

Two further cases of the 8p23.1 duplication syndrome

Sophie Laird¹, Mark Bateman¹, John Barber², Simon Thomas¹, Frideriki Maggouta¹, Samantha Baker¹, Nicola Savage¹, Caroline Price¹, Denise Maxwell¹, Sarah Jones¹, Nicola Foulds³, John Crolla¹

(1) Wessex Regional Genetics Laboratory, Salisbury NHS Foundation Trust Salisbury. (2) Human Genetics Division, University of Southampton School of Medicine, Southampton. (3) Wessex Clinical Genetics Service, Southampton University Hospital NHS Trust, Southampton



Introduction

The 8p23.1 duplication syndrome is a rare disorder associated with a variable phenotype that may include developmental delay, speech delay, mild facial dysmorphism (including prominent forehead and arched eyebrows), and congenital heart disease (CHD). The estimated prevalence of this syndrome is 1 in 64,000 and, to date, only 11 cases have previously been reported in the scientific literature.

Implicated Genes

It is thought that the duplication of the *GATA4* (OMIM *600576) and *SOX7* (OMIM *612202) transcription factors underlie the heart defect component of this syndrome. *SOX7* has also been linked to developmental delay and the *TNKS* gene (OMIM *603303) for behavioural difficulties.

Diagnosis

The duplication that categorises this syndrome is located between the 8p23.1 olfactory receptor/defensin repeats (ORDRs) at REPD in distal 8p23.1 (REPeat Distal) and REPP (REPeat Proximal) in proximal 8p23.1. The ORDRs display a degree of copy number variability, and for diagnosis of the 8p23.1 duplication syndrome, the aberration must be distinguished from the 8p23.1 euchromatic variant which is cytogenetically identical. In this instance, fluorescence *in situ* hybridisation and array comparative genomic hybridisation were used to diagnose a genuine pathogenic duplication.

PROBAND 1 ♂ premature 33 +3 weeks weighing 2.2Kg.

Problems at birth: cleft hard/soft palate with cleft lip, unilateral; respiratory distress; multiple ventricular septal defects (VSDs); congenital stenosis of aortic valve (AS); and congenital pulmonary valve stenosis.

At 8 weeks: no other evidence of cardiac decompensation (later [11 weeks] admitted for elective ballooning of aortic valve). Neurologically, patient was developing well, although truncal tone appeared to be slightly reduced and he demonstrated a head lag.

PROBAND 2 ♂ premature 29+4 weeks weighing 1.5Kg.

Problems at birth: respiratory distress; coarctation of the aorta; ventricular septal defect (VSD); patent ductus arteriosus; bacterial sepsis/septicaemia; suspected necrotising enterocolitis; and neonatal jaundice due to infection.

At 8 weeks: deranged LFTs and hyperbilirubinaemia, the latter thought likely to be caused by hepatitis. Patient 2 was also found to have hydrocele (collection of fluid in scrotum), for which no treatment was required at that time. **At 3 months,** a slight head tilt was noted.

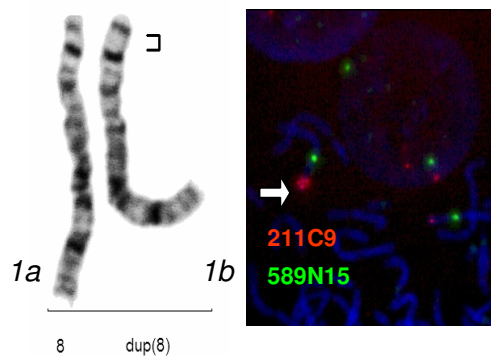


Figure 1- 1a A partial karyotype of Proband 1. Note the increased interval between 8p22 and 8p23.2 (see bracket). **1b** Representative dual colour FISH in metaphases from Proband 1; a duplication of RP11-211C9 (red).

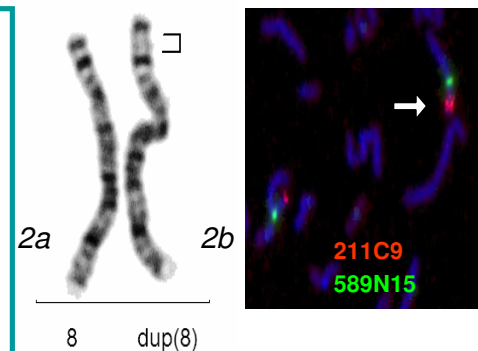


Figure 2- 2a A partial karyotype of Proband 2. Note the increased interval between 8p22 and 8p23.2 (see bracket). **2b** Representative dual colour FISH in metaphases from Proband 2; a duplication of RP11-211C9 (red).

Conventional karyotyping revealed an 8p23.1p23.1duplication in Proband 1 and Proband 2, see **figure 1a** and **2a**, respectively. Parental follow-up studies showed that both duplications had arisen *de novo*.

Molecular cytogenetic analysis Dual colour fluorescence *in situ* hybridisation (FISH) using in-house BAC probes RP11-122N11, RP11-211C9, RP11-589N15, and RP11-24D9 determined that the aberration was the pathogenic duplication of 8p23.1 in both patients, see **figure 1b** and **2b**.

Molecular analysis PCR analysis of microsatellites within the duplicated region of family 1 gave 3 fully informative results and showed that the duplication in Proband 1 is maternal and intrachromosomal in origin (i.e. unequal exchange between sister chromatids), see **figure 3**. PCR analysis of family 2 was limited due to an absence of a paternal DNA sample but it appears that the duplication in Proband 2 is also maternal and intrachromosomal in origin, see **figure 4**.

Array comparative genomic hybridisation (aCGH) confirmed the duplication and excluded any additional pathogenic copy number variants in either patient.

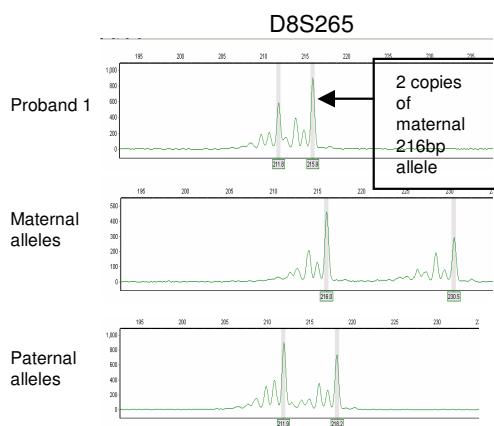


Figure 3 Microsatellite analysis for the locus D8S265 showing 2 copies of the maternal 216bp allele in Proband 1.

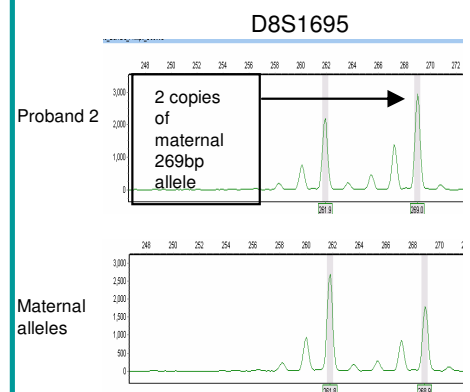


Figure 4 Microsatellite analysis for the locus D8S1695 showing 2 copies of the maternal 269bp allele in Proband 2.