The underlying mechanisms of neurobehavioral risks in sex chromosome trisomies

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Considering the exceptionally high density of genes on the sex chromosomes that are essential for the development of the brain, it is not surprising that children with sex chromosome trisomies (SCT), i.e. 47,XXY, 47,XXX, and 47, XYY) are at increased risk for neurodevelopmental problems. Over the last decade there has been an increasing interest in SCT, driven by an increasing awareness that we can gain important knowledge about mechanisms of developmental risk by studying such genetically defined populations. Also, there have been recent technological advances that allow for safe and early screening for genetic syndromes. As the number of children prenatally diagnosed with SCT is expected to increase, this calls for more knowledge about the phenotype of SCT.

This need for knowledge may be most pressing for the neurobehavioral domain: so far, most studies (about 75%) have focused on the somatic/medical phenotype, with only 25% studying the neurobehavioral phenotype. Traditionally, most studies in this field are of a descriptive nature and many focus on the behavioral aspects. What is also needed, is a better understanding of the mechanisms underlying the behavioral phenotype. Similar behavioral problems may arise from different underlying information processing dysfunctions in the brain. Knowledge about these building blocks of behavior has consequences for diagnostic assessment and treatment, as it helps in identifying the exact type of vulnerability, as well as specific targets for intervention, enabling more tailored mental health care.

One of the major domains of vulnerability in SCT is language development. To illustrate, a robust finding is that 70% to 80% of children with 47,XXY have language difficulties, already from a young age. The study of Wilson and Bishop, showing typical language lateralization in 75 children with SCT using functional transcranial Doppler ultrasonography, is an excellent example of a research study providing the need to better understand the underlying mechanisms. It is a great addition to the field because of the large sample size, the various SCT subgroups and the sensitive and objective techniques used. What we need in addition to this, is the study of language from a longitudinal, developmental perspective. Brain development is thought to continue into (at least) the mid-twenties – in part until the thirties. It would be interesting to better understand the developmental course of language deficits in SCT from infancy onwards, especially as this might help explain potential differences between findings in childhood, adolescence, and adulthood. For example, a functional magnetic resonance imaging study on language lateralization in adults with SCT showed increased involvement of the right hemisphere during language, leading to reduced lateralization. We cannot exclude that this increased activation is a compensatory neural mechanism that develops over time. Although the adult study had a much smaller sample size, the findings remained significant at \( p=0.038 \) after removing outliers. Although very speculative, only longitudinal studies will help to gain insight into how the brain (both structurally and functionally) develops over time in SCT, not only in the language domain but in other cognitive domains as well.

One of the next steps in the field of SCT is to not only take a more longitudinal perspective, but also to study the phenotype of SCT from an early age onwards. This genetic condition can already be diagnosed prenatally, which provides the responsibility and unique opportunity to identify early markers of ‘at-risk’ development and the evaluation of effectiveness of early interventions. This is especially relevant for language difficulties, as these are present in most children with SCT from an early age, presenting a window of opportunity to positively influence the development of language areas in the brain.

REFERENCES


