Williams Syndrome: The Extraordinary Profile of a Micro-deletion

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Abstract

Williams Syndrome (WS) is a rare genetic disorder caused by variable hemizygous micro-deletions on chromosome 7. Depending on the exact genes deleted, WS results in distinct cognitive, behavioral, and physical phenotypic profiles. Our lab characterized various deficits and gifts of WS. Deficits include hypersociability, poor visual-spatial skills, inferior cognitive abilities, and supravalvar aortic stenosis (SVAS). Gifts include musical proficiency, preserved linguistic abilities, and face recognition. Neuroanatomically, others and we have identified decreased brain size, preserved cerebellar volume, decreased cerebral midline length, larger corpus callosum bend, reduced occipital lobes, and superior longitudinal fasciculi (SLF) abnormalities linked to visual-spatial and other deficits. Other colleagues have mapped key hemizygous genes to distinct phenotypes; the five best-characterized genes are Elastin, LIMK1, CLIP2, GTF2I, and GTF2IRD1. ELN is important for proper neuronal development; hemizygous deletion is linked to SVAS. LIMK1 and CLIP2 work together in neuronal morphology and neurogenesis by regulating actin and microtubule dynamics, respectively. Hemizygous deletions in LIMK1 and CLIP2 affect proper neuronal development and synapse formation. Deficits in GTF2I produce hypersensitivity and anxiety, while lack of GTF2IRD1 causes craniofacial defects. Despite such major advances in WS, for the future, many other hemizygous genes will need similar characterization, increasing the possibility for effective molecular-based treatments for WS.

Introduction

Human variations grant scientists the opportunity to expand what is known about human biology. The rare genetic disorder Williams Syndrome (WS) in particular is providing groundbreaking expansions in the scientific field. Williams Syndrome was first discovered in 1952 by Fanconi and Williams. WS occurs in approximately 1 in 20,000 births and is caused by variable hemizygous micro-deletions on chromosome 7. Five of the best-characterized hemizygous gene deletions include Elastin, LIMK1Kinase, CLIP2, GTF2I, and GTF2IRD1. Variations of these micro-deletions result in distinct cognitive, behavioral, and physical phenotypic profiles; all of which attribute to the extraordinary profile of WS; this is exemplified in figure 1. Individuals with WS have very distinct physical phenotypes such as SVAS, a potentially fatal heart defect, hypercalcemia, and spine curvature abnormalities linked to visual-spatial and other deficits. Other colleagues have mapped key hemizygous genes to distinct phenotypes; the five best-characterized genes are Elastin, LIMK1, CLIP2, GTF2I, and GTF2IRD1. ELN is important for proper neuronal development; hemizygous deletion is linked to SVAS. LIMK1 and CLIP2 work together in neuronal morphology and neurogenesis by regulating actin and microtubule dynamics, respectively. Hemizygous deletions in LIMK1 and CLIP2 affect proper neuronal development and synapse formation. Deficits in GTF2I produce hypersensitivity and anxiety, while lack of GTF2IRD1 causes craniofacial defects. Despite such major advances in WS, for the future, many other hemizygous genes will need similar characterization, increasing the possibility for effective molecular-based treatments for WS.

Cognitive Abnormalities

Cognitive abnormalities linked to visual-spatial and other deficits. Other colleagues have mapped key hemizygous genes to distinct phenotypes; the five best-characterized genes are Elastin, LIMK1, CLIP2, GTF2I, and GTF2IRD1. ELN is important for proper neuronal development; hemizygous deletion is linked to SVAS. LIMK1 and CLIP2 work together in neuronal morphology and neurogenesis by regulating actin and microtubule dynamics, respectively. Hemizygous deletions in LIMK1 and CLIP2 affect proper neuronal development and synapse formation. Deficits in GTF2I produce hypersensitivity and anxiety, while lack of GTF2IRD1 causes craniofacial defects. Despite such major advances in WS, for the future, many other hemizygous genes will need similar characterization, increasing the possibility for effective molecular-based treatments for WS.

Neurocognitive Profile

Our lab used previous knowledge about the relationship between neurobiological systems and cognitive functions to develop our experimental framework. Our method was to match cognitive abnormalities with specific neurobiological causes; allowing us to map neurocognitive abnormalities with distinctive phenotypic features, highlighting both the strengths and weaknesses of WS. All subjects in our studies were recruited through family contacts, Williams Syndrome Association, national and regional conferences, private physicians, geneticists, cardiologists, and others. We administered a general IQ test to act as our foundation for a neurocognitive profile of WS. WS individuals displayed severe cognitive impairment across and array of general cognitive tasks, placing them in the mild-to-moderate mentally retarded range. Global standard scores ranged from 40-90 with a mean of approximately 55; this range indicates individual variations within the WS population. Depending on the severity of cognitive incompetence some WS adults are able to live independently or semi-independently, while others require a great deal of help. Out of all cognitive tasks, mathematics was the area of greatest difficulty within the WS population. The general IQ test also demonstrated a delay in conceptual knowledge, as well as deficits in spatial cognition.

Deficits in Spatial Cognition

WS individuals are characterized as having severe spatial cognition deficits. We assessed spatial cognition using the Block Design subset of the Wechsler Intelligence Scale for Children-Revised (WISC-R), which required...
subjects to arrange a set of blocks to replicate increasingly complex stimulus patterns\(^2\). WS subjects received extremely low global scores compared to local scores\(^2\) suggesting difficulty with the overall configuration of stimulus patterns and strength in local aspects of the pattern\(^2\). These spatial difficulties are also depicted in pen and paper tasks. When asked to copy a Navon-styled hierarchical local/global figure, WS patients are able to identify the local image but not the global image, for example when shown a large letter “D” composed of lower case “Y’s,” they only identify the “Y’s”; this is displayed in figure 2.

**Facial Recognition: Hey I know you!**

Apart from visuo-spatial deficits, WS individuals have a remarkable ability to recognize faces\(^6\); recognizing almost any face, discriminating and remembering familiar and unfamiliar faces alike\(^6\). WS individuals are able to recognize faces in various lighting and dimensions\(^6\). The Benton Test of Facial Recognition is a face-discrimination task which we used to assess facial recognition strengths within WS subjects\(^6\). The Benton test shows the same face under different conditions and assesses the WS subject’s ability to identify the face as familiar or unfamiliar\(^6\). Other test such as the Warrington Recognition Memory Test and the Mooney Closure task assessed unfamiliar face recognition and facial closure abilities\(^6\). In these studies WS subjects performed incredibly well in each task compared to DS subjects and normal controls, emphasizing the facial recognition proficiency of WS individuals\(^6\).

**Elaborate Language**

Another cognitive ability that is spared within the WS population is linguistic abilities\(^8\). We compared WS linguistic abilities disorders such as Down syndrome (DS) and Autism\(^12\). Our results showed WS individuals have the most elaborate and preserved verbal skills compared to both DS and Autism\(^10\). WS adolescents and adults are extremely articulate and talkative\(^9\). Linguistic skills serve as a characterized gift among WS individuals, however early development does not depict this\(^11\). During the initial stages of life, WS individuals speak their first words between 20-30 months old similar to DS individuals, displaying strong grammatical skills later in development\(^11\). Our lab collected data using the MacArthur Communicative Development Inventory (CDI), a parental report, to measure language development on two scales, Words and Gestures Scale and Words and Sentences Scales; assessing developing communication and grammatical skills in both WS and DS\(^11\). Data revealed that at the point of grammatical acquisition WS individuals show rapid and significant improvement compared to DS individuals; these reports indicate a linguistic phenotype divergence between the two groups\(^11\). Our lab also assessed grammatical skills using syntax testing\(^2\); during these test WS subjects were asked to detect and correct glitches in the arrangement of a sentence. Results indicated WS subjects scored significantly higher than DS subjects in syntax testing, further indicating the linguistic divergence between the two disorders\(^1\).

Further results indicate rather complex conversational language among WS individuals; WS individuals typically produce an array of complex language within their everyday diction\(^1\). WS individuals’ diction is so complex at times that it often times is categorized unusual\(^2\). WS individual tend to use very sophisticated wording in inappropriate context, for example in one of our studies a subject said, “I have to evacuate the glass” instead of simply saying empty the glass\(^2\). WS individuals use their language abilities to engage others socially\(^7\). Oddly enough WS individuals’ sociability acts more as a deficit than a gift\(^8\).

**Dangers of Hypersociability**

Our lab assessed WS hypersociability using the parent questionnaire, the Salk Institute Sociability Questionnaire (SISO)\(^8\). Parents reported that their WS children appear unable to resist approaching strangers, hence placing themselves in great danger\(^8\). These reports support the results of our previous study, which indicated WS individuals are unable to differentiate approachability based on facial expressions and rely on superficial signals as positive cues of approachability\(^8\). Another study showed that hypersociability occurs as early as infancy in WS individuals\(^7\). During a parental separation task, WS infants less frequently showed negative facial expression, and when a stranger (assessor) entered the room the infant became instantly intrigued and approached the stranger in a fearless manner. Infants were particularly interested in the face of the stranger\(^7\).

This unusual social phenotype drew the attention of our lab as well as other labs\(^1\). Quantifiable measures were used to assess the unrestrained social behavior in efforts of understanding the usual social phenotype (Jones et al., 2000). Sociability was first measured in association with linguistic expression based on affect and language through storytelling and interviews\(^1\). WS and DS subjects were asked to create a story based on a cartooned photograph; the extravagant wording style of WS subjects vividly depicted the expressive and engaging nature of WS subjects\(^1\). WS subjects not only use very expressive language but also modified their voices to match with certain expressions, as well as “audience hookers” such as guess what happens next?, to further engage their listeners\(^1\). We have encountered WS children who have stated there is no such thing as strangers, and act as everyone in the world is their friend\(^7\). An example of this overt friendliness was seen in a study assessing social expression through a biological interview tasks\(^1\). Subjects were asked to describe themselves, family, friends, and activities that interested them\(^1\). During the interviews after answering a question WS subjects asked the interviewers the same question, seeking information from them\(^1\). WS cognitive deficits and gifts led our lab to the brain morphology of WS individuals. We hypothesized brain morphology acted as the foundation blocks of these behaviors\(^1\).

**Neuroanatomical Profile**

**Gross Anatomical Observation**

We began by conducting a series of gross anatomical observations on fours autopsy specimens, of individuals who had been diagnosed with WS at some point in their lives\(^1\). Overall MRI images indicate that an overall reduction of gray matters (GM) and white matter (WM) volumes, along with disproportionate decreases in thalamus and occipital lobe sizes\(^1\). WS brains are also relatively low in weight, weighing approximately 800-1000g\(^1\). MRI images conducted on living WS patients also revealed low brain weight, with a total volume decrease of 13% in brain volume compared to normal controls\(^1\); with cerebral volumes showing a 13% decrease compared to a 7% cerebellar volume decrease, representing a preservation of cerebellar volume\(^1\). Various studies have shown that both the right and left cerebral hemispheres of WS bend significantly less\(^7\). Revealing curtailed shape from the top to the bottom, particularly within the posterior cerebral portion of the hemispheres\(^8\). Observations also indicated the central sulcus appears shortened compare to normal control in the central sulcus continues until reaching the midline\(^1\). These observations led us to create cortical thickness maps, to depict a full image of the WS brain\(^1\).

**Cortical Complexity & Integrity**

We define cortical complexity as the amount of
our attention to genetic associations. The relationship between brain morphology and behavior, we turned our labs linked insular volume reduction particularly in the right hemisphere to decreased total brain volumes and occipital gray volumes to the abnormalities in the WS brain (Luders et al., 2007). Such as, heightened affective expression cortex responsible for visual–spatial deficits deficit of abnormal social behavior but is also partially responsible for the gift of face recognition, and musical proficiency. The dorsal portion of the amygdala’s lateral nucleus (LNd) appears to be largely reduced in the WS brain seems to be partially responsible for visual–spatial deficits due to the fact being that lateral nucleus connections ascend from the visual association cortex. MRI images also revealed an enlarged cerebellar vermis in WS, which we believe is linked to hyper-sociality and heightened affective expression.

We and our colleagues also observed many corpus callosum abnormalities in the WS brain (Luders et al., 2007). Such as, shorter corpus callosumes, loss of curvature, smaller midline lengths, and thinner regions along the posterior surface compared normal controls. We attribute these morphological alterations to the unique cognitive and behavioral profiles of WS individuals. Our lab also performed numerous studies attempting to map visual–spatial deficits with specific brain areas. We attribute decreased total brain volumes and occipital gray volumes to the deficits within the visual spatial system of WS. Most recently our labs linked insular volume reduction particularly in the right hemisphere to the development of social–emotional processing and severe phobias. After gathering significant data about the relationship between brain morphology and behavior, we turned our attention to genetic associations.

Genetic Profile

WS behavior and morphology cannot be fully understood without investigating the molecular genetics of the disorder. Currently our lab is seeking the assistance of our colleagues, for further knowledge about the molecular genetics of WS. The contributions of our colleagues presents information about five of the best characterized hemizygous genes deleted on chromosome 7q: Elastin, LIMK1Kinase, CLIP2, GTF2I, and GTF2IRD1. Each of these hemizygous gene micro-deletions lead to distinct cognitive, behavioral, and physical phenotypic profiles all of which attribute to the extraordinary profile of WS.

Elastin’s Impact on the Heart

Elastin (Eln) protein allows blood vessels and connective tissues to remain flexible and elastic. WS individual have a hemizygous deletion of the elastin gene which leads to sever cardiac disorder such as supravalvar aortic stenosis (SVAS); SVAS causes narrowing of the aorta and pulmonary arteries and is linked to hypertension and even death. A study conducted in a colleagues’ lab revealed loss-of-function mutation in one elastin gene caused inherited arterial disease and SVAS. Another study by this same lab also revealed elastin deficiency leads to increased cellularity; specifically smooth muscle cell proliferation, and lumen narrowing. Mouse models also depict the importance of elastin during embryonic and postnatal development. In hemizygous Eln mice (Eln +/-) at embryonic day 18 cardiac morphology is similar to wild type mice, it is not until birth that morphological differences are seen. At birth the Eln +/- mouse has significantly increased left ventricle (LV) pressure and reduced compliance; ability to yield to pressure without elastic disruption. Further studies also revealed early Eln deficiency can lead to extreme arterial diameter decrease, thinner lamellae, shorter distance between lamellae, and increased fragmentation within the lamellae. Comparatively, postnatal mice models revealed Eln (+/-) mice have decreased aortic diameters by postnatal day 7 and significantly high systolic blood pressure by postnatal day 14. Our colleagues are also exploring the development adaptation of Eln +/- mice in efforts of creating possible therapeutic treatments. Angiotensin II receptor blockers (ARBs) used to treat high blood pressure and heart failure were administered to Eln +/- mice and dramatically decreased blood pressure. These results indicate there are possible treatments for hemizygous Eln deletion; however, constant treatment is required.

LIMK1 & CLIP2: Neuronal Development

Other colleagues are looking into the connections between LIMK1 and CLIP2. LIMK1 and CLIP2 work together in neuronal morphology and neurogenesis respectively regulating actin and microtubule dynamics. LIMK1 is critical for proper development of the central nervous system and is indirectly activated by Rac; a small GTPase of the Rho family which mediates stimulus induced actin cytoskeletal organization. Together the two mediate the phosphorylation of ADF/cofilin in the brain. ADF/cofilin are key regulators of actin cytoskeleton dynamics, which have been implicated in growth cone motility and neurite extension. LIMK1 not only promotes and stabilizes cofilin expression but it also co-precipitates with neuregulin in regulating synaptic formation and maintenance. The absence of LIMK1 leads to abnormalities in synaptic structures, spine development, and cytoskeletal functioning. Conversely CLIP2 regulates microtubule dynamics and is expressed in various areas of the central nervous system such as the amygdala, hippocampus, and cerebellum. Normal CLIP2 has an amino terminal head with two microtubule-binding (MTB) motifs and are surrounded by serine-rich regions and long coiled-coil regions. Mutated CLIP2, however, lack efficient MTBs and cause profound bundling in microtubule networks at the distal ends of microtubules. CLIP2 mutations are suggested to contribute to the altered neurodevelopment in WS due to altered microtubule dynamics. Hemizygous deletions in both LIMK1 and CLIP2 are suggested to have a combined effect on cytoskeletal deficits seen in WS such as growth deficiency and motor coordination. These deficits linked to CLIP2 mutation and heightened locomotor...
activity and impaired spatial learning linked to LIMK1 mutations36.

GTF2I & GT2IRD: Phenotypic Resemblance to WS

Additional genetic mapping has been conducted on genes GTF2I and GT2IRD. GTF2I normally helps regulate neurocognitive development37, hemizygous deletion of GTF2I causes neurodevelopmental deficits resulting in hypersensitivity, visual-spatial deficits, hypersociability, and anxiety37. GTF2I +/- mice models showed significantly increase maternal separation-induced anxiety compared to wild type mice32 anxiety levels were measured by ultrasound vocalization37. Another study showed GTF2I +/- mice have increased social interaction with unfamiliar mice38. Both of these results resemble specific WS phenotypes of hypersociability and anxiety37,38. The gene GTF2IRD however is required for proper craniofacial development40. Deficits in GTF2IRD cause abnormalities to facial development, motor functioning, and behavior40. These abnormalities have been seen in various mouse models40 with images depicting excess tissue in the nose and lips, smaller body sizes, round faces, and short noses40. These results suggest GTF2IRD is a key contributor of the facial appearance of WS individuals. A novel study reported on the linking effect on GTF2 +/- and GT2IRD +/-, suggesting the two are associated with visual-spatial deficits seen in WS41. This research, however, is not as concrete as the results of previous studies, but does open possibilities for future studies.

![Fig 2: Spatial Deficits in WS: A. Block Design subset of the Wechsler Intelligence Scale for Children-Revised (WISC-R), assessing WS subjects ability to arrange a set of blocks to replicate a model figure4. WS subjects are unable to properly construct the model figure, indicating deficits in visual-spatial construction3. B. Navon-styled hierarchical local/global task assessing WS subjects ability to recognize local and global figures in a model2. WS subjects recognize the local letter “Y” but are unable to recognize the global letter “D”; suggesting deficits in visuo-spatial cognition1.](image)

Conclusion

The research of our lab and the labs of our colleagues has greatly contributed to what is presently known about WS1. Our lab has mainly contributed to creating cognitive and anatomical profiles of WS13; characterizing both gifts and deficits of the disorder13. Additionally the contributions our colleagues have led to major advances about the underpinning molecular genetic basis of WS13. Nonetheless there is still a large amount of gene characterization that needs to done40. Thus far WS research has yielded many advances in the scientific field amongst an array of disciplines13,40 allowing the phenotypic profile of WS to be logically connected to its anatomical and genotypic profiles1. For example we now know the characteristic visual spatial deficits seen in WS are attributed to decreased cerebral volumes32 as well as LIMK135, GTF2 and GT2IRD deficits41. Such descriptive mapping would not have been possible in past years32.

Unfortunately there is still no cure for WS treatments are still only being given to reduce symptoms and not to treat WS as a whole12. Hence requiring research into other specific genes within the deletion area of chromosome 714. By continuing research we and our colleague are in fact increasing the possibility of effective molecular- bases treatments and therapies14,36. Presently the work of our colleagues has led to innovative diagnostic tools allowing for infancy diagnosis based on genetic and metabolic markers12. Prior to genetic diagnosis, many WS individual were left undiagnosed until mid-adolescence or even adulthood12. Early diagnosis may actually expose more WS cases than previously reported12.

Without the collaborative assistance and diligence of our colleagues, WS would only be cognitively and anatomically mapped12. For that reason we sincerely appreciate the works of our colleagues. As we all know WS is a genetically based disorder; without extensive research into its molecular underpinnings several aspects of the disorder will remain unclear15. Therefore it is essential that our lab and the labs of our colleagues continue to work diligently in solving the medical mysteries of WS. At this time our colleagues and we plan to continue WS research in efforts to answer unsolved questions about the disorder14. We hypothesize that our future research as well as our previous research hopefully will give insight into potential treatments and therapies5. Also we believe that with the knowledge already known about WS and the knowledge that will be obtained in future studies, finding a cure for WS is more than probable41.

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