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Review article

Williams syndrome deletions and duplications: Genetic windows to understanding anxiety, sociality, autism, and schizophrenia

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ABSTRACT

We describe and evaluate an integrative hypothesis for helping to explain the major neurocognitive features of individuals with Williams syndrome region deletions and duplications. First, we demonstrate how the cognitive differences between Williams syndrome individuals, individuals with duplications of this region, and healthy individuals parallel the differences between individuals subject to effects of increased or decreased oxytocin. Second, we synthesize evidence showing that variation in expression of the gene GTF2I (General Transcription Factor II–I) underlies the primary social phenotypes of Williams syndrome and that common genetic variation in GTF2I mediates oxytocin reactivity, and its correlates, in healthy populations. Third, we describe findings relevant to the hypothesis that the GTF2I gene is subject to parent of origin effects whose behavioral expression fits with predictions from the kinship theory of genomic imprinting. Fourth, we describe how Williams syndrome can be considered, in part, as an autistic syndrome of Lorna Wing's 'active-but-odd' autism subtype, in contrast to associations of duplications with both schizophrenia and autism.

1. Introduction

Human disorders mediated by copy number variants (CNVs) and imprinted genes often exhibit opposite effects of gene loss versus gain on gene expression and resultant genetically-mediated phenotypes (e. g., Eggermann et al., 2008; Crespi, 2013; Qureshi et al., 2014; Arbogast et al., 2016). Copy number variants involve deletions, or duplications, of the same genomic region, leading to haploid or triploidy for the genes that they comprise (e.g., Henrichsen et al., 2009). By contrast, imprinted-gene disorders engender losses or gains of expression for genes that are normally expressed from only one copy, leading to either reduced or lost expression, or doubled expression for the relevant loci (e.g., da Rocha et al., 2009). Such opposite changes in gene expression have often been associated with opposite phenotypes: for example, reciprocal CNVs at the chromosomal regions 1q21.1 and 16p11.2 have been linked with microcephaly versus macrocephaly (Brunetti-Pierri et al., 2008; Shinawi et al., 2010), and Silver-Russell syndrome and Beckwith-Weidemann syndrome, which are due mainly to opposite alterations to imprinted genes at 11p15, are characterized by reduced versus increased birth weight and growth (Eggermann et al., 2008). Diametric disorders provide unique opportunities to analyze the effects of opposite changes to gene expression on developmental, endocrine, psychological and psychiatric phenotypes as well as such morphological ones; for example, for CNVs at 22q11.21, deletions have been associated with greatly-elevated schizophrenia risk, while duplications have been linked with reduced susceptibility to this disorder (Rees et al., 2014a).

Williams syndrome is a well-studied condition caused by hemizygous deletion (loss of one copy) of about 25 genes at 7q11.23. This syndrome has been of particular interest among geneticists, neurobiologists, and psychologists, because it involves a striking neurocognitive profile of hyper-sociality, decreased social anxiety, preserved expressive language, increased non-social anxiety and phobias, and reduced skills in visual-spatial domains (Schubert 2009; Morris 2010; Järvinen and Bellugi, 2013; Järvinen et al., 2013). High social motivation coincides, however, with reduced social-communication and reciprocity skills, such that ability to form and maintain friendships is reduced (Järvinen et al., 2013; Thurman and Fisher, 2015). Analyses of the genetic and neurological bases of such Williams syndrome neurocognitive phenotypes have provided novel insights into the proximate mechanisms that mediate the genomic and neurological architectures of human sociality, development, language and cognition (Järvinen et al., 2013).

Like many other CNV loci, the Williams syndrome exhibits duplications as well as deletions. The phenotypic traits associated with Williams syndrome region duplications have been less well characterized than deletions, although they are known to involve reductions in expressive language skills, and high levels of separation anxiety, such

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Table 1
Similarities in anatomical, cognitive, social and behavioral phenotypes between effects of oxytocin, and traits associated with Williams syndrome or Williams syndrome region duplications.

Phenotype	Oxytocin effect (serum levels, administration compared to placebo), or OXTR SNP (genotype variation) in typically-developing individuals	Williams syndrome deletion or duplication differences (comparisons to typically-developing-individuals)
Social approach, engagement	Increased (review in Kemp and Guastella, 2011)	Increased, relatively indiscriminate in WS (Losh et al., 2000; Meyer-Lindenberg et al., 2006; Martens et al., 2008; Järvinen et al., 2013)
Positive prosocial affect	Increased (Andari et al., 2010; Guastella et al., 2010)	Increased in WS (Järvinen-Pasley et al., 2008; Dodd and Porter, 2010)
Trust	Increased and can be perseverative (Baumgartner et al., 2008; Theodoridou et al., 2009; Zhong et al., 2012)	Increased in WS (Martens et al., 2012; Godbee and Porter, 2013)
Gaze at faces, eyes	Increased (Guastella et al., 2008; Andari et al., 2010; Gamer et al., 2010)	Increased in WS (Zitzer-Comfort et al., 2007; Riby and Hancock, 2008; Riby and Hancock, 2009; Porter et al., 2010)
Affective empathy, responsivity	Increased (Barraza and Zak, 2009; Hurlemann et al., 2010)	Increased in WS (Sullivan and Tager-Flusberg, 1999; Tager-Flusberg and Sullivan, 2000; Fidler et al., 2007).
Salience of social stimuli	Increased, may be central effect (Shamay-Tsoory et al., 2009; Bartz et al., 2011; Groppe et al., 2013; Tabak, 2013)	Increased in WS (Frigerio et al., 2006; Järvinen et al., 2013)
Social attention in relation to social skills	Increased social processing but lower accuracy of ratings (Cardoso et al., 2014; Voorthuis et al., 2014)	Higher serum oxytocin in WS associated with lower social adaptive behavior (Dai et al., 2012)
Anxiety	Higher oxytocin associated with increased anxiety in some situations (Hoge et al., 2008; Grillon et al., 2013; Guzmán et al., 2013; Macdonald et al., 2013; Miller et al., 2013)	High generalized, anticipatory anxiety, high phobia and non-social anxiety in WS (Dykens 2003; Klein-Tasman and Mervis, 2003; Leyfer et al., 2006; Woodruff-Borden et al., 2010; Riby et al., 2013a, 2013b)
Separation anxiety	Lower plasma oxytocin associated with more symptoms of separation anxiety during pregnancy (Eapen et al., 2014); low oxytocin genotype of SNP rs2254298 linked with higher adult separation anxiety (Thompson et al., 2011)	Lower separation anxiety in WS, and higher separation anxiety in WS-region duplications (Mervis et al., 2012, 2015a,b);
Aggression (non-defensive)	SNPs in OXTR gene, and lower plasma oxytocin, associated with higher aggression (Lee et al., 2009; Beitchman et al., 2012; Malik et al., 2012)	Higher prosociality in WS (e.g., Järvinen-Pasley et al., 2008); high aggression and oppositional defiant behavior in WS-region duplications (Mervis et al., 2015a,b)
Acoustic startle response	Higher with higher oxytocin (Striepens et al., 2012; Grillon et al., 2013)	Higher in WS (Gallo et al., 2008) and associated with GTF2I-LIMK1 region in mice (Li et al., 2009).
Amygdala size	High-empathy/high oxytocin genotypes for rs53576 and rs2254298 associated with larger amygdala (Inoue et al., 2010; Furman et al., 2011; Wang et al., 2013)	Larger amygdala relative to overall brain size in WS (Capitão et al., 2011; Haas et al., 2012)
Amygdala response to faces	Lower for negative faces (Kirsch et al., 2005; Domes et al., 2007; Haas et al., 2009; Gamer et al., 2010)	Lower for negative faces in WS (Mimura et al., 2010)
Sensitivity to happy faces	Increased (Marsh et al., 2010)	Increased in WS (Dodd and Porter, 2010)
Heart rate variability	Higher following OT administration (Järvinen and Bellugi, 2013)	Higher in WS, for auditory and for happy stimuli (Järvinen and Bellugi, 2013)
Visual spatial abilities	Oxytocin inhibits spatial learning in rats (Wu and Yu, 2004); spatial ability negatively correlated with serum oxytocin in women (Kocoska-Maras et al., 2013); high-oxytocin genotypes for rs1042778 and rs2254298 associated with lower mental rotation performance (Thompson et al., 2013)	Greatly-reduced visual-spatial skills in WS (Mervis and Klein-Tasman, 2000); reduced performance on mental rotation test (Farran et al., 2001; Farran and Jarrold, 2003; Vicari et al., 2006; Stinton et al., 2008)
Creativity and imagination	Increased novelty-seeking, creativity, fluency, originality (De Dreu et al., 2013)	Relatively preserved/increased expressive language, including evidence of unusual word choices, good use of prosody in WS (e.g. Bellugi et al., 1994; Skwerer et al., 2007)
Religious belief and participation	Associated with higher oxytocin levels (Zak 2012; Zak and Barraza, 2013)	Increased in WS (Plesa-Skwerer et al., 2004)
Music appreciation and participation	Associated with increased oxytocin (Nilsson 2009; Chanda and Levitin, 2013)	Increased in WS (Lense et al., 2014; Ng et al., 2013)
Hugging	High oxytocin associated with tendency to hug, and mood-altering effects of hugging (Light et al., 2005; Campbell 2008; Holt-Lunstad et al., 2008)	Increased tendency to hug others in WS (Davies et al., 1998; Thurman and Fisher, 2015)

that affected individuals are notably-fearful of separation from their primary caregivers (Somerville et al., 2005; Mervis et al., 2012, 2015a, 2015b; Dixit et al., 2013). These neuropsychological phenotypes represent clear opposites to those found in Williams syndrome, suggesting that they are mediated by diametric changes to gene expression and aspects of neurodevelopment.

Key unresolved questions in the study of individuals with Williams syndrome region deletions and duplications are how such opposite changes come about genetically, epigenetically, developmentally, hormonally, and neurologically (Strong et al., 2015), and how they are associated with the psychiatric phenotypes and disorders. The Williams syndrome region is especially interesting in this regard because duplications have been associated with autism in children (Sanders et al., 2011) and with schizophrenia in adults (Mulle et al., 2014). CNVs in this region may thus be useful in evaluating the relationship between autism and schizophrenia (Chisholm et al., 2015; Crespi, 2016), and in linking each of these disorders to specific underlying causes. Alternative hypotheses for the relationship of autism and schizophrenia include independence, partial overlap, and an opposite relationship whereby these conditions are caused by, and associated with, diametric changes in gene expression and phenotypic traits (Crespi and Badcock, 2008; Crespi et al., 2010; Chisholm et al., 2015).

In this article we apply an interdisciplinary framework to understanding the primary social, psychological and psychiatric alterations found in individuals with Williams syndrome region deletions or duplications. The framework is based on consilience and convergence of evidence from diverse fields of study, including evolutionary theory, which has not previously been applied in this context.

First, we discuss evidence salient to the hypothesis that cognitive and behavioral divergences of Williams syndrome region deletion and duplication individuals from healthy individuals parallel the effects of oxytocin, a neuropeptide associated with aspects of human emotionality, anxiety, and sociality, in healthy individuals. These findings suggest that dysregulation of the oxytocinergic system can account for many of the primary cognitive and behavioral features of William-syndrome region CNVs.

Second, we review evidence regarding the degree to which expression of the gene GTF2I (General Transcription Factor II–I) underlies the