williams syndrome is thought to affect between approximately 1 in 7,500 to 1 in 20,000 people. WS is caused by the deletion of ~1.6 Mb of chromosome 7q11.23 [1-3]. This deletion is caused by an unequal crossing over of repeats during mitosis and results in the hemizygotic deletion of about 28 genes[3]. Many of these genes have been investigated and characterized. Four genes, elastin (ELN), Lim Kinase (LimK), WSTF and GTF, and their effects on WS individuals will be discussed in this paper. While my lab's focus is the anatomical and cognitive aspects of WS, the goal of this review is to elucidate the link between cognition, the brain, and genes.

Williams syndrome and Downs Syndrome

Linguistic Abilities

We have done previous studies investigating the various cognitive, anatomical, behavioral, and biological aspects of different developmental disorders[4-6]. While we know some of the cognitive facets of the disorder many other aspects of the disorder, such as a specific profile for Williams syndrome, remain to be clarified.

Our previous research has shown that Williams Syndrome patients show notable strengths in language and facial processing but weaknesses in their special cognitive abilities. In contrast, Down syndrome patients have significant cognitive, language, and visuospatial deficits[4-6]. The difference in cognitive abilities of DS and WS make it of interest to us to compare the two groups. Both WS and DS patients have been shown to have a delayed onset of first words[4]. Although both groups are delayed when compared to normally developing children, WS patients overcome this extreme delay in words, while DS patients do not. Our early research focused on the comparison between IQ matched DS and WS, which would allow us to begin to understand the systems that regulate language and cognitive abilities[4-6].

A comparison of the two groups showed that WS patients have conserved semantic abilities. After hearing a word, WS patients were more readily able to choose the correct picture out of a group. In this same task all DS patients fell below their mental age equivalents. When being tested at a different task, this one requiring a verbal cue and a verbal response, WS patients also produce an increased amount of words, including unusual and uncommon words, showing greater word fluency when compared to DS patients [4-6]. Together these results show that not only do WS patients show an increased lexical semantic ability, but they also show increased grammatical abilities when compared to DS patients. Some of the differences between DS and WS were established. A better cognitive profile for WS has been establish, but the

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direct cause for the cognitive differences in DS and WS has yet to be determined.

Sociability and Language

We have shown that WS patients exhibit significant abilities in some cognitive aspects. Another aspect of the WS profile to be studied is their sociable personality. WS patients show an excessively social behavior, often times being overly talkative and fearless of social interactions[7]. Hypersociability may be a phenotype that also differentiates WS patients from other disorders. Therefore, we thought it relevant to study hypersociability and its neurological and genetic basis for this syndrome.

Our experiments showed that WS patients use language as a way to engage their audience[7]. Not only do WS patients use a longer and more complex language, they also tend to use more expressive language, such as voice changes, sound effects, character speech, voice lengthening, and other linguistic devices. This excessive trend is significantly different from DS and normal control patients[7]. Collectively, our results indicated that despite language delays WS patients use their language for social purposes[7]. These finding allowed us to better understand this aspect of the WS profile.

Spatial Cognition

While we have shown that WS patients have increased linguistic abilities, we also found WS patients have strong deficits in spatial cognition[4-6]. We used several task in order to test and compare the visuospatial cognitive abilities of our WS and DS patients. In a block design task both groups are unsuccessful but in different ways. WS patients make designs that show non-joined fragments, while DS patients have joined blocks but poor internal organization. In a task requiring a freehand drawing, we saw that WS patients make illogical drawings. This occurred even as the patients talked their way through the drawing process. DS patients in contrast draw logical drawings, but demonstrate poor internal organization. A third task requiring visuospatial processing was administered. This one required the subject to look at an angled line and match it to a line found within a group. Both WS and DS patients performed poorly[4-6]. This finding was not surprising as it further demonstrated the visuospatial deficits previously found in WS patients [6].

Face Recognition

Thus far, our investigations showed that WS patients have strong deficits in some aspects of special cognition including block design, drawing special transformations, and spatial memory[6]. Surprisingly, one aspect of visuospatial cognition, face processing, and recognition was found to be relatively spared in WS patients.

Our initial study compared DS patients to WS patients in order to better understand the strengths and weaknesses generated by this syndrome[4-6]. The Benton Facial Recognition test was used in order to evaluate the facial recognition abilities of WS and DS patients. This test requires the patients to look at a photograph and then choose the matching face from a group of six photographs. Our initial findings suggested that WS patients have a better ability to discriminate between faces. All WS patient tested, between the ages of 10 and 17, performed at or above the level of an average adult. DS patients, unlike WS patients, show a severe inability in this visuospatial task.

Later studies verified our previous findings[7]. The Benton Upright Face Task, The Warrington Face Memory Test, and the Mooney Closure Test, three distinct face processing tasks, showed similar results[4]. Although variations in lighting, shadow, and orientation were occurred throughout the tasks all WS patients performed at an average level when compared to controls and performed significantly better than DS patients[4-6].

It then became of interest to us to investigate the differences in accuracy and timing of facial recognition. Investigating these aspects, along with our previous findings, would allow us to explore the cognitive profile of WS patients. WS patients, like the normal control, were typically faster and more accurate at identifying matched versus mismatched photographs. Furthermore, WS patients like normal controls, were faster and more accurate when processing upright versus inverted faces[8]. This was important as we wanted to explore the hypothesis that there may be two different manners of processing upright and inverted data. Farah *et al* (1998) found in recent studies that upright facial recognition require processing of faces as a whole, while inverted pictures require the processing of parts of a picture[8]. The differences in timing and accuracy found in our recent studies may be linked to this data.

Cognition: Three Trajectories

Through various studies we acquired an understanding of the differences in cognitive abilities between WS and DS patients. We have established that DS patients have below average face recognition, spatial and lexical knowledge. Their below average achievement as seen from an early age tends to not increase as patients get older[4, 6].

WS patients in contrast, begin with an exceedingly low vocabulary and lexical knowledge, but these abilities are significantly strengthened with age. When examining spatial cognition WS patients start with below average abilities, and their performances remain substandard with age. The exact reasons between the differences in the cognitive profiles seen in WS and DS are yet to be elucidated. Our studies have helped elucidate the strengths and weaknesses of WS patients and have helped in improving the understanding of the cognitive profile of WS.

The next major goal is to link the cognitive, morphological, and physiological aspects of WS, in order to shed light on the relationships between cognition and the brain.

The Anatomy of Williams Syndrome

Our effort to understand the possible underlying anatomical difference that may be linked to the differences in cognitive profiles of WS and DS lead to our early anatomy research. We focused on the anatomical differences between WS and DS patients.

In contrast to the DS patient findings, the corpus collosum of WS patients was found to resemble control specimen with no changes in volume. Although there is a similar collosum volume, WS patients had a reduced corpus collosum perimeter[9]. Subsequent examination of WS brain reflected a difference in the bend angle of the corpus collosum with the angle being larger than controls[10]. These shape differences, we believe are a result of parieto-occipital region variation. Our lab's preliminary studies, which show morphological differences, showed a decreased

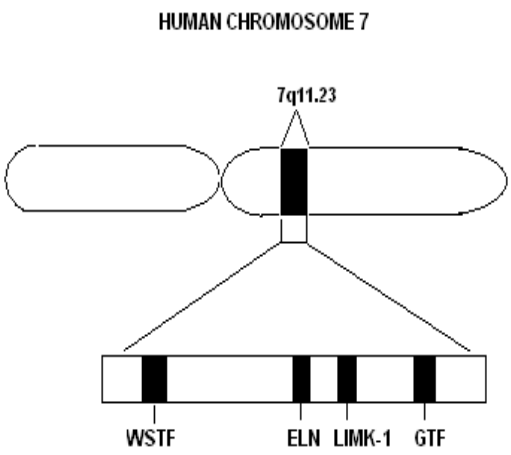

Figure 1. The Deletions in WS. WS is caused by the hemizygotic deletion of about 28 genes in human chromosome 7q11.23. The genes elastin, LIM-kinase, WSTF and GTF are known to be four of the 28 genes in the ~1.5 Mb deleted region. (Adapted from Smoot et. al. 2005, Tipney et al. 2004, and Meyer-Lindenberg et al. 2006)

splenium size. This size change is significant as it would help explain the visuospatial deficits since the splenium connects bilateral parieto-occipital regions[10].

Collectively, the WS corpus collosum findings, which are generally similar to controls, may be an explanation for the preservation of frontal lobe structure and better conserved frontal lobe function[9]. It is our belief that the preserved linguistic abilities seen in WS patients may result from the sparing of frontal and cerebellar structures, as well as the normal development of limbic structures in WS.

Limbic Structures

Our studies showed that limbic structures, such as the uncus, amygdala, and hippocampus showed conserved sizes. Intriguingly, studies done by Meyer-Lindenberg *et al*[11], also focused on a limbic structure, but their investigation focused primarily on functional neuroimaging. Their results showed that there is reduced reactivity in the amygdala of WS patients to threatening images, but also showed an increased reactivity to threatening scenes compared to normal control. The reduced activation of the amygdala in the presence of a threatening face may contribute to WS patients' diminished fear of strangers[11]. The increased reactivity of the amygdala to social situations is of particular importance as it may be a possible explanation for the increased anxiety often seen in WS patients[11].

Genetics

Chromosomal Deletion

The hemizygotic deletion of chromosome 7q11.23 results in the deletion of about 28 genes, including ELN, LimK, WSTF and GTF[1-3] (Figure 1). Many of these genes have now been characterized, and the result of their deletion is understood. While our research focuses on the cognitive, behavioral, and anatomical aspects of the disease it is important to understand the underlying genetic explanations for the disease. In order to better understand this aspect of the disease, we use other research in the field to explain the function and deletion of the previously mentioned four genes.

Among the constituents of the extracellular matrix of arteries is elastin. Li *et al* had previously shown that the lack of one allele of elastin causes an arterial disease, supravavular aortic stenosis (SVAS)[12,13]. In order to investigate elastin's role in the development of arteries as well as its role in SVAS, various knockout studies were done.

Initial studies demonstrate that the deletion of elastin reduces the amount of elastin mRNA and protein. Also shown was that an elastin deficiency had a profound effect on the development of arteries[12]. While there is no difference seen between knockout mice ($ELN^{-/-}$) and control mice ($ELN^{+/+}$) aortae before embryonic day 15.5, there are significant changes in $ELN^{-/-}$ aortic diameter and cell count thereafter. Cross-sections of different developmental stages show a significant increase in the amount of cells in the arteries of $ELN^{-/-}$ as well as reduced artery size. Results indicated that while there was an increase in arterial wall thickness, as a result of increased lamellar units[13,] there was also a reduction in inner arterial diameter. This data suggests that the development of arteries in mice lacking elastin is atypical[12].

Further studies were done in order to better understand the reason for subendothelial accumulation of smooth muscles cells (SMCs). To do this, cells were stained with antisera containing Proliferating-cell nuclear antigen (PCNA) [12]. Results indicated that 85% of $ELN^{-/-}$ cells stained for the antigen versus 35% of $ELN^{+/+}$ cells. This indicates that there is an increased cell proliferation in elastin deficient mice[12]. This increased proliferation was later linked to the reduced elastin deposition seen in SVAS patients[13].

Through various studies, a link has been made between the reduced ELN deposition and the deficiency of ELN[14]. Studies have also shown, through the use of knock-out mice, that the lack of elastin is a direct cause of SVAS[13]. Collectively, the results of elastin studies show that elastin is necessary for normal arterial development and SMC proliferation and that the deletion of this gene results in the SVAS, commonly seen in WS patients.

LIM- kinase

In order to understand the effect of the deletion of LIM-kinase (LIMK-1) it was essential to first understand its' function. Studies first focused on the role of LIMK-1 in actin reorganization. It was first established that LIMK-1 associated with actin. This was done with the use of rat brain, a LIMK-1 fusion protein, and immunoblotting. Sequencing indicated that LIMK-1 associated with actin[15]. Yang *et al* believed that the previously established association may have been involved in regulation of actin cytoskeleton organization. This was later established, as experiments showed that LIMK-1 tagged cells show actin reorganization.[15]

Pathways, Pathways, Pathways

Once it had been demonstrated that there was an interaction between actin and LIMK-1 and that this association resulted in the reorganization of actin, it became of interest to determine the mechanism by which changes in actin organization occurred. *In vitro* studies showed that LIMK-1 phosphorylated colifin and

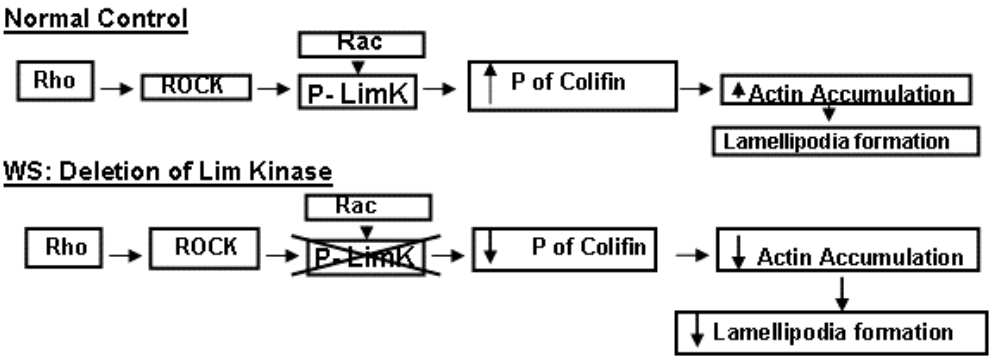

Figure 2. Lim Kinase Pathway In Williams Syndrome. Rho, a small GTPase, activates ROCK, a protein kinase. The activation of ROCK leads to the phosphorylation and subsequent inactivation of colifin, an actin binding protein required for actin filament depolymerization. The inactivation leads to increase actin accumulation and lamellipodia formation. Rac, a small GTPase increases LimK autophoshorylation, resulting in lamellipodia formation. In WS, LimK is deleted, resulting in a decrease in lamellipodia formation.

proteins with depolymerizing and actin-binding abilities[15]. The phosphorylation of colifin thereby inactivated it, completely hindering colifin's depolymerization activities[15].

It was also known that Rac, a small GTPase, was involved in regulation of actin cytoskeleton reorganization[15]. Yang *et al* therefore became interested in determining if LIMK was involved in the Rac-induced signaling pathway for actin organization[15]. It was determined that Rac induced lamellipodia formation through the activation of LIMK-1. These finding were confirmed by Arber *et al,* who established that Rac leads to an increased autophosphorylation of LIMK; increased amount of LIMK-1 causes the phosphorylation and subsequent inactivation of colifin, which then lead to the accumulation of actin filaments[16]

While one mechanism for the actin cytoskeleton had been clarified a second mechanism, this one involving a GTPase Rho and a Rho-associated kinase ROCK, had yet to be clarified. In an *in vitro* study Maekawa *et al* show that LIMK-1 activity was greatly increased in the presence of a dominant active ROCK mutant (ROCKΔ1) and a dominant inactive Rac mutant (N17-Rac) [1]. These results indicated that there was, in fact, ROCK activation of Lim kinase.

In conjunction, the results of these studies showed a pathway that now included Rho and ROCK, where Rho activated ROCK, leading to the phosphorylation and subsequent inactivation of colifin. The inactivation of colifin then lead to the inhibition of actin depolymerization, thereby leading to its accumulation[17] (Figure 2).

The mechanism by which Lim kinase regulates actin organization had now been demonstrated *in vivo*. Few studies had been done to observe actin activity in Lim kinase knockout mice. Furthermore, the link between the deletion of LIMK-1 and the WS profile had yet to be established. Meng *et al* proposed that LIMK-1 was involved in brain fuction through regulation of actin[18].

Knockout out mice were generated in order to investigate this hypothesis. It was shown that the organization of the actin cytoskeleton of neurons was abnormal in knockout mice. This distribution abnormality was especially evident in neuron dendrites, where morphology of spines was also significantly affected[18]. Knockout mice also showed a reduction in the size of their growth cones. These results indicate that LIMK-1 is necessary for the proper organization and distribution of actin filaments in neurons as well as for the maintenance of spine morphology in neuronal dendrites[18]. Furthermore, later studies demonstrated that LIMK-1 is linked to changes in fear response and spatial learning.

WS patients are characterized by impaired cognitive ability. These studies have shown that LIMK-1 deletions are both responsible for abnormal neuronal actin organization. These finding lead researchers in the field to believe the affects that LIMK-1 has on neurons and actin organization may be linked to the cognitive impairments seen in WS patients, although there is some disagreement on this issue. Further research is needed in order to confirm this hypothesis.

WSTF Deletion

Williams Syndrome Transcription factor (WSTF) is the product of WSCR9 genes. This gene, previously known as WCRF, encodes a 1425 amino acid protein and is deleted in WS patients[19, 20]. Studies have shown through the use of antibodies and immunoprecipitation that WSTF and SNF2I, an isotope ISWI, form a chromosome remodelling complex, WICH [21]. Results indicate that this WSTF-ISWI remodelling complex is partly responsible for the change of irregular chromatin to a regular chromosomal array.

Along with WSTF's role in reconfiguring chromatin, a second important role was also elucidated. Studies showed that WSTF localizes with M31, a marker for pericentromeric heterochromatin[19]. WSTF was also shown to accumulate at the foci of replicating heterochromatin[21]. Bozhenok *et al* hypothesized that the accumulation of WSTF at pericentromeric heterochromatin may point to a possible role for WSTF in the replication of condensed heterochromatin or a role in the assembly of heterochromatin after replication has occurred. They also suggest that given pericentromeric heterochromatin's role in chromosome stability, WSTF's deletion may affect cell's survival[21].

WICH: A chromatin remodelling complex

WICH, a multi-protein complex that contains WSTF and SNF2I, is now known to be part of a larger complex. This larger complex contains nuclear actin and myosin 1 (NM1), a regulator of gene transcription[22]. It is also now known that NM1 is found in the nucleus and is required for the transcription of RNA polymerases. Therefore, comprehending the role of WICH and NM1 may elucidate new roles for WSTFs.

A recent study has shown that NM1 is localized within the nucleoli of cells and that it is

required for polymerase 1 transcription. The previous finding was established as antibodies for NM1 inhibited the transcription of polymerase 1 [22].

NM1, WSTF, and SNF2l were also shown to associate with rDNA and promote the synthesis of pre-rRNA. Given the complex's ability to promote the synthesis of pre-rRNA, it was thought relevant to investigate the effect of WSTF depletion through RNA interference. The depletion of WSTF resulted in the inhibition of pre-rRNA synthesis[22]. This finding suggests a new role for WSTF that was not previously established.

The combined findings of various studies suggest that the deletion of WSTF leads to some of the phenotypes of WS. More research is still need to be done to define the exact outcome of the WSTF deletion.

The GTFIRD1Contribution

GTFIRD1 was identified, characterized, and found to be in the WS deletion region[23]. This gene was known to be involved in the development and differentiation of tissues. GTFRD1 was thought to contribute to the phenotype of WS, but this hypothesis was not thoroughly tested until recently. The role of GTFIRD1 was investigated by examining gtfird1 mice. It was shown that GTFIRD1 null mutants exhibit significant weight loss relative to normal controls and growth deficiencies. Null mutant mice also exhibit misaligned jaws, dysmorphic faces, and shorter snots[24].

The previously stated findings suggested that the depletion of GTFIRD1, through a homozygous deletion, results in craniofacial abnormalities similar to those found in WS patients. GTFIRD1 was known to be a positive regulator of *goosecoid*, a transcription factor involved in development[24]. This may suggest that there is a mechanism involving GTFIRD1 and goosecoid that is responsible for proper jaw and skull development[24]. This suggestion remains to be clarified.

Conclusion

Our studies have attempted to elucidate the cognitive, behavioral, and anatomical differences between Down syndrome and Williams Syndrome patients. Research in the field has also made advances in understanding the genetic aspects of WS. We have made many advances in the field, as we now have a better understanding of the behavioral, cognitive, and anatomical aspects related to the disease. What is yet to be clarified is the specific reasons for all the characteristics seen in WS and the effects of all gene deletions. It is our future goal to be able to fully understand the link between cognition, the brain, and genes.

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