Y-chromosome microdeletions are not associated with SHOX haploinsufficiency

Dear Sir,

Dr Chianese et al. (2013) expressed concerns about their results reported in ‘Y-chromosome microdeletions are not associated with SHOX haploinsufficiency’ and our earlier publication ‘Aberrations in pseudoautosomal regions (PARs) found in infertile men with Y-chromosome microdeletions’ (Jorgez et al., 2011). We wish to respond to several of their statements regarding our work in hopes of clarifying our findings.

Deletions of Yq and isodicentric Y-chromosomes are two relatively common structural abnormalities affecting male fertility. Deletions of distal Yq frequently include pseudoautosomal region 2 (PAR2) while the isodicentric-Y is characterized by duplication of PAR1 and sex determining region of the Y-chromosome (SRY) and deletion of PAR2 (Lange et al., 2009). We evaluated 87 men with Y-chromosome microdeletions by array comparative genomic hybridization (aCGH) and/or qPCR for PARs abnormalities. Thirteen men (15%) had an abnormal karyotype involving the Y-chromosome; they had PAR abnormalities. In addition, seven men with a normal karyotype also displayed PAR abnormalities. The Chianese et al.’s study included 11 patients (6%) with abnormal karyotypes, but PAR-copy number variations (CNVs) were reported in five patients. If the karyotype of the remaining six involved Y-chromosome aberrations, then PAR-CNVs should be evident. Also, if an isodicentric Y-chromosome is present, then CNVs should be present in both PARs. Since PAR-CNVs were not reported, the sensitivity of the methods employed is a concern and may explain the difference in the results since the majority of their patients were analyzed by qPCR only.

Chianese et al. stated that their discrepancy with our data may be due to methodological issues although no specific problems were mentioned. Our study included a complete analysis of high density X- and Y-chromosome aCGH performed in 25 men with non obstructive azoospermia (NOA). We confirmed the CNVs detected by aCGH and identified CNVs using qPCR for at least three genes in each PAR and the SRY gene in the additional patients. Chianese et al. analyzed only SHOX gene CNVs in the majority of samples studied. Therefore, it is possible that PAR microdeletions or microduplications not encompassing SHOX were missed. Notably, one of our patients had a PAR1 duplication that did not encompass SHOX and this was confirmed by both aCGH and SHOX qPCR-analysis. A sub-set of NOA-men in our study with Y-microdeletion and normal karyotype (5.4%, 4/74) had PAR1 deletions that included SHOX (height not available). Chianese et al. identified men with a normal karyotype (2/177), normal height and SHOX CNVs (duplications) but at a lower frequency (1.1%). The normal height of these two individuals is not surprising as individuals with SHOX duplications have variable height.

Chianese et al. mentioned that our patients’ phenotype was not fully described. Our paper states that patients were evaluated according to the American Urological Association Practice Guidelines (Gangel, 2002). Diagnosis was idiopathic NOA prior to Y-chromosome microdeletion testing. Our paper focused on SHOX aberrations as a co-existing genomic syndrome because height is an easily measured physical characteristic. Dosage changes of other PAR genes are associated with clear phenotypic anomalies, such as intellectual disability, but these characteristics may be difficult to ascertain. In our study, height was noted in the charts for only seven patients, with three men <10th percentile and one male >95th percentile (outside defined ranges of normalcy). One Y-isodicentric man displayed the typical body habitus and arm deformities characteristic of SHOX syndrome.

Over 200 individuals who were not infertile (C.J. Jorgez and D.J. Lamb, unpublished) and 112 normospermic, but apparently infertile, controls by Chianese et al. did not exhibit CNVs in SHOX. SHOX-CNVs were present only in Y-chromosome microdeleated patients. The Database of Chromosomal Imbalance and Phenotype in Humans using Ensembl Resources (DECIPHER database) (https://decipher.sanger.ac.uk/) indicates that 35 of 29 626 subjects (0.11%) have SHOX CNVs. Of those patients with a phenotype described, 89% have intellectual disability. One DECIPHER male with a PAR1-gain and Yq-deletion had azoospermia, as well as glaucoma and abnormalities of pyramidal motor function. Thus, SHOX CNVs rarely occur in the general population, which further supports the significance of identifying PAR-CNVs in Y-chromosome microdeleated patients.

In conclusion, we are pleased that the findings of Chianese et al., essentially confirm our earlier publication. Molecular studies using aCGH and CNV-qPCR of patients with Y-chromosome microdeletions allow the identification of additional, previously unrecognized Y structural variations in NOA men. Additional Y-chromosome microdeletion men should be tested for PAR CNVs to define the incidence with certainty. Although the function of many PAR genes is under investigation, there may be consequences for male offspring of NOA men with PAR rearrangements who conceive using assisted reproductive technologies. Accordingly, further studies are needed to better understand the risks that may be present and this is an area where Chianese et al. and our laboratory certainly agree.

References


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Reply: Y-chromosome microdeletions are not associated with SHOX haploinsufficiency

Dear Sir,

This letter addresses the debate between our recently published paper (Chianese et al., 2013) and the earlier publication of Jorgez et al. (2011). Overall, we feel that Jorgez et al. missed the main objective of our study, which was SHOX gene dosage and not pseudoautosomal region-1 (PAR1)-related copy number variations (CNVs). We investigated this specific aspect, as the alarming finding of SHOX haploinsufficiency in 5.4% of azoospermia factor (AZF) deletion carriers with normal karyotype is poor and unclear about SHOX over-dosage, which has been reported in association with normal to tall stature. We actually find it strange that in their publication, information on height is not reported for the four patients with normal karyotype carrying SHOX deletions. In general, if SHOX deletions are present then short stature and/or skeletal abnormalities should be present as well, but this is not reported by Jorgez et al.

We are sorry but we do not agree with the statement: ‘[...] the findings of Chianese et al. (2013) essentially confirm our earlier publication’. Although we did find SHOX duplications in 1.1% of men with Y microdeletions and normal karyotype, it does not mean that this category of patients is at higher risk for SHOX CNVs compared with the general population. The reference that Jorgez et al. make to the DECIPHER database (Database of Chromosomal Imbalance and Phenotype in Humans using Ensembl Resources), reporting only 0.11% of SHOX CNVs, is misleading. This database is mainly based on arrays with a relatively low resolution (probes every 0.5–1 Mb) that may not allow the detection of small rearrangements such as ours. Moreover, all CNVs involving SHOX in the DECIPHER database had a huge size (the majority ranging from 5–58 Mb). It is worth noting that the pathologic phenotype of the azoospermic man with Yq microdeletion and a duplication of 11.6 Mb mentioned in the letter by Jorgez et al. is not an appropriate example to demonstrate an association between Yq deletions and PAR1 linked duplications. For instance, this large duplication extends over PAR1 and clearly affects the X chromosome, duplicating a total of 43 genes.

The only point we agree on with Jorgez et al. is the need for further studies concerning SHOX duplications; in fact, we considered the low number of analyzed controls a limitation to prove that these CNVs are actually associated with the presence of microdeletions.

In conclusion, we provided the largest collection of men carrying Y-chromosome microdeletions analyzed so far in association with SHOX CNV. Our data show no association between Y-chromosome microdeletions and SHOX haploinsufficiency in men with normal karyotype, which is in net discordance with the previous findings of 5.4% of NOA-men with Y-microdeletion and normal karyotype.


Carolina J. Jorgez1,2,*, John W. Weedin2, Aysegul Sahin2, Mounia Tannour-Louet2, Shuo Han3, Juan C. Bournat1, Anna Mielnik4, Sau Wai Cheung5, Ajay Nangia6, Peter N. Schlegel1, Larry I. Lipshtiz1,2 and Dolores J. Lamb1,2,*. 1Center for Reproductive Medicine, Houston, TX, USA 2Scott Department of Urology, Baylor College of Medicine, Houston, TX, USA 3Department of Molecular and Cell Biology, Baylor College of Medicine, Houston, TX, USA 4Department of Urology, Weill Medical College of Cornell University, New York, NY, USA 5Department of Molecular and Human Genetics, Baylor College of Medicine, Houston, TX, USA 6Department of Urology, The University of Kansas Medical Center, Kansas City, KS, USA

*Correspondence address. Center for Reproductive Medicine and Scott Department of Urology, Baylor College of Medicine, Houston, TX 77030, USA. Tel: +1-713-798-3541; E-mail: cj129804@bcm.edu (C.J.J.); Center for Reproductive Medicine and Scott Department of Urology, Baylor College of Medicine, Houston, TX 77030, USA. Tel: +1-713-798-7266; E-mail: dlamb@bcm.edu (D.J.L.)

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