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ARTICLE

Array comparative genomic hybridization analysis of small supernumerary marker chromosomes in human infertility

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Dr Narjes Guediche, MD, was born in Lausanne, Switzerland in 1982. She graduated from Medical School at Sousse University, Tunisia in 2008. There, she was resident in the Department of Cytogenetic and Reproductive Biology (A Saad). She completed and finished her residency in histology and embryology in France, where she is currently pursuing a PhD at Paris-Sud University. Under the supervision of G Tachdjian in the Cytogenetic and Reproductive Biology Center at Antoine Béclère Hospital in Clamart, Narjes is undergoing in-depth studies on small supernumerary marker chromosomes and infertility. Her fields of interest are genetic reproduction, IVF and embryo development.

Abstract Small supernumerary marker chromosomes (sSMC) are structurally abnormal chromosomes that cannot be unambiguously identified by conventional banding cytogenetics. This study describes four patients with sSMC in relation with infertility. Patient 1 had primary infertility. His brother, fertile, carried the same sSMC (patient 2). Patient 3 presented polycystic ovary syndrome and patient 4 primary ovarian insufficiency. Cytogenetic studies, array comparative genomic hybridization (CGH) and sperm analyses were compared with cases previously reported. sSMC corresponded to the 15q11.2 region (patients 1 and 2), the centromeric chromosome 15 region (patient 3) and the 21p11.2 region (patient 4). Array CGH showed 3.6-Mb gain for patients 1 and 2 and 0.266-Mb gain for patient 4. Sperm fluorescent in-situ hybridization analyses found ratios of 0.37 and 0.30 of sperm nuclei with sSMC(15) for patients 1 and 2, respectively ($P < 0.001$). An increase of sperm nuclei with disomy X, Y and 18 was noted for patient 1 compared with control and patient 2 ($P < 0.001$). Among the genes mapped in the unbalanced chromosomal regions, *POTE B* and *BAGE* are related to the testis and ovary, respectively. The implication of sSMC in infertility could be due to duplication, but also to mechanical effects perturbing meiosis.

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KEYWORDS: array CGH, infertility, small supernumerary marker chromosome, spermatozoa

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Introduction

Small marker chromosomes are structurally abnormal chromosomes that cannot be unambiguously identified by conventional banding cytogenetics. They are frequently supernumerary and occur at a frequency of about 0.3–0.5/1000 in humans (Liehr et al., 2004). Most small supernumerary marker chromosomes (sSMC) are derived from short arms and pericentric regions of acrocentric chromosomes. Those derived from nonacrocentric autosomes occur with a frequency of 40% of total sSMC (Liehr, http://www.med.uni-jena.de/fish/sSMC/00START.htm).

The most common sSMC in human is derived from chromosome 15 and it accounts for as much as 25–30% of all sSMC observed (Liehr, http://www.med.uni-jena.de/fish/sSMC/00START.htm). In addition, sSMC(15) occurs predominantly as small pseudodicentric chromosomes referred to as psu dic(15;15) or inv dup(15) (Koç et al., 2009). The risk of phenotypic abnormalities associated with detection of sSMC(15) depends essentially on the presence of the Prader–Willi/Angelman syndrome critical region (PWACR). Carriers of sSMC(15) without euchromatin or only proximal euchromatin that do not contain PWACR are expected to be normal except for recurrent miscarriage and an increased risk of spermatogenesis impairment in men (Koç et al., 2009; Manvelyan et al., 2008). It is currently thought that spermatogenesis impairment due to the presence of chromosomal abnormalities including sSMC is the main cause of oligoasthenoteratozoospermia (OAT) (Koç et al., 2009; Mau et al., 1997). In familial cases, sSMC are predominantly inherited via the maternal line and may lead to infertile male offspring while females present a normal fertility (Liehr, 2006).

The frequency of sSMC(21) is much lower than that of sSMC(15) (Manvelyan et al., 2008). Until now, this cytogenetic finding has not been clearly associated with infertility or other phenotypic modifications. As far as is known, more than 1000 cases of sSMC(15) and 36 cases of sSMC(21) have been previously described and analysed by fluorescent in-situ hybridization (FISH) (Ahlbom et al., 2003; Bakshi et al., 2008; Baldwin et al., 2008; Battaglia, 2008; Cotter et al., 2000; Eggermann et al., 2002; Huang et al., 1997; Koç et al., 2009; Liehr, http://www.med.uni-jena.de/fish/sSMC/00START.htm; Manvelyan et al., 2008; Oracova et al., 2009; Paetzold et al., 2006).

Nevertheless, for these reported cases of sSMC(15) and sSMC(21), only Wang et al. (2004) has studied the size, chromosomal regions and genes involved by array comparative genomic hybridization (CGH). Thus, a genotype–phenotype correlation is difficult to establish. The current paper describes three cases of sSMC(15) and one case of sSMC(21) presenting infertility. Conventional and molecular cytogenetic as well as phenotypic findings are compared with previously reported cases.

Clinical reports

Patients 1 and 2

Patient 1, a 39-year-old North African man, presented with primary infertility and was referred for preconceptional genetic counselling. His parents were a healthy nonconsanguineous couple. He had a 47-year-old brother (patient 2) who had two healthy children. Except for the infertility for patient 1, the probands were phenotypically normal. There was no familial history of infertility, congenital anomalies or mental retardation.

Patient 3

Patient 3 was a 42-year-old caucasian woman referred for primary infertility. Her parents were a healthy nonconsanguineous couple. Patient 3 and her husband had no other reported health problems. There was no familial history of infertility, congenital anomalies or mental retardation.

Patient 3 presented with 5 years of infertility related to polycystic ovary syndrome. Physical examination proved normal. Laboratory data showed high LH concentrations (17.8 IU/ml) (normal values during the follicular phase: LH: 0.5–6 IU/ml). There were no other biological endocrinal anomalies such as hypocorticism or hypothyroidism. She had undergone successful IVF in 2005 that gave a monofetal pregnancy. During this pregnancy, amniocentesis was performed due to maternal serum screening. Fetal karyotype was 47,XY,+mar. After genetic counselling, the couple decided to continue the pregnancy and a healthy boy was born in 2006. Parental karyotypes showed that the marker was inherited from the mother. The couple had then three transfers with frozen embryos. The third one was successful but the pregnancy was terminated due to a cytomegalovirus seroconversion. The fetal karyotype was 46,XX.

Patient 3 then had a spontaneous pregnancy. Fetal karyotype on amniocytes was realized and showed the presence of the maternally inherited small supernumerary marker chromosome. A girl was born and is phenotypically normal.

Patient 4

Patient 4 was a 40-year-old North African woman that consulted for primary ovarian insufficiency (POI). Her parents were healthy and nonconsanguineous. She had five brothers and five sisters. All her brothers, except one, had healthy children and reported no particular health problems. The oldest sister was 48 years old and had three children. She presented secondary amenorrhoea at the age of 41. The other four sisters were all nulligest and had no child desire at the time of the investigation. The parents and family members were unavailable for chromosome analysis.

Patient 4 had her first menstrual period when she was 13 years old. Her menstrual cycles were regular. She presented a secondary amenorrhoea at the age of 33. Physical examination proved normal. Laboratory data showed high FSH and LH concentrations (88 IU/ml and 28 IU/ml, respectively) and low oestradiol concentration (<0.2 ng/ml): normal values during the follicular phase were 2–10 IU/ml FSH, 0.5–6 IU/ml LH and 20–150 ng/ml oestradiol). There were no other biological/endocrinological anomalies such as hypocorticism or hypothyroidism. A pelvic ultrasound at the age of 40 showed a normal median uterus. The left ovary showed no follicles. The right ovary could not be seen.

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