

Nuchal translucency distributions for different chromosomal anomalies
in a large unselected population cohort

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Marianne Christiansen^{1*}, Charlotte K. Ekelund², Olav Bjørn Petersen¹, Jon Hyett³,
Nathan Eastwood⁴, Susan Ball⁵, Ann Tabor² and Ida Vogel⁶

¹Fetal Medicine Unit, Department of Obstetrics and Gynecology, Aarhus University Hospital, Aarhus, Denmark; ²Center for Fetal Medicine, Department of Obstetrics, Copenhagen University Hospital Rigshospitalet, Copenhagen, Denmark;

³Department of High Risk Obstetrics, Royal Prince Alfred Hospital, Sydney, Australia; ⁴Centre for Biostatistics, Bioinformatics and Biomarkers, Plymouth University, Plymouth, United Kingdom; ⁵NIHR CLAHRC South West Peninsula (PenCLAHRC), University of Exeter Medical School, Exeter, United Kingdom;

⁶Department of Clinical Genetics, Aarhus University Hospital, Aarhus, Denmark

*Corresponding author: Marianne Christiansen, Fetal Medicine Unit, Department of Obstetrics and Gynecology, Aarhus University Hospital, Palle Juul-Jensens Boulevard 99, DK-8200 Aarhus N, Denmark. Tel. +4525211891. E-mail: manchi@rm.dk.

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What is already known about this topic?

The distributions of the fetal nuchal translucency thickness (NT) for trisomy 21, trisomy 18, trisomy 13, monosomy X and unbalanced translocations are shifted towards larger values.

What does this study add?

We present visually the distributions of the fetal nuchal translucency thickness (NT) for different chromosomal anomalies obtained from a large, unselected cohort with postnatal follow-up. The NTs of the common autosomal trisomies, monosomy X, and unbalanced translocations were shifted towards larger values, while the distributions for the balanced translocations, the uncommon autosomal trisomies and the triploidies more closely resembled that of the normal/no karyotype population.

Accepted Article

Abstract

Objective:

To describe the distribution of the fetal nuchal translucency thickness (NT) according to type of chromosomal aberration in a large unselected population.

Methods:

Data on pregnancies with an NT measurement performed at gestational age 11+3 – 13+6 weeks from 2008–2011 were retrieved from the Danish National Fetal Medicine Database. Information on any genetic analysis for aneuploidy performed pre- or postnatally was also obtained. The abnormal results were grouped into 14 types of chromosomal anomalies. Distributions of NT measurements were summarized by aberration and compared with the normal/no karyotype group.

Results:

215,223 singleton pregnancies were included in the cohort. 10,548 had a normal karyotype and 1,286 had an aberration. Plots of the NT measurements showed that like trisomy 21,18, and 13 and monosomy X, the distribution for the unbalanced translocations was shifted towards larger NTs. The distributions for the balanced translocations, the uncommon trisomies and the triploidies more closely resembled that of the normal/no karyotype population.

Conclusion:

Fetuses with aneuploidies have NT distributions visually different from normal fetuses, with the exception of triploidies and uncommon autosomal trisomies. The distributions differ in shape according to type of chromosomal anomaly.

Accepted Article

Introduction:

Combined first trimester screening for Down's Syndrome is based on the observation that the distribution of the Nuchal Translucency thickness (NT) is shifted towards larger values in the majority (95%) of fetuses with trisomy 21.¹ The NT is also increased in cases of trisomy 18 and 13, and Kagan *et al.*² found that while the NT was less than 4.5 mm in approximately 50% of fetuses with trisomy 21, the NT was 4.5 mm or more in approximately 60% of fetuses with trisomy 13, 75% of those with trisomy 18, and 90% of fetuses with monosomy X. These authors concluded that in fetuses with increased NT, approximately one half of the chromosomally abnormal group was affected by defects other than trisomy 21, and that the distribution of NT was different for each type of chromosomal defect. Their study was based on 11,315 selected high-risk patients from the period 1992-2005;

all had a fetal karyotype performed, and the fetal karyotype was abnormal in 2,168 (19,2%) cases.

Trisomy 21 is the most common chromosomal anomaly, and trisomy 18 and trisomy 13 are the second and third most common aneuploidy, respectively.³ Recently, non-invasive prenatal testing (NIPT) using cell free fetal DNA (cffDNA) for trisomy 21, 18 and 13 and sex chromosomal aneuploidies has become an alternative to traditional karyotyping. However, it has been shown that a significant proportion (23%) of chromosomal anomalies will be missed by targeted screening by NIPT.⁴ The potential power of NIPT is not in dispute, but NIPT still has to find its place in future prenatal screening programs.

An improved understanding of the NT distributions in chromosomal anomalies other than trisomy 21, 18 and 13 would enable development of better risk algorithms that can inform future screening programs based on a combination of the combined First Trimester Screening and NIPT. The aim of this study was to create visual representations of the different distributions of NTs in a range of chromosomal anomalies, based on an analysis of data from a Danish national low risk population.

Methods:

This is a study where data were collected prospectively and analysed retrospectively. The study is based on data from The Danish Fetal Medicine Database and the Danish Central Cytogenetic Registry. Since 2004 all pregnant women in Denmark have been offered a publicly financed combined First Trimester Screening (maternal age, maternal serum free- β hCG and PAPP-A, fetal nuchal translucency scan). All NT scans were performed by FMF certified sonographers and doctors, and all data were stored in the local fetal medicine database (Astraia GmbH software, Munich, Germany). Data on maternal characteristics, biochemical and ultrasonic markers were continuously sent electronically from the 15 local fetal medicine databases in Denmark to a central database. Here data for each pregnancy was linked via the Danish unique personal registration number with outcome data from the National Birth Registry, as well as information about any test result concerning aneuploidy of the fetus/infant obtained from the Danish Central Cytogenetic Registry. This registry received data on karyotype, molecular karyotype and specific genetic analyses performed by all the five Clinical Genetic departments in Denmark; this includes prenatal, postmortem and liveborn tests. Detailed description of this dataflow has recently been published.⁵

We searched the Danish Fetal Medicine Database for all pregnancies with a first trimester NT measurement performed from January 2008 – December 2011. Owing to variations in clinical practice and the impact of patient choice we chose to include all obtained data in our analysis. Cytogenetic, including molecular cytogenetic, data

on aneuploidy were collected for all cases in which prenatal, abortion or postnatal karyotyping had been performed. The obtained data included all those obtained by G- or Q-banded chromosome analyses, fluorescence in situ hybridization, quantitative fluorescence polymerase chain reaction, chromosomal microarray analyses or multiplex ligation dependent probe amplification. A specialist in Clinical Genetics reviewed all genetic test results, and an additional Cytogeneticist reviewed the atypical chromosomal aberrations.⁴

Statistics:

For the normal/no karyotype group and for each group of chromosomal aberrations, the distribution of NTs was described numerically using summary statistics, and visually using density plots and boxplots.

The two-sample Kolmogorov-Smirnov test was used to test for any statistical difference between the distributions of the normal/no karyotype NTs and each group of chromosomal aberration NTs. A Bonferroni correction was applied to allow for multiple comparisons.

Results:

In the years 2008-2011 the uptake of first trimester NT scan in Denmark was 89-92%, and all of these scans were registered in the Danish Fetal Medicine Database.⁶

In total 215,223 singleton pregnancies were included in the cohort, all with a CRL between 45-84 mm. 11,864 had a pre- or postnatal genetic analysis registered, of these 10,548 were normal, 1,286 had an abnormal result, while in 30 cases there was an analytic failure and hence no result was obtained.

The abnormal results were clustered into 14 groups: trisomy 21, trisomy 18, trisomy 13, uncommon autosomal trisomies, monosomy X, monosomy X mosaicism, 47,XXX, 47,XXY, 47,XYY, other sex chromosomal aneuploidies, triploidy, balanced translocations, unbalanced translocations, other aberrations.

Table 1 gives the number of NT measurements in each of the 15 groups (14 groups of chromosomal aberrations and 1 group of normal/no karyotype) and the summary statistics for the NT thickness. Figure 1 shows density plots for the NTs in each of the groups of aberrations compared to the normal/no karyotype group. Figure 2 shows boxplots of the NTs for each group with individual NTs overlaid.

Here Table 1, Figure 1 and Figure 2 should be inserted.

Autosomal trisomies:

The density plots (Figure 1), boxplots (Figure 2) and Kolmogorov-Smirnov Test p -values (unadjusted and Bonferroni adjusted) (Table 1) showed that the distribution of NTs in the trisomy 21 cases was shifted toward larger NTs, and this was also the case for trisomy 18 and trisomy 13. For the groups of trisomy 18 and trisomy 13 the density plots were more flat, so that proportionally more fetuses seemed to have even larger NTs than the trisomy 21 fetuses. The group of uncommon autosomal trisomies had a biphasic distribution with the majority close to the normal/no karyotype group, but there were some with larger NTs. However, as a group the distribution was not significantly different from the normal/no karyotype group, according to the Kolmogorov-Smirnov Test (adjusted p -value = 1).

Sex chromosomal aneuploidies:

Most of the monosomy X group had larger NTs than the normal, and the shape of the distribution was very flat (Figure 1), so many had a very large NT. This group was found to be significantly different from the normal/no karyotype group (adjusted p -value < 0.0001). The majority of the group with monosomy X in a mosaic form had normal NTs, whereas a subgroup seemed to have larger NTs (Figure 1), however the differences were not found to be statistically significant (adjusted p -value = 1). The sex chromosomal trisomies (47,XXX, 47,XXY and 47,XYY) and other sex

chromosomal aneuploidies seemed to have larger NTs, although no formal statistical tests were carried out due to the small numbers in each of these groups.

Triploidies:

The group of triploidies more closely resembled that of the normal/no karyotype population, but both Figures 1 and 2 did show some larger NTs. There was some indication that the distribution was different from that of the normal/no karyotype NTs (unadjusted p -value = 0.01), which was not statistically significant after adjusting for multiple comparisons (adjusted p -value = 0.1).

Translocations:

The unbalanced translocations had a relatively higher proportion of larger sized NTs compared to the normal/no karyotype group, and the two groups were found to be statistically different (adjusted p -value < 0.002). The balanced translocations in contrast had a distribution, which was much closer to the normal, but by looking at the shape of the density plot (Figure 1) and individual NTs (Figure 1 and 2), one could suspect a small subgroup with larger NTs. However no significant difference between the balanced translocations group and the group of normal/no karyotype was found (adjusted p -value = 1).

Other aberrations:

The mixed group of other aberrations was a large group in this study, comprising 217 out of a total of 1,286 aberrations. The aberrations in this group were all the abnormal genetic test results that did not fall within the definition of any of the other abnormal groups. This group is a heterogeneous group: Microdeletions and duplications, isochromosomes, ring chromosomes, tetraploidies, marker chromosomes, inversions and other mosaicisms (than for monosomy X). As a group it had significantly different distribution of NTs than the normal/no karyotype group (adjusted p -value = 0.04).

Discussion:

The findings of this study confirm that the distribution of NTs varies for many chromosomal anomalies, as already shown by Kagan *et al.*² These authors calculated the Observed-to-Expected Ratio of different chromosomal defects in fetuses with increased NT according to ranges of NTs. Their data included all fetal karyotypes for cases with NTs above the 95th percentile from a database of high-risk pregnancies, and the expected number of each chromosomal defect was estimated from the maternal and gestational age distribution and the previously published risk for each chromosomal defect.² We describe the distributions by a different approach. Since our data is from a large unselected cohort including postnatal data,

we were able to describe the NT distribution of each chromosomal defect for all NTs including the small NTs, and to visualise the phenotypic variance in NT for each karyotype. Kagan *et al.* found that the observed-to-expected ratio increased significantly with NT for trisomy 21, 18 and 13, for monosomy X and other sex chromosomal anomalies, but not for triploidy.² These findings are in accordance with those of our study. Kagan *et al.* also found that the NT was less than 4,5 mm in approximately 50% of fetuses with trisomy 21 and those with triploidy.² Again these findings appear to be in accordance with those of our study, where we found the median NT to be 3,00 mm for trisomy 21 and 1,83 mm for triploidy (Table 1). However, it is important to note that Kagan *et al.* only looked at the chromosomal defects with NTs above the 95th percentile, thus explaining the differences.

Kagan *et al.*² found increased NT for other sex chromosomal anomalies than monosomy X, and Vaknin *et al.*⁷ found that increased NT was found among cases of 47,XXY. In our study, the groups of 47,XXY and 47,XXX also seemed to have increased NTs, however no formal statistical tests were carried out due to the small group sizes. Our study confirms that the NTs are shifted towards larger values in fetuses with unbalanced translocations,^{8,9} and contrary to Arigita *et al.*⁹ we found the distribution significantly different from the distribution of the normal/no karyotype group, probably due to the larger number of translocations in our study.

Alamillo *et al.*¹⁰ concluded from their study that although First Trimester Screening

was found to be efficacious in identifying pregnancies with trisomies 13, 18, and 21, 29% of chromosomally abnormal fetuses identified to be at increased risk for these aneuploidies actually had a different chromosome complement. With the possible exceptions of 47,XYY and monosomy X, their dataset suggested that these different chromosome complements were likely to be randomly distributed among both screen positive and screen negative pregnancies. The present study indicates that this is not the case for all the other chromosomal anomalies, since unbalanced translocations and the heterogeneous group of other chromosomal aberrations are also shifted towards larger NTs, which should make them more likely to be identified as increased risk by combined First Trimester Screening. The different conclusions could be due to the much larger number of chromosomal anomalies in the data presented here.

By looking at the density plots (Figure 1) and boxplots (Figure 2) of many of the groups, i.e. uncommon autosomal trisomies, monosomy X mosaicism, triploidy, balanced translocations and unbalanced translocations, one could get the impression of subgroups with larger NTs. Theoretically, there could be different explanations for the possible subgroups. For the uncommon autosomal trisomies, it could be that the NT depends on the actual chromosome involved. For the group of triploidy it has earlier been shown that the NTs are larger in the *diandric* triploidy, where the additional chromosome set is of paternal origin, than in the *digynic* triploidy, where the additional chromosome set is of maternal origin.^{11,12} There are

also likely to be differences in the lengths of intrauterine survival between these two. These factors together could result in subgroups with different NT distributions. Our cases with triploidy cannot be subdivided according to whether they were paternally or maternally inherited, as these analyses were not performed on a routine basis. For the group of balanced translocations some may appear balanced translocations by conventional karyotyping while in reality they have a cryptic imbalance that is missed by conventional karyotyping, and it could be that the distribution of the NTs for this subgroup was different from the distribution for the rest of the balanced translocations, and closer to the larger NTs of the group of unbalanced translocations. For the group of unbalanced translocations the NT may be dependent on the size of the aberration and the actual genes involved. However the numbers in each subgroup were very small, and the genetic analyses were heterogeneous (conventional chromosome analyses, MLPA, QF-PCR or microarray analyses), and therefore it was not possible to carry out any formal statistical analysis for these subgroups.

Limitations:

There could be a bias in our study in that the children with less pronounced symptoms caused by a chromosomal anomaly may not yet have had a postnatal investigation done, since the postnatal data only includes data up to the year 2012. This would mean that the cases with a large NT could be overrepresented in our

data. Examples of this could be cases of sex chromosomal aneuploidies not diagnosed until much later in life.

One might also argue that the reference normal/no karyotype group does not represent the normal karyotypes, since most of the fetuses/infants in this group have not had a genetic analysis performed. This group could therefore potentially include cases with aberrations not yet detected, and these could therefore tend to increase the range of the NT distribution. However, these missed abnormal cases are highly diluted by the much larger number of normal cases, so this might only minimally underestimate the difference in NTs between normal and abnormal groups.

Implications:

Density plots and boxplots are effective ways of visually describing the distributions of NTs in each group. The distributions vary according to type of chromosomal anomaly, and the density plots may be useful as a reference for clinicians. For example, if a fetus with a balanced translocation has a large NT, by looking at the density plot of the distribution for this group, there is a high likelihood that the large NT is due to something different than merely the translocation. This should encourage the clinician to continue looking for other structural anomalies related to

a large NT, e.g. a heart defect, but also to consider the possibility of doing a microarray analysis to ascertain whether the rearrangement is truly balanced.

During recent years, NIPT has provided an alternative to combined First Trimester Screening, and this technique promises a paradigm shift in prenatal diagnosis. In a study published recently, Quezada *et al.*¹³ looked at the outcome data of a group of selected women who had both NIPT (at gestational age 10-11) and combined First Trimester Screening, and concluded that the results of other screening tools should be included as the *a priori risk* for the interpretation of NIPT results, particularly in cases with a low fetal fraction. Combined First Trimester Screening has other benefits, like early detection of many major structural defects. We have previously shown that a significant proportion of chromosomal anomalies (23%) will be missed by targeted NIPT alone using this dataset.⁴ A proportion of such magnitude has also been found by Norton *et al.*,¹⁴ and these data suggest that there is value in combined First Trimester Screening in the NIPT era. Lichtenbelt *et al.*¹⁵ found comparable numbers in first trimester, but argue consequences to be less severe, as many of the missed cases by NIPT will end with fetal demise, or be picked up later in pregnancy due to the finding of malformations by ultrasound.

Currently there is a rapid development of new non-invasive prenatal tests, and it seems possible to detect genomewide fetal aneuploidies by NIPT.¹⁶ Such tests are now being performed and analysed.¹⁷ However, there are many practical, ethical

and economical considerations to take into account in planning future prenatal screening programs. Therefore we suggest that there is value in further developing risk algorithms and performance of the combined First Trimester Screening Test.

Conclusion:

The distribution of NTs varies for many chromosomal anomalies. In this study, based on data from a large unselected population, the distributions of NTs for 14 groups of aberrations were described numerically using summary statistics and visually using density plots and boxplots. Like trisomy 21, 18, and 13 and monosomy X, the distribution for the unbalanced translocations was shifted towards larger NTs. The distributions for the groups of sex chromosomal aneuploidies other than monosomy X also seemed shifted towards larger NTs, but these groups were too small for statistical analyses. For the groups of balanced translocations and triploidy, the distributions more closely resembled those of the normal/no karyotype population. All the distributions differed in shape, according to the type of chromosomal anomaly. An improved understanding of the NT distribution of the different chromosomal anomalies would enable preparation of more specific risk algorithms for all types of chromosomal anomalies, but greater numbers are needed in order to differentiate subgroups within the groups of chromosomal anomalies defined here.

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Members of the Danish Fetal Medicine Study Group:

Eske Bendtsen, Department of Gynecology and Obstetrics, Esbjerg Hospital, Esbjerg;

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Lene Brendstrup, Department of Gynecology and Obstetrics, Sønderjylland Hospital,
Aabenraa;

Anette Hessellund, Department of Gynecology and Obstetrics, Næstved Hospital,
Næstved;

Hanne Søndergaard Jensen, Department of Gynecology and Obstetrics, Herning
Hospital, Herning;

Finn Stener Jørgensen, Fetal Medicine Unit, Department of Gynecology and
Obstetrics, Copenhagen University Hospital Hvidovre, Copenhagen;

Annette Wind Olesen, Department of Gynecology and Obstetrics, Kolding Hospital,
Kolding;

Anne-Cathrine Shalmi, Department of Gynecology and Obstetrics, Hillerød Hospital,
Hillerød;

Lillian Skibsted, Department of Gynecology and Obstetrics, Roskilde Hospital,
Roskilde;

Steffen Sommer, Department of Gynecology and Obstetrics, Horsens Hospital,
Horsens;

Lene Sperling, Fetal Medicine Unit, Department of Gynecology and Obstetrics,
Odense University Hospital, Odense;

Birgitte Størup, Department of Gynecology and Obstetrics, Vendsyssel Hospital,
Hjørring;

Anne Sørensen, Department of Gynecology and Obstetrics, Aalborg Hospital,
Aalborg;

Ida Thagaard, Department of Gynecology and Obstetrics, Holbæk Hospital, Holbæk;

Laura Vase, Department of Gynecology and Obstetrics, Viborg Hospital, Viborg;

Helle Zingenberg, Fetal Medicine Unit, Department of Gynecology and Obstetrics,

Herlev Hospital, Herlev;

Marianne Østergaard, Department of Gynecology and Obstetrics, Randers Hospital,

Randers;

Members of the Danish Clinical Genetics Study Group:

Anders Bojesen, Department of Clinical Genetics, Vejle Hospital;

Christina Fagerberg, Department of Clinical Genetics, Odense University Hospital,

Odense;

Michael Bjørn Petersen, Department of Clinical Genetics, Aalborg University

Hospital;

Susanne Timshel, Department of Clinical Genetics, Copenhagen University Hospital

Rigshospitalet, Copenhagen;

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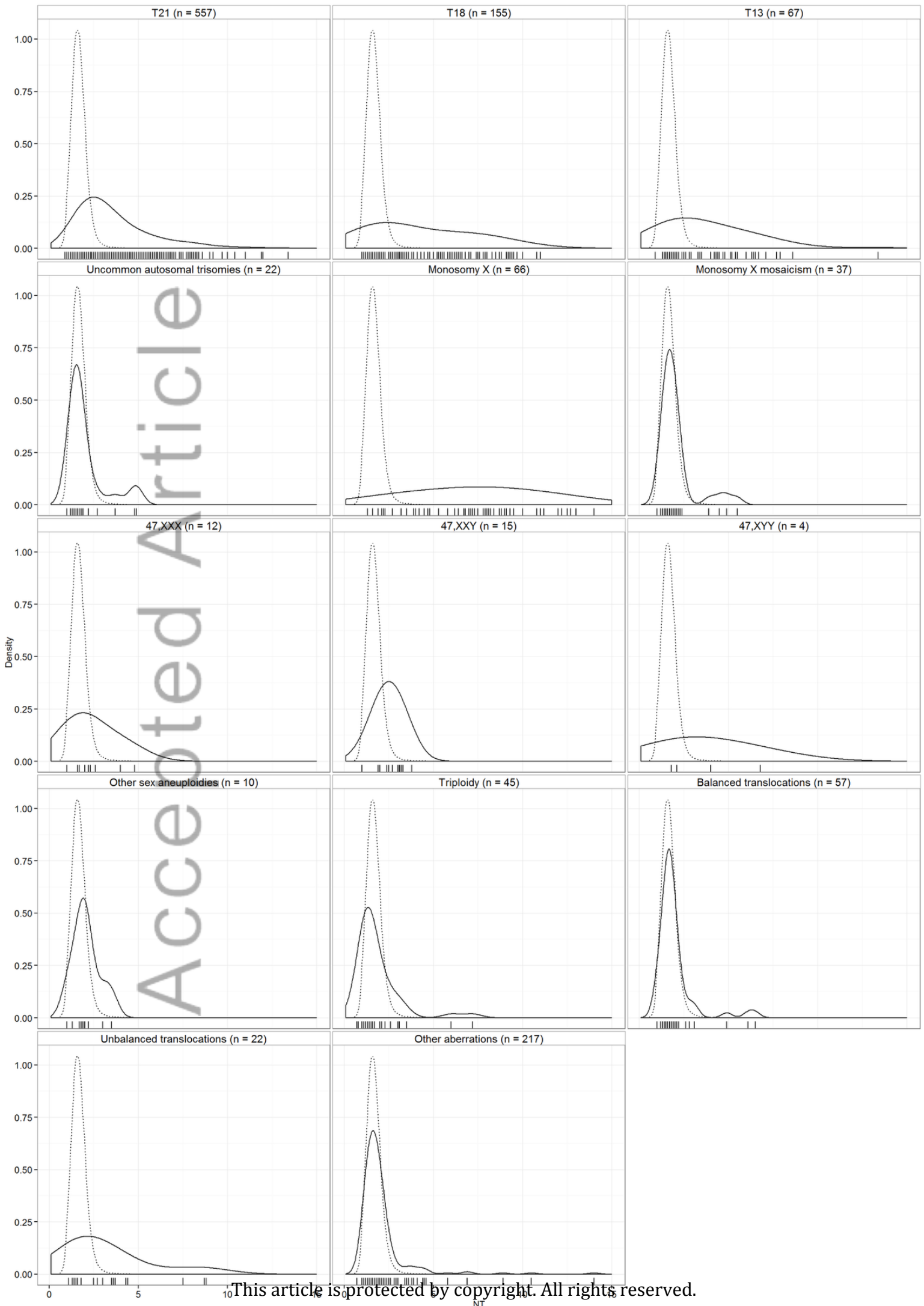
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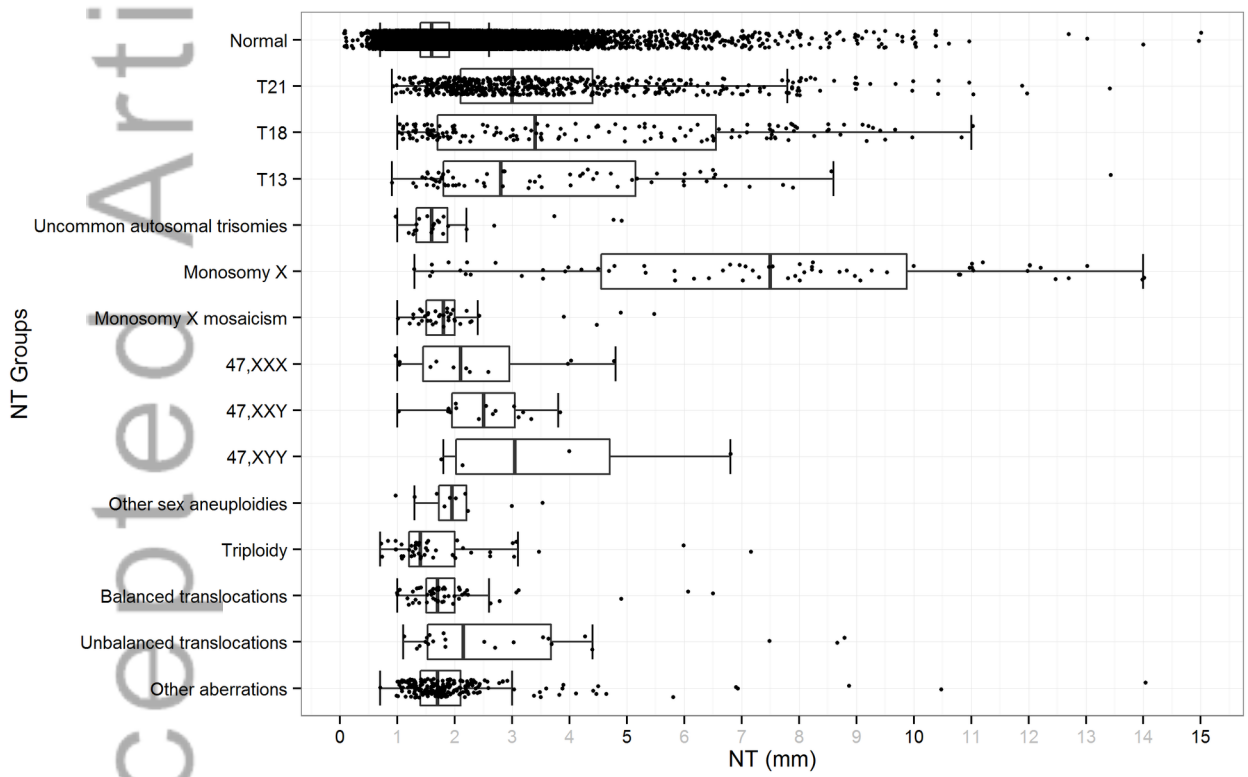
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Table 1: Summary statistics for normal and abnormal NT scans as well as p-values for the Kolmogorov-Smirnov test

| | Summary Statistics | | | | | | | p-value (unadjusted) ¹ | p-value (adjusted) ² |
|------------------------------------|--------------------|------|--------|------|-----|------|---|-----------------------------------|---------------------------------|
| | N | Mean | Median | SD | Min | Max | 25 th and 75 th percentiles | | |
| Normal NTs | | | | | | | | | |
| Normal/no karyotype | 213907 | 1.68 | 1.60 | 0.45 | 0.1 | 15.0 | (1.40, 1.90) | | |
| Abnormal NTs | | | | | | | | | |
| Trisomy 21 | 557 | 3.54 | 3.00 | 2.03 | 0.9 | 13.4 | (2.10, 4.40) | < 0.0001 | < 0.0001 |
| Trisomy 18 | 155 | 4.24 | 3.40 | 2.77 | 1.0 | 11.0 | (1.70, 6.55) | < 0.0001 | < 0.0001 |
| Trisomy 13 | 67 | 3.65 | 2.80 | 2.35 | 0.9 | 13.4 | (1.80, 5.15) | < 0.0001 | < 0.0001 |
| Uncommon autosomal trisomies | 22 | 2.00 | 1.60 | 1.09 | 1.0 | 4.9 | (1.33, 1.87) | 0.6178 | 1 |
| Monosomy X | 66 | 7.32 | 7.50 | 3.50 | 1.3 | 14.0 | (4.55, 9.88) | < 0.0001 | < 0.0001 |
| Monosomy X mosaicism | 37 | 2.04 | 1.80 | 1.01 | 1.0 | 5.5 | (1.50, 2.00) | 0.2660 | 1 |
| 47,XXX | 12 | 2.35 | 2.10 | 1.28 | 1.0 | 4.8 | (1.45, 2.95) | | |
| 47,XXY | 15 | 2.49 | 2.50 | 0.72 | 1.0 | 3.8 | (1.95, 3.05) | | |
| 47,XYY | 4 | 3.67 | 3.05 | 2.30 | 1.8 | 6.8 | (2.03, 4.70) | | |
| Other sex chromosomal aneuploidies | 10 | 2.06 | 1.95 | 0.74 | 1.0 | 3.5 | (1.72, 2.20) | | |
| Triploidy | 45 | 1.83 | 1.40 | 1.24 | 0.7 | 7.2 | (1.20, 2.00) | 0.0122 | 0.1223 |
| Balanced translocations | 57 | 1.95 | 1.70 | 1.04 | 1.0 | 6.5 | (1.50, 2.00) | 0.1926 | 1 |
| Unbalanced translocations | 22 | 3.16 | 2.15 | 2.34 | 1.1 | 8.8 | (1.52, 3.68) | 0.0002 | 0.0018 |
| Other | 217 | 2.02 | 1.70 | 1.41 | 0.7 | 14.0 | (1.40, 2.10) | 0.0042 | 0.0421 |

¹ p-values from the Kolmogorov-Smirnov test are provided for abnormal NT categories with > 20 scans only

² p-values adjusted for multiple comparisons using Bonferroni's correction