Received: 15 May 2020 | Accepted: 15 May 2020
DOI: 10.1002/ajmg.c.31808

COMMENTARY

AMERICAN JOURNAL OF medical genetics PART C Seminars in Medical Genetics WILEY

Sex chromosome aneuploidies in 2020—The state of care and research in the world

Claus H. Gravholt[1,2] | Nicole Tartaglia[3,4] | Christine Disteche[5,6]

[1]Department of Molecular Medicine, Aarhus University Hospital, Aarhus, Denmark

[2]Department of Endocrinology, Aarhus University Hospital, Aarhus, Denmark

[3]Department of Pediatrics, University of Colorado School of Medicine, Aurora, Colorado

[4]Developmental Pediatrics, Children's Hospital Colorado, Aurora, Colorado

[5]Department of Pathology, University of Washington, Seattle, Washington

[6]Department of Medicine, University of Washington, Seattle, Washington

Correspondence
Claus H. Gravholt, Department of Endocrinology, Aarhus University Hospital, 8200 Aarhus N, Denmark.
Email: ch.gravholt@dadlnet.dk

Funding information
Novo Nordisk Fonden, Grant/Award Numbers: NNF13OC0003234, NNF15OC0016474; National Institutes of Health, Grant/Award Number: GM131745

This special issue considers various aspects of sex chromosome abnormalities (SCA's) including Klinefelter syndrome (47,XXY), Triple-X syndrome (47,XXX), 47,XYY syndrome, and conditions with rarer X or Y types of aneuploidy. This issue follows a successful special issue on Turner syndrome entitled "Proceedings of the Turner syndrome network symposium" published last year in the American Journal of Medical Genetics Part C. A survey of the scientific literature demonstrates reveals a great deal of information on Klinefelter syndrome, but also a paucity of papers on conditions such as 47,XXX and 47,XYY syndromes, not to mention syndromes with multiple additional sex chromosomes such as 48,XXXY, 48,XXYY or 49,XXXXY. In addition to a lack of information on clinical aspects of these SCA conditions there is limited research about understanding the molecular mechanisms that link the presence of additional sex chromosomes to phenotypes. The goal of this new issue of the American Journal of Medical Genetics Part C is to discuss issues related to the diagnosis, phenotypic features, and clinical care of SCA patients and to provide a better understanding of the molecular basis of the disease processes.

The lack of a comprehensive compilation of information regarding all aspects of life with a SCA condition hampers diagnosis and clinical care of patients. A few specialty clinics around the world care for people with SCA's and thus have accumulated important knowledge concerning various aspects of life with an SCA, but a comprehensive review and integration of the literature informing evidence-based practice guidelines is lacking. This results in uncertainty about best care practices, disparities in care, and variable outcomes. Due in part to the lack of robust scientific research in SCA's, the little literature available can become over-generalized and prematurely adopted into clinical practice. For example, we note that early uncontrolled studies without randomization has led to androgen treatment of young boys with Klinefelter syndrome in the United States and other countries, based on the unproven belief that such treatment may alleviate some of the neurocognitive deficits associated with the condition (Samango-Sprouse et al., 2015). Only recently have properly randomized and placebo-controlled studies reported results of the effects of early androgen treatment. In one study in infants, testosterone treatment led to a decrease in adiposity, which is otherwise increased in infants with XXY (Davis et al., 2019). In another study, oxandrolone treatment of boys aged 4–12 years, led to limited improvements in one (visual motor skills) of five primary endpoints concerning cognition (Ross et al., 2017), but also led to a 20-fold increased risk of early gonadarche (Davis et al., 2018). Thus, introduction of seemingly innocuous treatments aimed at improving one aspect of life can lead to adverse effects on other aspects and illustrates the importance of rigorous scientific investigation. Large, collaborative, interdisciplinary studies with robust research methods are needed in addition to international effort to develop evidence-based clinical practice guidelines for all SCAs.

Another important question discussed in this special issue that is not properly addressed in the current literature is diagnosis of SCA's. Although, in theory a very simple question, it turns out that in practice it is exceedingly difficult to diagnose most patients with SCA. Available evidence shows that most patients with SCA are not being diagnosed, and when they are, it is often after lengthy diagnostic odysseys through the health care system (Berglund et al., 2019). This may seem trivial, but probably contorts most clinical research due to

ascertainment bias, as pediatric research projects include only the most affected individuals who have received a diagnosis combined with those diagnosed prenatally, while many others with SCA are only diagnosed during late adolescent or adult life, or not at all. There is no easy solution to increase diagnostic rates, but we, and others, have suggested inclusion of SCA testing in newborn screening programs (Berglund et al., in press). In order to do so, however, certain conditions need to be fulfilled—the disorder in question needs to represent an important health problem with a latent, early asymptomatic stage and a well-understood natural history for which there are accepted treatments that clearly impact outcomes, as well as associated facilities for diagnoses and treatment (Grosse et al., 2010). While some of these criteria may be considered fulfilled for Klinefelter syndrome (and Turner syndrome), they certainly are not for the other SCA's. Clearly more research and more awareness are needed in this area, and in this issue Tartaglia et al. introduce a prospective study of prenatally diagnosed infants with SCAs that is designed to better characterize the early natural history and predictors of phenotypic variability in order to identify early targets for intervention and inform discussions around newborn screening (Tartaglia et al., in press). New data related to the diagnostic problems with non-invasive prenatal testing and monosomy X is also discussed (Sund et al., in press).

Being a parent and receiving a SCA diagnosis for a child of any age can be challenging, and many parents ask themselves where to go for information and what can be done about the condition. Family experiences about receiving a diagnosis are discussed here in the US context (Riggan et al., 2020) and results of a national survey are presented about the types of services and therapies that parents currently utilize for young children (Thompson et al., 2020). Following a new diagnosis questions also arise about which of the many risks associated with SCAs may be most important in overall adaptive functioning in day-to-day life, and this question is explored among children with Trisomy X syndrome (Wigby et al., in press).

Epidemiology has greatly improved our knowledge concerning many aspects of life with SCA. However, such studies are based on national registries, which are currently only available in three Northern European countries—UK, Sweden, and Denmark. Thus, there is an urgent need for epidemiological studies from other parts of the world. National registries are excellent tools not only for assessing mortality, morbidity, socio-economic conditions, but also for evaluating quality of care, for example, by determining adherence to relevant treatment, such as testosterone substitution therapy in Klinefelter syndrome (Berglund et al., in press; Chang et al., 2019). Since all SCA's are rare conditions themselves, epidemiology can also help discover less frequent associations of a SCA with other rare conditions.

The current issue provides a wealth of new information and detailed reviews on cognitive, neuroanatomical, and psychological aspects of SCA's, and the broad phenotypic variability seen within each condition. Neurocognitive challenges are more common in all SCA's, with some overlap between syndromes, but also with unique profiles for specific SCA's. Here, we include reviews on psychological features, specific learning disorders, and neuroanatomical pathways in SCAs, (Karipidis et al., in press; Skakkebaek et al., in press), as well as new research exploring relationships of cognitive skills with neuroanatomical findings (Warling et al., in press). New research is also presented that addresses important questions seeking to identify origins of later, well-known psychological risks by looking at early behavioral profiles in the first years of life (Urbanus et al., 2020). Executive functioning deficits are well recognized as part of the neuropsychological phenotype in SCA, and these are further characterized in 47,XXY with consideration of how EF deficits are measured in clinical settings (Janusz et al., in press). Further, one report specifically on adults with SCA is an excellent example of a preliminary study exploring interrelationships between actigraph measures of sleep with executive functioning and mental health (Fjermestad et al., 2020), and these types of studies that explore the link between psychological and medical features deserve more attention across all SCA conditions.

A specific group of SCA's we have little information about is the group of rare patients with more than 47 chromosomes. These patients clearly have additional considerations often related to more significant cognitive deficits, behavioral challenges, and medical comorbidities. One of these conditions, 48,XXYY syndrome, is reviewed in this issue with a summary of medical and psychological features, as well as an emphasis on the need for more patient-center research targeting problems and concerns of patients and their families (Blumling et al., in press). There is no doubt that additional research is needed to better understand these rare disorders, especially with regard to genomic anomalies in relation to medical problems and neurocognition, and with emphasis on how and where care guidelines may be different compared to trisomies.

The genetics of SCA is truly intriguing and currently seems to be on the verge of various breakthroughs. Fascinatingly, a molecular understanding of SCA is much more complicated than previously envisioned. In SCA all but one X chromosome are subject to silencing X inactivation. Thus, in theory there should be no deleterious effects. However, a number of genes escape X inactivation, a phenomenon that varies between tissues/cell types, and several genes are expressed from the Y chromosome (Fang, Disteche, & Berletch, 2019). Here we include an update on the process of X chromosome inactivation and escape from X inactivation and how these processes may play a role in SCA (Navarro-Cobos et al., 2020). In addition, an interesting review shows that gene expression and epigenetic effects in SCA not only relate to the sex chromosomes, but also to the entire genome, illustrating that numerical changes in sex chromosomes have global effects (Skakkebæk et al., in press). A new paper including original data describes changes in DNA methylation and RNA expression in 47,XXX syndrome, with the unexpected findings of less efficient inactivation of the supernumerary X chromosome in this condition (Nielsen et al., in press). This issue also discusses the role of additional genomic copy number variants in enhancing variability in the neurodevelopmental phenotype of patients with SCA, similar to what has been reported in Turner syndrome (Mountford et al., 2020; Prakash et al., 2016). Finally, a review of mouse models designed to replicate SCA's, for example, Klinefelter syndrome describes a promising area of in vivo research (Arnold, 2017; Wistuba et al., 2020). While

it is clear that both genetic and epigenetic features of the entire genome are dysregulated in SCA, there is still a lack of understanding about the specific genes that may cause specific phenotypes, and more research is needed on specific cell types.

Medical care of SCA's is partly hampered by lack of knowledge by providers who often care for only a limited number of patients in their practice, and several papers in this issue address medical care of patients with SCA. In particular, we include reviews on the hypothalamic–pituitary–gonadal axis in SCA (Rogol, 2020), and a new study on cardiometabolic risk factors in youth with Klinefelter syndrome with suggestions for clinical screening (Davis et al., in press). We also review medical problems related to Klinefelter syndrome and the effects of testosterone treatment in men with Klinefelter syndrome (Chang et al., in press; Zitzmann et al., 2020). The cardiovascular aspects of Klinefelter syndrome are also reviewed (Spaziani et al., 2020). One review examines the mini-puberty in infants with Klinefelter syndrome and how this may affect the phenotype (Aksglaede et al., in press).

Among adults with Klinefelter syndrome, infertility is the most frequent cause for diagnosis and often also poses the most important health problem. Until recently, it was thought that infertility was omnipresent, but recent research has shown that many males with Klinefelter syndrome indeed harbor normal spermatocytes in their small testicles. Here, many aspects of gonadal function are discussed. One review reports on transcriptomics and DNA methylation data in the testis (Winge et al., 2020) and another focuses on how germ cell loss may occur in Klinefelter syndrome (Willems et al., 2020). Currently, many males with Klinefelter syndrome can hope to achieve fertility after testicular sperm extraction (TESE) followed by in vitro fertilization. However, much still needs to be learned about the most appropriate age for performing TESE and whether medication such as testosterone supplementation might interfere with the success of the procedure. Finally, although impaired gonadal function was previously primarily associated with males harboring an additional X chromosome (47,XXY), novel findings of reduced testicular hormone production in youth with 47,XYY indicate we have much to learn about the implications of SCA's on gonadal function and reproduction (Davis et al., in press).

Care for patients with SCA's clearly needs to integrate several specialty clinics in order to provide high quality multi-disciplinary care. How this is best provided is not well defined. Indeed, there are no international consensus or guidelines to provide best quality care for Klinefelter syndrome, Triple X syndrome, and 47,XYY syndrome. In contrast, there are international guidelines for Turner syndrome (Gravholt et al., 2017). In addition to providing guidelines for care, the Turner syndrome community has also been instrumental in staging international workshops, creating multidisciplinary clinics, fostering international research collaborations, and pinpointing areas for future research. The Denver group has previously published on their pediatric model of care called the eXtraordinarY Kids Clinic (Tartaglia et al., 2015), and this has served as a model for several other interdisciplinary clinics in the US and establishment of the AXYS Clinical and Research Consortium that aims to provide consensus for best clinical care and an infrastructure for conducting multicenter research in SCA populations. The creation of European Reference Networks, especially the European Reference Network on Rare Endocrine Conditions (Ali et al., 2019; Hiort et al., 2019), should also prove to be a leveraging mechanism for ensuring equal level and accessibility of care, as well as quality of life, fertility, and optimal care, for promoting cross-border research within the EU (and eventually also outside of the EU) in basic mechanisms and other aspects of SCA's. These US and EU efforts should also facilitate the creation of similar networks in other parts of the world.

We hope that this issue will provide clinicians and researchers around the world with updated information on supernumerary SCA's, and also highlight where more research is needed. We also hope that this initiative will foster focused workshops and international collaboration and ultimately the creation of multidisciplinary international evaluation and treatment guidelines.

ACKNOWLEDGMENTS

Claus H. Gravholt is a member of the European Reference Network on Rare Endocrine Conditions (ENDO-ERN), Project ID number 739543. This research did not receive any specific grant from the commercial or not-for-profit sector. This work was partly supported by grants from the National Institutes of Health to CD (GM131745), partly from The Novo Nordisk Foundation (grant agreement NNF13OC0003234 and NNF15OC0016474) to CHG.

CONFLICT OF INTEREST

We declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

AUTHOR CONTRIBUTIONS

Claus H. Gravholt, **Nicole Tartaglia**, **Christine Disteche:** wrote this editorial together.

ORCID

Claus H. Gravholt https://orcid.org/0000-0001-5924-1720
Nicole Tartaglia https://orcid.org/0000-0002-8529-6722

REFERENCES

Ali, S. R., Bryce, J., Cools, M., Korbonits, M., Beun, J. G., Taruscio, D., … Ahmed, S. F. (2019). The current landscape of European registries for rare endocrine conditions. *European Journal of Endocrinology*, *180*, 89–98.

Aksglaede, L., Davis, S., Ross, J., & Juul, A. (in press). Minipuberty in Klinefelter Syndrome - Current Status and Future Directions. *American Journal of Medical Genetics. Part C, Seminars in Medical Genetics*.

Arnold, A. P. (2017). A general theory of sexual differentiation. *Journal of Neuroscience Research*, *95*, 291–300.

Berglund, A., Stochholm, K., & Gravholt, C. H. (in press). The epidemiology of sex chromosome abnormalities. *American Journal of Medical Genetics. Part C, Seminars in Medical Genetics*.

Berglund, A., Viuff, M. H., Skakkebaek, A., Chang, S., Stochholm, K., & Gravholt, C. H. (2019). Changes in the cohort composition of turner syndrome and severe non-diagnosis of Klinefelter, 47,XXX and 47,XYY syndrome: A nationwide cohort study. *Orphanet Journal of Rare Diseases*, *14*, 16–0976.

Blumling, A., Martyn, K., Talboy, A., & Close, S. (in press). Rare sex chromosome variation 48,XXYY: An integrative review. *American Journal of Medical Genetics. Part C, Seminars in Medical Genetics*.

Chang, S., Christiansen, C. F., Bojesen, A., Juul, S., Munster, A. B., & Gravholt, C. H. (2019). Klinefelter syndrome and testosterone treatment: A national cohort study on thrombosis risk. *Endocrine Connections*, *9*(1), 34–43. https://doi.org/10.1530/EC-19-0433.

Chang, S., Skakkebæk, A., Davis, S. M., & Gravholt, C. H. (in press). Morbidity in Klinefelter syndrome and the effect of testosterone treatment. *American Journal of Medical Genetics. Part C, Seminars in Medical Genetics*.

Davis, S. M., Lahlou, N., Cox-Martin, M., Kowal, K., Zeitler, P. S., & Ross, J. L. (2018). Oxandrolone treatment results in an increased risk of gonadarche in prepubertal boys with Klinefelter syndrome. *The Journal of Clinical Endocrinology and Metabolism*, *103*, 3449–3455.

Davis, S. M., Reynolds, R. M., Dabelea, D. M., Zeitler, P. S., & Tartaglia, N. R. (2019). Testosterone treatment in infants with 47,XXY: Effects on body composition. *Journal of the Endocrine Society*, *3*(12), 2276–2285. http://dx.doi.org/10.1210/js.2019-00274.

Davis, S., Bloy, L., Roberts, T., Kowal, K., Alston, A., Tahsin, A., Truxon, A., & Ross, J. (in press). Testicular function in boys with 47,XYY and relationship to phenotype. *American Journal of Medical Genetics. Part C, Seminars in Medical Genetics*.

Davis, S., DeKlotz, S., Nadeau, K., Kelsey, M., Zeitler, P., & Tartaglia, N. (in press). High prevalence of cardiometabolic risk features in adolescents with 47,XXY / Klinefelter syndrome. *American Journal of Medical Genetics. Part C, Seminars in Medical Genetics*.

Fang, H., Disteche, C. M., & Berletch, J. B. (2019). X inactivation and escape: Epigenetic and structural features. *Frontiers in Cell and Developmental Biology*, *7*, 219. https://doi.org/10.3389/fcell.2019.00219

Fjermestad, K. W., Huster, R., Thunberg, C., Stokke, S., Gravholt, C. H., & Solbakk, A-K. (2020). Neuropsychological functions, sleep, and mental health in adults with Klinefelter syndrome. *American Journal of Medical Genetics Part C: Seminars in Medical Genetics*, http://dx.doi.org/10.1002/ajmg.c.31797.

Gravholt, C. H., Andersen, N. H., Conway, G. S., Dekkers, O. M., Geffner, M. E., Klein, K. O., … Backeljauw, P. F. (2017). Clinical practice guidelines for the care of girls and women with turner syndrome: Proceedings from the 2016 Cincinnati international turner syndrome meeting. *European Journal of Endocrinology*, *177*, G1–G70.

Grosse, S. D., Rogowski, W. H., Ross, L. F., Cornel, M. C., Dondorp, W. J., & Khoury, M. J. (2010). Population screening for genetic disorders in the 21st century: Evidence, economics, and ethics. *Public Health Genomics*, *13*, 106–115.

Hiort, O., Cools, M., Springer, A., McElreavey, K., Greenfield, A., Wudy, S. A., … Audi, L. (2019). Addressing gaps in care of people with conditions affecting sex development and maturation. *Nature Reviews. Endocrinology*, *15*, 615–622.

Janusz, J., Harrison, C., Boada, C., Cordeiro, L., Howell, S., Tartaglia, N., & Boada, R. (in press). Executive function in XXY: Comparison of performance-based measures and rating scales. *American Journal of Medical Genetics. Part C, Seminars in Medical Genetics*.

Karipidis, I. I., & Hong, D. (in press). Specific learning disorders in sex chromosome aneuploidies: Neural circuits of literacy and mathematics. *American Journal of Medical Genetics. Part C, Seminars in Medical Genetics*.

Mountford, H. S., Bishop, D. V. M., Thompson, P. A., Simpson, N. H., & Newbury, D. F. (2020). Copy number variation burden does not predict severity of neurodevelopmental phenotype in children with a sex chromosome trisomy. *American Journal of Medical Genetics Part C: Seminars in Medical Genetics*, http://dx.doi.org/10.1002/ajmg.c.31791.

Navarro-Cobos, M. J., Balaton, B. P., & Brown, C. J. (2020). Genes that escape from X-chromosome inactivation: Potential contributors to Klinefelter syndrome. *American Journal of Medical Genetics Part C: Seminars in Medical Genetics*, http://dx.doi.org/10.1002/ajmg.c.31800.

Nielsen, M. M., Trolle, C., Vang, S., Hornshøj, H., Skakkebæk, A., Hedegaard, J., & Gravholt, C. H. (in press). Epigenetic and transcriptomic consequences of excess X-chromosome material in 47,XXX syndrome – a comparison with Turner syndrome and 46,XX females. *American Journal of Medical Genetics. Part C, Seminars in Medical Genetics*.

Prakash, S. K., Bondy, C. A., Maslen, C. L., Silberbach, M., Lin, A. E., Perrone, L., … Milewicz, D. M. (2016). Autosomal and X chromosome structural variants are associated with congenital heart defects in Turner syndrome: The NHLBI GenTAC registry. *American Journal of Medical Genetics. Part A*, *170*, 3157–3164.

Riggan, K. A., Close, S., & Allyse, M. A. (2020). Family experiences and attitudes about receiving the diagnosis of sex chromosome aneuploidy in a child. *American Journal of Medical Genetics Part C: Seminars in Medical Genetics*, http://dx.doi.org/10.1002/ajmg.c.31781.

Rogol, A. D. (2020). Human sex chromosome aneuploidies: The hypothalamic–pituitary–gonadal axis. *American Journal of Medical Genetics Part C: Seminars in Medical Genetics*, http://dx.doi.org/10.1002/ajmg.c.31782.

Ross, J. L., Kushner, H., Kowal, K., Bardsley, M., Davis, S., Reiss, A. L., … Roeltgen, D. (2017). Androgen treatment effects on motor function, cognition, and behavior in boys with Klinefelter syndrome. *Journal of Pediatrics*, *185*.193–199.e4. https://doi.org/10.1016/j.jpeds.2017.02.036.

Samango-Sprouse, C., Stapleton, E. J., Lawson, P., Mitchell, F., Sadeghin, T., Powell, S., & Gropman, A. L. (2015). Positive effects of early androgen therapy on the behavioral phenotype of boys with 47,XXY. *American Journal of Medical Genetics. Part C, Seminars in Medical Genetics*, *169*, 150–157.

Skakkebæk, A., Gravholt, C. H., Chang, S., Moore, P., Wallentin, M. (in press). Psychological functioning, brain morphology and functional neuroimaging in Klinefelter syndrome. *American Journal of Medical Genetics. Part C, Seminars in Medical Genetics*.

Spaziani, M., & Radicioni, A. F. (2020). Metabolic and cardiovascular risk factors in Klinefelter syndrome. *American Journal of Medical Genetics Part C: Seminars in Medical Genetics*, http://dx.doi.org/10.1002/ajmg.c.31792.

Sund, K., Khattar, D., Boomer, T., Caldwell, S., Dyer, L., Hopkin, R., & Smolarek, T. (2020). Confirmatory testing illustrates additional risks for structural sex chromosome abnormalities in fetuses with a non-invasive prenatal screen positive for monosomy X. *American Journal of Medical Genetics. Part C, Seminars in Medical Genetics*.

Tartaglia, N., Boada, C., Tanda, T., Brown, M., Crawford, L., Alston, A., & Ross, J. (in press). Early neurodevelopmental and medical profile in children with sex chromosome trisomies: Background for the prospective eXtraordinarY Babies Study to identify early risk factors and targets for intervention. *American Journal of Medical Genetics. Part C, Seminars in Medical Genetics*.

Tartaglia, N., Howell, S., Wilson, R., Janusz, J., Boada, R., Martin, S., … Zeitler, P. (2015). The eXtraordinarY Kids Clinic: An interdisciplinary model of care for children and adolescents with sex chromosome aneuploidy. *Journal of Multidisciplinary Healthcare*, *8*, 323–334. https://doi.org/10.2147/JMDH.S80242

Thompson, T., Howell, S., Davis, S., Wilson, R., Janusz, J., Boada, R., Pyle, L., & Tartaglia, N. (2020). Current survey of early childhood intervention services in infants and young children with sex chromosome aneuploidies. *American Journal of Medical Genetics Part C: Seminars in Medical Genetics*, http://dx.doi.org/10.1002/ajmg.c.31785.

Urbanus, E., Swaab, H., Tartaglia, N., Cordeiro, L., & Rijn, S. (2020). The behavioral profile of children aged 1–5 years with sex chromosome trisomy (47, XXX, 47, XXY, 47, XYY). *American Journal of Medical Genetics Part C: Seminars in Medical Genetics*, http://dx.doi.org/10.1002/ajmg.c.31788.

Warling, A., Liu, S., Wilson, K., Whitman, E., Lalonde, F., Clasen, L., Blumenthal, J., & Raznahan, A. (in press). Sex chromosome aneuploidy

alters the relationship between neuroanatomy and cognition. *American Journal of Medical Genetics. Part C, Seminars in Medical Genetics*.

Wigby, K., Cordeiro, L., Wilson, R., Angkustsiri, K., Simon, T., & Tartaglia, N. (in press). Adaptive functioning in children and adolescents with trisomy X: An exploratory analysis. *American Journal of Medical Genetics. Part C, Seminars in Medical Genetics*.

Willems, M., Gies, I., & Van Saen, D. (2020). Germ cell loss in Klinefelter syndrome: When and why?. *American Journal of Medical Genetics Part C: Seminars in Medical Genetics*, http://dx.doi.org/10.1002/ajmg.c.31787.

Winge, S. B., Soraggi, S., Schierup, M. H., Rajpert-De Meyts, E., & Almstrup, K. (2020). Integration and reanalysis of transcriptomics and methylomics data derived from blood and testis tissue of men with 47,XXY Klinefelter syndrome indicates the primary involvement of Sertoli cells in the testicular pathogenesis. *American Journal of Medical Genetics Part C: Seminars in Medical Genetics*, http://dx.doi.org/10.1002/ajmg.c.31793.

Wistuba, J., Beumer, C., Brehm, R., & Gromoll, J. (2020). 41, XXY* male mice: An animal model for Klinefelter syndrome. *American Journal of Medical Genetics Part C: Seminars in Medical Genetics*, http://dx.doi.org/10.1002/ajmg.c.31796.

Zitzmann, M., & Rohayem, J. (2020). Gonadal dysfunction and beyond: Clinical challenges in children, adolescents, and adults with 47,XXY Klinefelter syndrome. *American Journal of Medical Genetics Part C: Seminars in Medical Genetics*, http://dx.doi.org/10.1002/ajmg.c.31786.