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LETTER

# Incidence of microduplication 22q11.2 in patients referred for FISH testing for velo cardiofacial and DiGeorge syndromes

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Microduplication of 22q11.2 has recently emerged as a new chromosomal syndrome. The first patient was described by Edelman *et al*.[1] More recently, Ensenauer *et al*[2] reported a series of patients with microduplication of 22q11.2 ascertained from a population of patients referred for FISH testing for velo cardiofacial syndrome (VCF) or DiGeorge syndrome (DGS). Of the 653 patients referred for VCF/DGS testing, 40 were found to have the 22q11.2 microdeletion (6.1%) and 13 had the microduplication (2%). Additional patients with the 22q11.2 microduplication have subsequently been reported.[3–5] To further evaluate the incidence of the 22q11.2 microduplication, we prospectively screened all VCF/DGS patient referrals over a two-year period from April 2003 through May 2005.

In total, 372 patients were referred for FISH testing with VCF/DGS as part of the clinical differential diagnosis. Patient samples were obtained with IRB approval. FISH analysis was performed using either the TUPLE1/ARSA probe set (Vysis, Downer's Grove, IL, USA) or the D22S75/n85a3 probe set (Cytocell, Banbury, UK) according to the manufacturers' instructions. In all, 20 metaphases were scored for the microdeletion by FISH in each patient. In addition, 50 interphase nuclei were scored to look for the additional signal associated with the 22q11.2 microduplication (Figure 1). In a control sample, both the TUPLE1 and D22S75 probes readily identified the microduplication at interphase, but somewhat less reliably at metaphase (Figure 1). The 22q11.2 microduplication control was independently confirmed using array CGH containing the TUPLE1 BAC clone (data not shown).

We identified 30 patients (8%) with 22q11.2 deletions by FISH on metaphase chromosomes from the 372 patients referred. No patients were identified with the 22q11.2 microduplication by interphase FISH.

The 22q11.2 deletion associated with VCF/DGS results from recombination at meiosis between flanking low-copy repeat sequences on chromosome 22.[6,7] The population incidence of the 22q11.2 microdeletion is estimated at 1/4000–1/6000.[8] Since the microdeletion is the reciprocal product to the microdeletion, there would likely be a similar population incidence (assuming no different selection against it).[2] Our data suggest that, in an unselected population of patients referred for VCF/DGS testing, the incidence of the microduplication might be lower than previously reported.[2] Our rate of 22q11.2 deletions in this patient population referred for VCF/DGS testing was 8%, compared to 6.1% reported by Ensenauer *et al*,[2] suggesting that these were comparable population samples.

While some reported patients have a phenotype that overlaps VCF/DGS,[2–4] Yobb *et al*[5] reported that the phenotype associated with the 22q11.2 microduplication

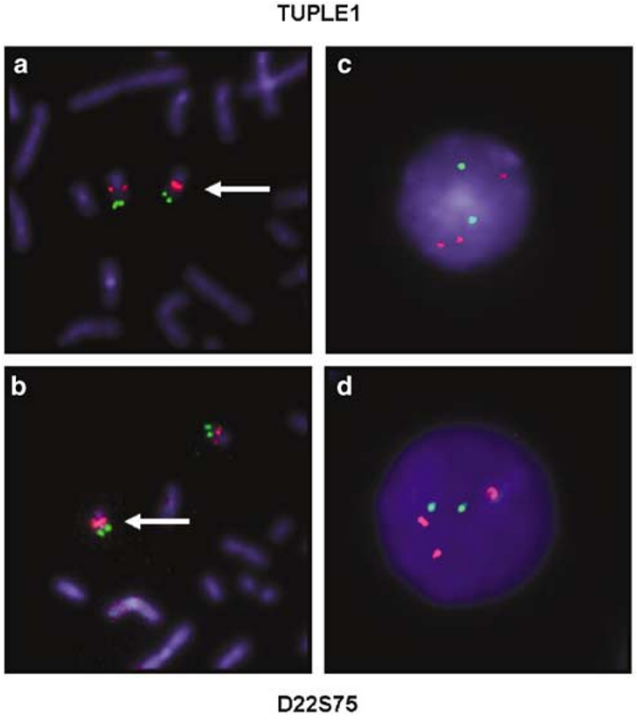


**Figure 1** FISH analysis for detection of the 22q11.2 microduplication in a control sample. Metaphase analysis with the (**a**) TUPLE1 and (**b**) D22S75 probes. The dup(22) is arrowed and shows a larger hybridization area. Interphase FISH analysis with (**c**) TUPLE1 and (**d**) D22S75, clearly showing an additional signal.

was extremely diverse. The phenotypic spectrum ranged from individuals who were classified as normal to those with developmental delay and multiple congenital anomalies. Only a few patients were found to have a phenotype overlapping the VCF/DGS phenotype. Interestingly, the incidence of microduplication 22q11.2 in Fragile X negative females was twice that seen in the VCF/DGS group.[5] Given this diversity in the phenotype, the lack of 22q11.2 microduplications in our VCF/DGS referral population is not surprising. While there is some overlap in phenotype, the identification of microduplications in the VCF/DGS population[2–4] may have been largely serendipitous, much like the identification of the 22qter deletion syndrome in some patients referred for VCF/DGS.[9]

Although the incidence of microduplication 22q11.2 might be low in the VCF/DGS population undergoing FISH testing, additional screening of interphase nuclei to look for a duplication would seem reasonable. A systematic evaluation of more diverse patient population, including normal individuals, will better characterize the frequency and phenotype for microduplication 22q11.2 syndrome and define a more appropriate target population for testing.

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