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# Fertility and infant survival in men and women from rural regions of Northern Tanzania: gene candidates and sex-specific genetic associations

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**Summary -** *Numerous factors, including family planning and modern contraception, disturb the potential associations between the number of children born and genetic factors in modern Western societies. The current progress of medicine and a relatively high level of well-being make it hard to test the association between children's survival rates and genetic factors in Western societies either. The goal of the current study was to reveal the possible associations between the number of children born and the number of children survived till the age of 5 y. by the time of our study with a set of six genetic polymorphisms associated with serotonin, dopamine, androgen oxytocin behavioral effects; and to test for sex-specific effects of these polymorphisms in a traditional rural sample from Arusha and Singida Districts of Northern Tanzania. The data on 965 healthy individuals (520 men and 415 women) from traditional rural communities with high reproduction profiles were collected. All participants provided information on the number of children born and survived, and other demographic information, as well as buccal epithelium samples for DNA analysis. The data were analyzed using GLM ANCOVA and the APSampler nonparametric methodology. The gene association effects on reproduction and infant survival in men and women were demonstrated. We suggest that sex differences revealed in this study are in line with sexual selection pressure on reproduction and parenting in traditional societies.*

**Keywords -** *Infant survival, Fertility, Parental care, Genetic polymorphisms, Rural population, Northern Tanzania.*

## Introduction

Many factors, such as effective contraception, family planning, current economic and environmental pressures, disturb the potential relationship between the number of children born and genetic basis, making it very difficult to study the relationship between these two elements in contemporary Western societies. The current progress of medicine and a relatively high level of well-being make it hard to test the association between children's survival rates and genetic factors in Western societies either. With certain variations (religious and cultural factors,

variations in access to medical help and its quality in a particular region) situation is radically different in non-Western traditional societies in Africa, Asia, and South America. Along with a natural (or nearly natural) birth-rate profile, with limited or no access to modern means of contraception, the death rate for children before five years old remained very high in many countries of Sub-Saharan Africa (particularly in rural areas). Besides, objective estimates' problem remains, since a substantial proportion of deliveries in rural areas are given outside modern hospitals, partly unregistered, and the same is true concerning early infant mortality. Tanzania is not an exception. Overall, it demonstrates one of the highest fertility rates, although with negative dynamics over the last 60 years. According to official statistics, the average fertility rate is 6.82 children per woman in 1960, 5.02 in 2016, and 4.92 children in 2020 (World Population Review, 2020). Roughly, one in seven children does not survive until their fifth birthday in rural Tanzania in 1997 (Armstrong Schellenberg *et al.*, 2002). According to the Institute for Health Metrics and Evaluation (Healthdata, 2020), the mortality rate for children under 5 y. per 1000 in 1990 was 148.8 and decreased to 56.5 in 2019. The most common causes of child deaths are thought to be malaria, acute respiratory infections, diarrhea, and malnutrition (Feachem & Jamieson, 1991; Murray & Lopez, 1997; INDEPTH, 2001).

Studies of reproductive choice have examined the predictive power of fertility intentions on behavior in a socio-psychological framework that consists of attitudes (perceived costs and benefits), norms (influence social network), and perception of control over individual choice (Rodgers *et al.*, 2001). It is important to realize that, along with various medical problems with reproduction and child care. There are numerous behavioral and psychological factors affecting both reproductive efforts and reproductive success (resulting in infant survival). Environmental factors, such as women's gains in education and labor market participation, gender equity, and economic uncertainty have been strongly affecting the tempo and quantum of fertility (Mills *et al.,* 2011).

The high level of reproduction in small-scale societies, where modern contraception is not available, may reflect (at least to some extent) an evolutionary adaptation to ensure offspring survival in a harsh environment full of parasites and infections. Recently we demonstrated, that love between spouses may be associated with fitness and reproductive success (children survive better) among the Hadza (Tanzania, Africa), a hunter-gatherer society whose lifestyle is in many ways remained traditional (Sorokowski *et al.,* 2017). Particularly, evidence has been provided that passion and commitment were among the key factors increasing children's survival. Mutual attachments and care between spouses, as well as, parent's attachments with infants, provide better chances for offspring survival (Bjorlund & Pellegrini, 2000; Bjorklund *et al.*, 2002; Geary, 2015).

Various factors may increase the probability of child survival, economic and social status of the family, mother's education, admittance to hospitals and other sources of a medical care, mother's and father's personality traits, as well as a complex interaction of genetic factors with various social and environmental factors. Monogamous and polygynous societies provide different options for children's socialization and differ in parental investment styles. Recent studies from the non-industrial world demonstrated a significant diversity of paternal roles in various types of societies ranging from egalitarian and peaceful to hierarchical and actively engaged in warfare as a mode of existence (Hewlett, 2017).

Universally in our human societies, mother care is among the primary factors ensuring an infant's survival in humans, and caring mothers had to be increasingly selected for in human evolution (Hrdy, 1999; Pavard *et al.*, 2007). Particularly, secure attachments between mother and child universally provide a solid basis for infant survival (Zeifman & College, 2018). For example, in rural Tanzania, the strong positive association between child survival and mothers carrying their children on their backs when cooking was reported (Armstrong Schellenberg

*et al.*, 2002). Same authors suggested that "Mothers who carried their children while they cooked presumably cared for their children differently in other ways as well, and it is likely that carrying the child when cooking is simply a proxy measure of this nonspecific positive maternal behavior" (Armstrong Schellenberg *et al.,* 2002, p. 510). Along with body security, mother care provides a better brain development and psychological comfort of offspring. As reported by recent neuronal studies, positive attachment stimuli from mothers elicit a strong neuronal response in children that spread over a wide range of oscillation, underscoring the considerable neural resources allocated to this survival-related cue (Pratt *et al.*, 2018).

Previous research has successfully demonstrated that there is a genetic component associated with reproduction. However, in most cases, the main attention is directed towards medical problems, such as infertility risk worldwide (Elhussein *et al.*, 2019; Fakhro *et al.*, 2020). The genome-wide association studies, being conducted on miscarriages, fetus development, delivery problems and breastfeeding in women, and infertility, both in women and men, age at menarche and menopause (He *et al.,* 2009; Liu *et al.*, 2009; Perry *et al.,* 2009; Stolk *et al.,* 2009; Sulem *et al.*, 2009; Stolk *et al.,* 2012; Laisk-Podar *et al.,* 2016; Gajbhiye *et al.*, 2018; Chernus *et al.*, 2019; Thirumavalavan *et al.*, 2019; Zeng *et al.*, 2019; Kyrgiafini *et al.*, 2020; Nemanja *et al.*, 2020; Patel *et al.*, 2020).

While the genome-wide association studies are used in order to reveal entirely new genes and to test the known genes, which functionality was not known to be directly related to the trait in question, the candidate gene approach exploiting genes with known biological functional impact on the trait in question may still be useful. Given the importance of particular personality traits, associated with passion and commitment between spouses, on the one hand, and attachment and caring mother style, on the other hand, in this paper we selected for analysis the six candidate genes (*AR*, *5-HTT*, *DRD4*, *COMT*, *MAOA,* and *OXTR*), and tested their association with reproduction (number of children born and number of children survived till the age of 5 y.) in men and women from rural population of North-Central Tanzania. Below follows the justification for our choice for the particular set of genes.

As the androgen receptor gene (*AR*) is expressed throughout the body and brain, the number of CAG repeats was supposed to be associated with higher androgenization of the whole organism (Simmons & Roney, 2011). Formerly, it was demonstrated that men with shorter sequences of CAG repeats have higher muscle mass and lower body fat, higher upper body strength, higher rates of sperm production, as well as a higher number of children born in cultures lacking modern methods of contraception (Nielsen *et al.,* 2010; Lukaszewski & Roney, 2011; Simmons & Roney, 2011; Butovskaya *et al.,* 2013, 2015a). As suggested by previous studies, shorter sequences of *AR*-CAG repeats translate into the more substantial phenotypic effect of androgens, such that men with fewer CAG repeats exhibit a more significant physiological response to testosterone compared to men with a higher CAG repeats number (Zitzmann & Nieschlag, 2007). The effects may also extend to psychological and personality traits, such that the lower number of *AR*-CAG repeats may be associated with higher extraversion, impulsiveness, aggression, violence, and dominance (Lukaszewski & Roney, 2011; Simmons & Roney, 2011; Aluja *et al.*, 2015; Butovskaya *et al.,* 2015b; Gettler *et al.*, 2017), while the higher number of CAG repeats associated with sexual jealousy (Lewis *et al.*, 2018).

Some studies suggest that 5HT dysregulation may be related to postpartum depression (Lucki 1998). Since the seminal studies of Caspi (Caspi *et al.*, 2003) on the serotonin receptor gene 5-HTTLPR variant, several studies have reported interactions with child maltreatment with 5-HTTLPR (Karg *et al.,* 2011). Mothers carrying an *S* allele, or functionally similar *Lg* allele, were more sensitive than those lacking these alleles (Fleming & Kraemer, 2019). Also, with the increasing quality of care, mothers with the

*Sa*, or *Lg* allele, tended to orient away from their babies less often and score higher on ratings of perceived attachment, whereas mothers lacking the *Sa* (or *Lg*) allele tend to exhibit an increased frequency of orienting away and lower ratings on perceived attachment with high early care quality (Mileva-Seitz *et al.,* 2011). Disorganized attachment is an important risk factor for socio-emotional problems from childhood to adulthood. Prevailing models of the etiology of disorganized attachment emphasize the role of dysfunctional parenting. The long-term effect of birth weight on child development is consistent with the prenatal programming hypothesis.

The *DRD4* VNTR polymorphism has been associated with child behavior problems in interaction with maternal insensitivity in European and American cohorts of preschoolers, with the 7-repeat (7R) allele associated with greater problems, and infants carrying the *DRD4*7R* allele showed greater effects of maternal insensitivity than non-carriers for behavioral problems at 18-months, in kindergarten, greater inattention in middle childhood and greater ADHD, conduct disorder, and psychopathy symptoms at age 15 in Europeans (Belsky & Pluess, 2013; Berry *et al.,* 2014; Nikitopoulos *et al.,* 2014; King *et al.,* 2016). Interestingly, a positive parenting intervention was also reported to be more effective in children carrying the *DRD4*7R* allele (Bakermans-Kranenburg *et al.,* 2008). The interaction study between the *DRD4* polymorphism and maternal sensitivity in both European and African ancestry children found potential differences in effects between ancestries (Propper *et al.*, 2007). Such associations were suggested to be adaptive for lower offspring investment strategies in dynamic social environments (Eisenberg *et al.*, 2007).

The catechol-*O*-methyltransferase (*COMT*) gene regulates catecholamine signaling in the prefrontal cortex and is implicated in anxiety, pain, and stress reactivity (Desbonnet *et al.,* 2012). *COMT* moderates the influence of early life stress on preschool-age symptoms of anxiety, and cortisol reactivity acts as a mechanistic mediator of the main-effect of *COMT* genotype on anxious child symptoms (Sheikh *et al.,* 2017). The association between maternal anxiety and in utero neurodevelopment is modified through complex genetic variation in *COMT*. An increased risk for anxiety may be transmitted from mother to child during fetal life, the effect is dependent upon infant *COMT* genotype (Qiu *et al.,* 2015).

The role of MAOA in mother caring and children's survival and well-being may be of high importance as well. The *MAOA* gene encodes the enzyme monoamine oxidase A involved in the oxidative deamination of dopamine, serotonin, epinephrine, and noradrenaline. In the gene promoter, there is a polymorphic region uVNTR, which may contain a different number of 30-nucleotide repeats, which affect the transcriptional activity of the gene. Short uVNTR alleles *2R* and *3R* have lower transcriptional activity, unlike the long uVNTR alleles *3.5R* and *4R* (Sabol *et al.*, 1998). Monoamine oxidase inhibitors are used in the treatment of depression of various genesis and other mental disorders. Inactivation of the *MAOA* gene as a result of the transition, as described in the Dutch pedigree, led to aggressive behavior in hemizygotic men (Brunner's syndrome), without affecting the behavior of heterozygous female carriers of the mutation (Brunner *et al.*, 1993). MAOA activity has been mainly discussed in association with problems of maternal maltreatment in childhood. Females with high-activity *MAOA* genotype who experienced early maltreatment had greater increases in emotional reactivity during adolescence, and higher levels of emotional reactivity predicted both antisocial personality disorder and borderline personality disorder symptom severity. Taken together, findings suggest that the interaction between *MAOA* and early maltreatment places women at risk for a broader range of personality pathology via effects on emotional reactivity (Byrd & Manuck, 2014; Heleiak *et al.,* 2016; Byrd *et al.*, 2019). Recent data supported the idea that the *MAOA* effect may be sex-specific (Aslund *et al.,* 2011; Holz *et al.,* 2016; Liu *et al.*, 2017). Chinese data demonstrated that *MAOA* genotypes interacted with maternal engagement

in parent-child activities in predicting boys' social competence. Boys with low activity genotype were at risk for high internalizing problems under high maternal parenting stress and low social competence if mothers displayed a low level of maternal engagement, but this effect was not demonstrated for girls (Liu *et al.,* 2017). On the other hand, in a big sample of Russian men, tested for association between the alleles of the monoamine oxidase A gene (*MAOA*) with well-being components, the *VNTR-3R* allele carriers men demonstrated more stress, were less happy and reported to live in unsafe environment (Gureev *et al.*, 2018). The same authors suggested that the gene plasticity concept provides a possible explanation for how the expression of genes related to behavior changes in different environmental conditions.

The *OXTR* gene was earlier selected as one of the candidate genes associated with affiliated, attachment, and cooperation. Particularly, the *OXTR* SNP rs53576, the allele *G* was reported to be associated with diminished stress after social support, adult separation anxiety, higher sensitivity in social cooperation settings (increased in males), higher empathic performance, and social connectedness in women (Costa *et al.,* 2009; Rodrigues *et al.,* 2009; Chen *et al.*, 2011; Feng *et al.,* 2015; Laursen *et al.,* 2014; Cattaneo *et al.,* 2016; Theofanopoulou *et al.,* 2018). The current data revealed the role of oxytocin-dopamine interactions in regulating mood and mothering during the postpartum period (Post & Leuner, 2018). The evolutionary increase in frequencies of *OXTR*G* alleles could be taken to lend some support to hypotheses that argue for early changes in our lineage associated with prosocial behavior (Theofanopoulou *et al.,* 2018).

The goal of the current study was to reveal the possible associations between the number of children born and the number of children survived with a set of six candidate genes related to serotonin, dopamine, androgen, and oxytocin systems and to test for a sex-specific effect of these polymorphisms on reproductive success in a traditional rural sample from Northern Tanzania.

## Materials and methods

*Study samples*

For this study, the data on healthy men and women from traditional rural communities settled around Lake Eyasi (Northern Tanzania, Arusha, and Singida Districts) were collected (Fig. 1). All participants were of East African origin: 935 individuals (520 men and 415 women). The first-degree relatives were not included in this study. The data were collected, using a snowball sampling procedure. All participants provided informed consent before study inclusion and were instructed that they could quit the procedure at any time. Most of the informants were illiterate, hence, the consent was oral. Participants responded orally to interviewer's questions in individual sessions. The local assistants read all questions aloud in one-to-one dialogues, and further explanations were provided if necessary. No other group members stay nearby. In this way, we reduced possible biases associated with social desirability and morality norms.

All participants provided demographic information. The age was mostly self-reported, and when the participants did not know it, the researchers helped them estimate the age based on various associated events from the past. The mean age of respondents being 36.1 y., the age ranged from 16 to 75yy. For this study, each participant was assigned to one of four age groups: 1<=29; 2=30–39; 3=40–49; 4>=50 y. Participants provided information on the number of children born, as well as the number of children survived till the age of 5y. for him/her by the time of this survey. Each respondent was asked to enumerate all their children alive by names. In this way, we control for the information about the mentioned number of children. We also conducted a cross-check for this information by asking other family members about the number of children for a particular individual. We did not ask for any information about the extrapair paternity, although the recent findings suggest that it may be high in some traditional African populations (Scelza *et al.*, 2020). However, we asked about the number of partners, as well as how many children


**Fig. 1 – The map of study region (source - https://www.mapsland.com).** ***The colour version of this figure is available at the JASs website.***

were born in each case, including the extrapair offspring (in this case, respondents were free to answer or not, but in the majority of cases, they find no problems with this question).

*Genotyping*

Buccal epithelium samples were collected for DNA analysis. Genomic DNA of participants was isolated using the Diatom DNA Prep 200 extraction kit (IsoGene Lab, Russia). The AR PCR was performed with the primers, 5'-(FAM)-tccagagcgtgcgcgaagtgat-3' and 5'-(FAM)-cgactgcggctgtgaaggttg-3'. The reaction mixture was as described previously (Butovskaya *et al.,* 2012). The following amplification profile was used: 4 min of initial denaturation at 94°C; 30 cycles of 1 min at 94°C, 1 min at 56°C, and 1 min at 72°C; followed by a final 10 min extension at 72°C. A reaction mixture containing no template DNA was used as a negative control for PCR assays. Reaction products were analyzed using an ABI PRISM 3100-Avant

automated DNA sequencer. Each PCR product was analyzed on the sequencer three times, and each panel contained at least one sample with a reaction product of known size. Moreover, several samples were sequenced in the automated sequencer, and the numbers of CAG repeats were determined.

Polymorphic variants of the genes *COMT* (rs4680), *OXTR* (rs53576), *MAOA* (VNTR), DRD4E3 (VNTR), and 5HTTLPR (VNTR, rs25531) were analyzed after locus-specific polymerase chain reaction (PCR) with a kit of GenePak® PCR Master-Mix Core (IsoGene Lab) according to the manufacturer's protocol (Supplementary Material, Tab. 1). For details of the sequences and annealing temperatures of the primers, as well as the restriction endonucleases, see Supplementary Material, Table 1. The amplification conditions included initial denaturation at 94°C for 4 min and 35 cycles consisting of three steps: denaturation for 1 min at 94°C, primer annealing for 1 min at X°C, and elongation for 1 min at 72°C. The last step included the final elongation for 2 min at 72°C. To identify the SNP, the amplification products were divided into equal aliquots of 10 μL, one of which was treated with the appropriate restriction endonuclease (5 units per sample) at $T_{opt}$ °C overnight. The amplification and restriction products were fractionated in 2% agarose gel with ethidium bromide staining. The results were analyzed and photographed on a BioDocAnalyze device.

The following alleles for the six genes alleles were tested: DRD4E3 (VNTR): ranged from 2 to 10; *MAOA* (VNTR): ranged from 2 to 5; *COMT* rs4680: *V* and *M*; 5HTTLPR (VNTR+rs25531): *La*, *Lg*, *Sa*, *xL*; *OXTR* rs53576: *A* and *G*; *AR*: CAGn repeat's: ranged from 12 to 34 (Supplementary Material, Tab. 2).

*Statistics*

Models were estimated with IBM SPSS software v. 22 for Windows with the level of significance set to p=0.05. To reveal the sex differences in the number of children born and survive in four age cohorts, we conducted the independent-samples T-test and used Cohen's *d* to reveal the effect sizes for these differences. In the case of different sample sizes, the Hedges'*g* has been used.

GLM-univariate six-way ANCOVAs were conducted separately for men and women with the number of children born (survived), standardized for age as dependent variables, and polymorphisms on DRD4E3-VNTR, 5HTTLPR-VNTR+rs25531, *COMT* rs4680, *MAOA*-VNTR, *OTXR* rs53576 as the fixed factors and *AR*-CAG number as a covariate. Main effects and two-way interaction effects were tested. In all cases, the estimates of effect sizes were provided (the Partial eta squared, ŋ).

To examine the possibility of the combined effect of the six genes candidates simultaneously on the number of children born and the number of children survived, in unrelated men and women the APSampler nonparametric methodology has been applied (Favorova *et al.*, 2006). The APSampler is a novel algorithm based on Markov chain Monte Carlo exploration using a Bayesian statistical basis, which allows the exploration of genotypes tied to phenotypic trait levels to identify possible combinations of allelic variants at multiple loci that could affect the development of a quantitative trait (Favorova *et al.*, 2006). The algorithm relies on the rank comparison of phenotype for individuals with and without specific combinations of allelic variants or patterns isolated in genetic backgrounds matched for the remaining significant patterns. It constructs a Markov chain to sample only potentially significant variants, minimizing large data sets' potential to overwhelm the search. The results are validated by traditional Fisher statistics and by permutation test based on the Fisher statistics. The details of the program has been provided on the site (Sourceforge, 2020), and the descriptions has been provided by Favorov with co-authros (Favorov *et al.*, 2005). Currently, this algorithm has been successfully applied in numerous multilocus association studies (Tsareva *et al.*, 2011; Timasheva *et al.*, 2019; Mamedov *et al.*, 2020). Following the procedure, men and women samples were split into two parts accordingly to the median values, low and high numbers of children born standardized for age/

number of children died, standardized for age. The differences in alleles' distributions, genotypes, and their combinations between these two categories of individuals were analyzed with the APSampler software. Independent validations of the results obtained by the APSampler software were tested using the exact Fisher's ($p_F$) and the permutation ($p_{perm}$) tests, based on the results of the exact Fisher's test. The vector of high and low numbers of children labels was permuted in a balanced way by assigning the same number of high number of children and low number of children individuals to two groups generated by permutation. The permutation test was repeated 100 times, and all possible combinations with the same number of alleles as the pattern considered were examined. For each permutation and each combination, a test of association was computed and the fraction of these tests that were larger than the observed test for the pattern was counted. The combination of the Fisher's exact P-value < 0.05 and the standard permutation $p \leq 0.05$ was considered a significance cut-off.

Allele frequencies and Hardy-Weinberg Equilibrium (HWE) tests were calculated in GenAlEx v.6.503 software (Peakall & Smouse, 2006; Peakall & Smouse, 2012). Probability values obtained in five HWE tests were corrected using the Benjamini-Hochberg method (Benjamini & Hochberg, 1995).

*Ethical statement*

Both the Commission for Science and Technology of Tanzania (Permits 2008-238-ER-2005-126, 2009-243-CC-2009-151, 2014-101-CC-2009-151), the National Institute for Medical Research (NIMR/HQ/R.8a/Vol. IX/458, dated September 5, 2006) and the Scientific Council of the Institute of Ethnology and Anthropology of the Russian Academy of Sciences (protocol number 1, dated February 19, 2015) approved the protocols used to recruit participants and to collect data before conducting this study. All subjects gave their informed, verbal, or written consent before participation. Verbal consent was deemed appropriate, given the low literacy rates of our participants.

## Results

The mean number of children born, as well as survived till the age of 5 y. for 520 men and 415 women in four age groups are presented in Table 1 and Figure 2. Women had more children born and survived in the first and second age groups, and the differences were significant, with the effect sizes from small to medium. In the third age group, men had more children in both categories, but these differences were not significant. In the oldest age group, men overtake women by the number of children born and survived, and these differences were significant, with small and medium effect sizes accordingly (Tab. 1, Fig. 2).

Before analyzing associations between the gene polymorphisms and the tested parameters of reproduction (number of children born/died/survived), the allele frequencies for six loci were tested for equilibrium using the Hardy-Weinberg test (Supplementary Material, Tab. 2). Due to a hemizygote status of the AR(CAG) locus located on the X chromosome, it was excluded from the analysis on the Hardy-Weinberg equilibrium (HWE). It was clear from the results that the genotype distributions of the four loci fitted well to HWE. The only exception was the DRD4E3 locus, which genotypes distribution departed from HWE. However, this does not prevent searching for associations of the loci studied with the numbers of born and dead/alive children.

To reveal the standardized number of children born, we regressed the real number of children per person for age. To measure the standardized number of children died, we first selected those respondents who reported at least one offspring born. On the next step, we estimated the differences between the number of children born and those remained alive till the age of 5 y. for each respondent. This amount has been regressed for age. These obtained figures were presented as a variable, entitled "the number of children died controlled for age". In this case, the minimum represented an adjusted maximum of children remained alive standardized for age, and maximum – the maximum number

of children died controlling for age. The association analysis between the number of children born with control for age and six polymorphisms was conducted on 787 individuals (457 males and 330 females). The six-way ANCOVAs with two-way interactions have been conducted for the number of children born/died, standardized for age as dependent variables, and polymorphic variants of *DRD4*, *COMT*, *MAOA*, *5HTT*, *OXTR* as fixed factors and AR-CAG as covariate (Supplementary Material, Tab. 3, 4). The main effects of the six tested polymorphisms and their two-way interactions were responsible for 5.4% of the total variation of the number of children born in men (Supplementary Material, Tab. 3). The only significant associations revealed were: the main effect of *COMT* (SS=6.086, F=5.824, p=0.016, $\eta^2$=0.013) and the interaction effect *COMT* × AR(CAG)n (SS=6.450, F=6.172, p=0.013, $\eta^2$=0.014). The same analysis, conducted for women, demonstrated that the six polymorphisms explained 13.3% of the total variation in the number of children born (Supplementary Material, Tab. 4). The following significant associations were found: DRD4E3 (SS=7.142, F=7.543, p=0.006, $\eta^2$=0.024), *COMT* × *OXTR* (SS=7.187, F=3.795, p=0.024, $\eta^2$=0.025), DRD4E3 × AR(CAG)n (SS=6.338, F=6.694, p=0.010, $\eta^2$=0.022). There were no any significant gene associations for the number of children died, controlled for age in men (Supplementary Material, Tab. 5), and only one significant interaction effect, revealed for women, *COMT* × *OXTR* ($R^2$=0.088, SS=6.794, F=3.308, P=0.038, $\eta^2$=0.024) (Supplementary Material, Tab. 6). In all cases, the effect sizes were small.

According to the ANCOVA analysis results, men with a higher number of AR-CAG repeats from the group of *COMT VV* carriers had more offspring. Women carriers of the following genotypes were more fertile: the non-carriers of the DRD4E3 +7 allele with a higher number of AR-CAG repeats, carriers of *OXTR GG* allele in combination with *COMT* M alleles. At the same time, it was found that more children died in women carriers of *OXTR AA* in association with *COMT M* genotypes.

On the next step, the joined effects of the six gene candidates on the number of children born/died/survived were tested using APSampler software (Supplementary Material, Tabs. 7-10).

Allele/genotype combinations of the six genes studied differing in the carriage between the men with low and high numbers of children born have been presented in Supplementary Material, Table 7. The top-ranked combination associated with low number of the born children in fathers was 5HTTLPR*La+DRD4E3*4+OXTR*A ($p_F$= 0.00098, $p_{perm}$=0.0125, odds ratio (OR)=0.55) (Supplementary Material, Tab. 7). Significant biallelic and monoallelic combinations were the three-allelic combination subsets, reliably differentiated between the fathers with low and high numbers of born children ($p_F$=0.002–0.005; $p_{perm}$=0.016-0.024 OR=0.63–0.59). All these allele combinations or patterns taken together testify in favor of the listed alleles' cumulative effects. This may be approximated to the additive effect of the three genes, each of which could be employed as an independent but less significant marker for the low or high number of children. Nevertheless, *A* allele of rs53576 (*OXTR* gene) became a member of the four combinations of alleles, which may indicate the strength of the influence of this locus. Suggested, the minus effect of the *A* allele on the number of born children increases with this allele dose. The opposite, e.g., positive effect of the homozygote *GG* ($p_F$=0.0054, $p_{perm}$=0.0244, odds ratio (OR)=1.59) was demonstrated as well. The last two allele combinations present a weak influence on the number of born children estimated by very low odd ratio values (0.15-0.12). The last one is even insignificant by the probability value of the permutation test (highlighted with red). The penultimate combination represents alleles of the other two loci, *MAOA* and AR-CAG. The frequencies of the *19* and lower numbers alleles up to allele *12* were higher in the group of low fertility fathers than in the group of higher fertility fathers, although this difference is insignificant (Supplementary Material, Tab. 7).

For the number of born children in mothers, the results were more complicated

***Tab. 1 - Sex differences in number of born and alive children in four age cohorts.*** **95% =95% CONFIDENCE INTERVAL OF THE DIFFERENCE**

| PARAMETERS | AGE COHORT | SEX | *N* | MEAN | SD | T | DF | P | 95% | | EFFECT SIZE |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | LOWER | UPPER | |
| **Number of born children** | <=29 years old | male | 163 | 0.890 | 1.186 | -6.460 | 312 | 4.0079E-10 | -1.360 | -0.725 | 0.695[a] |
| | | female | 178 | 1.933 | 1.761 | | | | | | |
| | 30-39 years old | male | 142 | 3.380 | 2.514 | -3.966 | 232 | 0.000097 | -1.871 | -0.629 | 0.531[b] |
| | | female | 92 | 4.630 | 2.085 | | | | | | |
| | 40-49 years old | male | 101 | 5.901 | 3.509 | -0.487 | 167 | 0.627 | -1.244 | 0.752 | 0.076[b] |
| | | female | 68 | 6.147 | 2.739 | | | | | | |
| | >=50 years old | male | 114 | 8.921 | 5.378 | 3.108 | 188 | 0.002 | 0.716 | 3.204 | 0.420[b] |
| | | female | 77 | 6.961 | 3.330 | | | | | | |
| **Number of alive children** | <=29 years old | male | 74 | 1.811 | 0.987 | -2.768 | 180 | 0.006 | -0.749 | -0.125 | 0.381[b] |
| | | female | 129 | 2.248 | 1.231 | | | | | | |
| | 30-39 years old | male | 118 | 3.381 | 1.939 | -1.176 | 207 | 0.241 | -0.832 | 0.210 | 0.165[a] |
| | | female | 91 | 3.692 | 1.836 | | | | | | |
| | 40-49 years old | male | 99 | 5.121 | 3.058 | 0.272 | 162 | 0.786 | -0.757 | 1.000 | 0.045[a] |
| | | female | 65 | 5.000 | 2.312 | | | | | | |
| | >=50 years old | male | 110 | 6.418 | 3.569 | 3.710 | 185 | 0.000 | 0.756 | 2.470 | 0.532[b] |
| | | female | 77 | 4.805 | 2.373 | | | | | | |

Sex differences presented according to Student's T test (t—test statistics, SD – Std. Deviation, df – degrees of freedom, p – statistical significance).

Effect size in case of same sample size or different sample sizes ([a] - Cohen's *d*; [b] - Hedges' *G*).

(Supplementary Material, Tab. 8). There was no top-ranked allele combination covering the most number of loci and 13 combinations in total, with the last one being insignificant due to the permutation test ($p_{perm}$=0.051). The most representative was the locus *COMT*-rs4680, its alleles were presented in eight combinations out of 13. The data revealed that the most powerful combination at this locus was a heterozygote *MV*. Most often, alleles of this locus were combined with allele *4* of the *MAOA*-(VNTR) locus and with the *AR*-CAG 24 repeats and higher. The *OXTR* locus appeared significant either in combination with the *COMT* locus or with the *AR*-CAG locus. Therefore, we can conclude that a high number of children in women were associated with a combination of polymorphisms in *COMT*, *OXTR,* and *AR*-CAG genes.

Interestingly, the frequency of alleles ranged from 24 to 28 repeats in *AR*-CAG locus was significantly higher in high fertility mothers than in mothers with a low number of children (n=0.003) (Supplementary Material, Tab. 8). Two loci, 5HTTLPR and DRD4E3, showed up only once and may be ignored. We also concluded that the interactions between the four loci's alleles were complex and ambiguous with some epistatic effects.

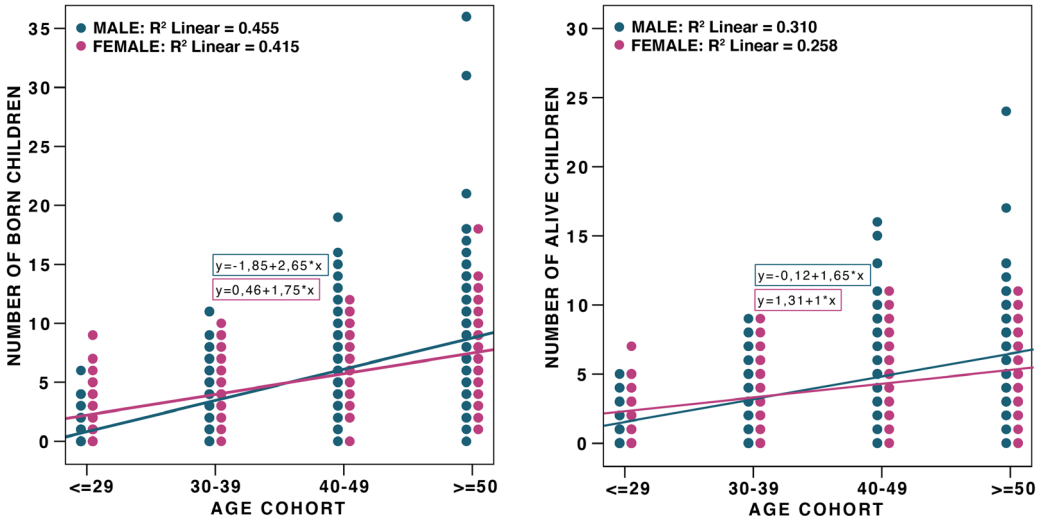


***Fig. 2 – Sex differences in number of born and alive children in four age cohorts. The colour version of this figure is available at the JASs website.***

Concerning the number of dead children in fathers, two opposite blocks of results were obtained (Supplementary Material, Tab. 9). A little group consisted of two allele patterns, *COMT*V* and DRD4E3**5R*, and just DRD4E3**5R* that were significantly more common in fathers with a higher number of children survived/low number of dead children. On the other hand, the allele *COMT*V* was found in association with a higher number of children died as well, in combination with other genes polymorphic variations. We suggested that this could be evidence of epistasis. Hence, this allele's association with the children's mortality/survival in fathers cannot be considered reliable.

On the other hand, allele *5R* of the DRD4E3 VNTR locus was significantly associated with a higher infant survival/reduced mortality of children in fathers (Supplementary Material, Tab. 9). In another group of allelic combinations, all six studied loci's alleles were involved, but only two alleles, *22* and *25*, of locus *AR*-CAG, occurred in all significant combinations (Supplementary Material, Tab. 9). Alleles of other loci were either rare, or their involvements in associations were generally contradictory. The alleles *A* and *G* of the *OXTR* rs53576 locus were such an example. Again, this may be due to epistatic gene interactions. In this study, the alleles *22* and *25* were associated with reduced child survival in fathers with a high probability of 0.0096 and 0.0119, respectively.

A smaller number of significant allelic combinations were identified in women using APSample tests, and their significance, judging by the probability of permutation tests, was lower (Supplementary Material, Tab. 10). Again, the *AR*-CAG locus was noted. The frequency of allele *22* repeatedly showed itself and was significantly higher (n=0.0465) in mothers with increased child survival/fewer children died.

## Discussion

We have demonstrated that the reproductive history of men and women in our sample were in line with expectations for the cultures with natural reproduction profile (no modern contraceptives being used, limited access to medical help). The study population from rural Northern Tanzania was still below the demographic transition point and exhibited a high

fertility level. Women were enrolled in reproduction in younger ages, compared to men, and outnumbered men by the number of children born (and survived till the age of 5 y.) in younger age cohorts. After the age of 40 y. men outnumbered women in the amount of offspring, again in line with expectation, given that women in their 40$^{th}$ were entering the menopausal stage, while men were still actively reproducing (being engaged in subsequent monogamous marriages, accumulating more wives in polygynous marriages, or getting partners in extra marriage relations).

It would be an oversimplification to expect that one of the sex gene candidates selected for this study may be responsible for expressions of the whole complex behavioral strategies related to reproductive success. However, we suggest that our data may be helpful for the understanding of possible adaptive benefits associated with these six genetic polymorphisms related to fertility and infant survival.

According to our knowledge, this is the first study testing the associations of six selected gene candidates with fertility and parenting care in men and women from rural traditional East African populations. Our data analysis, conducted by GLM ANCOVA and APSample tests, confirmed that the gene-candidates selected for this study had been associated with reproductive success (expressed in the number of children born and survived till the age of 5 y.). We have also demonstrated the presence of epistasis effects. These findings are not unexpected, given the complex multigene nature of tested traits. Men carriers of the combination of the three alleles, 5HTTLPR**La*, DRD4E3**4R,* and *OXTR*A*, had a lower number of offspring.

Conversely, the higher number of *AR* repeats combined with *COMT*VV* genotype was a positive predictor of men's reproduction. Polymorphisms of four out of six tested genes, *COMT*, *MAOA*, *OXTR,* and *AR*-CAG, were associated with women's reproduction. The presence of *COMT*V* allele, in combination with *OXTR*G* allele, *MAOA*4R,* and *AR*-CAG numbers equal to or higher than *24* repeats, were more frequent indicators of high fertility in females.

Our results revealed that more offspring survived in men carriers of DRDE3**5R,* and DRDE3**4R* in female carriers. The sex-specific effect of *AR*-CAG repeat numbers has been found. Men carriers of *22* and *25* repeats revealed lower children's survival, whereas women carriers of *22 AR*-CAG repeats revealed higher infant survival. It should be mentioned that the effect sizes of gene associations in our study were small. However, this is quite usual when the study concerns the gene phenotype trait data (Schinka *et al.*, 2004; Hysi *et al.*, 2014; Strawbridge *et al.*, 2018).

Except for the *AR*-CAG polymorphism, which may be directly related to fertility in males (Nielsen *et al.,* 2010; Lukaszewski & Roney, 2011; Simmons & Roney, 2011; Butovskaya *et al.,* 2013, 2015a), the rest of the gene-candidates seem to have more associations with personality qualities, empathy, cooperation and attachments between reproductive partners and parental qualities. Particularly, the *OXTR*G* allele in our study was associated with a higher number of children born, both in men and women and these are in line with earlier findings on higher empathy and attachment qualities of the *OXTR*G* allele carriers (Costa *et al.,* 2009; Rodrigues *et al.,* 2009; Chen *et al.*, 2011; Laursen *et al.,* 2014; Feng *et al.,* 2015; Cattaneo *et al.,* 2016; Theofanopoulou *et al.,* 2018). Our findings on the association of DRD4E3**4R* and **5R* carriers with better children survival may support earlier reported data on the association of the lower offspring investment strategy with the DRD4**7R* carriage (Eisenberg *et al.*, 2007). Earlier it was suggested that extraversion and neuroticism might be reliably associated with reproductive behavior in humans. However, these traits may be sex-specific (Penke & Jokela, 2016). The phenotypic relationships, with extraversion being positively, and neuroticism negatively associated with the number of children in Western populations (Jokela *et al.*, 2009; Jokela *et al.*, 2010; Jokela *et al.*, 2011; Berg *et al.*, 2013; Berg *et al.*, 2014; Berg *et al.*, 2016). The opposite results for the rural Senegalese women have been reported (positively associated neuroticism level with offspring number) (Alvergne *et al.*, 2010a).

The associations between personality and fertility may be environmental-specific (both ecological and cultural factors considered), but the common biological factors that underlie personality variation and reproductive functions may still exist (Berg *et al.*, 2016).

The pool of gene-candidates tested in this study demonstrated a more obvious relationship with reproduction (the number of children born) than with infant survival, both in men and women. One possible explanation may lie in the fact that tested gene polymorphisms may be more in association with marriage satisfaction and attachment between partners, rather than with direct parental investments (Butovskaya & Smirnov, 2005). The sexual selection pressure has been acting in the direction of more caring, kind, and more cooperative permanent partners, and the genes associated with personality traits may be involved in the first-rate (Buss, 1989; Weisfeld & Weisfeld, 2002; Weisfeld *et al.*, 2011; Olcay Imamoğlu *et al.,* 2019). Love and commitment have been positively and consistently related to both sexes' reproductive success in traditional hunter-gatherers (Sorokowski *et al.*, 2017). The oxytocin signaling system may operate with the dopaminergic signaling systems synergistically to excerpt various complex effects on cognition (Quintana *et al.*, 2019). Acevedo with co-authors recently presented evidence that romantic love is orchestrated by dopamine-, vasopressin- and oxytocin-rich brain regions in humans and monogamous animals (Acevedo *et al.,* 2020). Other studies also reported the links between the *OXTR* gene expression and marital quality, partner responsiveness, and attachments (Khajehei & Behroozpour, 2018; Acevedo *et al.,* 2019; Mattson *et al.,* 2019; Ponzi, & Dandy, 2019). The data from Western Societies showed that individuals who had the *OXTR* rs53576 *GG* genotype or had a spouse with the rs53576 *GG* genotype reported greater marital satisfaction and greater attachment security than individuals with *AA* or *AG* genotypes (Monin *et al.,* 2019). According to other findings, the DRD4E3**7R* genetic polymorphism has been negatively correlated with romantic love (Acevedo *et al.,* 2020) and positively with promiscuity (Garcia *et al.,* 2010; He *et al.*, 2018). Our gene candidate associations study, conducted in traditional rural East African population, pointed to similar allele/genotype makers concerning high/low fertility in men and women.

Our data failed to demonstrate clear associations between the selected gene-candidates and infant survival in both sexes may be due to several reasons. Humans are cooperative breeders (Meehan & Hawks, 2013; Burkart *et al.* 2017; Hrdy & Burkart, 2020). Although, in traditional African populations, the mother-infant caretaking model is clearly expressed, and mothers' vital role in infants' survival had been demonstrated (Hewlett & Lamb, 2002), alloparenting is highly widespread (Hrdy, 2017). It is mothers and fathers and a broad pool of relatives and parent's friends who are investing in children's survival and well-being in traditional societies (Crittenden & Marlowe, 2013; Pavard *et al.,* 2007). The investment of other caregivers, particularly maternal and paternal kin, in childcare has been reported in many non-industrial societies with different marriage patterns (Dyble *et al.,* 2015; Konner, 2016). Studies suggested that polygyny poses a challenge for infant survival in West Africa (Amey, 2002), but the role of grandmothers, aunts, older siblings, and other caregivers under these conditions remained highly significant.

Sanchez-Roine with co-authors currently suggested that different strategies (direct and indirect), increasing the chances of children survival, may be associated with various gene-personality associations (Sanchez-Roige *et al.,* 2018). Indeed, on the one hand, the caring-mother strategy, associated with a secure attachment style (Meins *et al.,* 2018), is beneficial. Our findings may be represented by women with a lower level of androgenization (higher *AR*-CAG numbers) and the presence of the *OXTR* rs53576 *G* allele. The polymorphism in *OXTR* rs53576 may play a particular role in the development of sensitive parenting. Carriers of the *G* allele (homozygous *GG* genotype) were described as more sociable, trustful, empathic to others, and supportive (Li *et al.*, 2015; Feldman *et al.,* 2016). Our data also suggested that children of the

DRD4E3*7R non-carriers survived better, both in men and women. Consequently, we suggest that: 1. our study revealed that combination of *OXTR*, 5HTTLPR, DRD4E3, and *AR* polymorphisms have been related to reproduction and has to be tested more carefully in the future in the context of permanent partner's attachment, marital satisfaction, and their reproductive success; 2. the APSampler methodology may be used as a valuable instrument in search of the genetic markers of fertility and parenting, associated with personality and behavioral strategies; 3. more studies have to be conducted in populations with natural reproduction profiles to reveal how general the results of our study are.

Our study has some limitations. No genetic tests for paternity were completed. Hence the number of children fathered by males may be in question. Although, given that our interviews were collected in one to one settings, without the presence of any other group members, and participants commented quite readily about the cases of extrapair offspring and the number of children razed by their wives, fathered by other men. Hence, our data on the number of children fathered by respondents may be close to reality. As demonstrated recently, in Himba, the traditional pastoralist culture from Namibia, where the rate of extrapair paternity is high, both men and women may be very accurate at detecting such cases. Under these circumstances, the high rate of extrapair paternity can be accompanied by high paternity confidence (Scelza *et al.*, 2020). Another limitation concerns the limited number of gene-candidates tested, given the current trend for applying the genome-wide association studies (GWAS) for testing the various genetic effects on fertility in humans (Kim & Lee, 2019; Mathieson *et al.,* 2020). It is also apparent that the gene-candidates selected for this study with the one possible exception (the *AR* gene) were not directly related to fertility and reproduction in terms of morphology or physiology. We have not considered some essential factors, earlier reported to mediate the genetic influence on human fertility and reproduction, such as the socioeconomic factors, particularly, years of education (Weeden *et al.,* 2006; Barban *et al.*, 2016; Kong *et al.*, 2017), intelligence (Meisenberg, 2010), or antisocial behavior (Tielbeek *et al.,* 2017), as well as the age of the first sex, both in men and women (Day *et al.*, 2016), time of menopause in women (Laven *et al.,* 2016; Moorad & Walling, 2017; Yang *et al.,* 2019). All these factors have to be considered in future studies to provide more sound conclusions on the investment of genes related to personality in associations with reproductive success and child survival in humans.

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## Ethics declarations

*The authors declare no competing interests.*

## Info on the web

http://worldpopulationreview.com/countries/total-fertility-rate/
*Total Fertility Rate in world populations*

http://www.healthdata.org/tanzania
*Health data of Tanzania*

https://sourceforge.net/projects/apsampler/
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