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**DOI**

[10.1136/hrt.2009.182642](https://doi.org/10.1136/hrt.2009.182642)

**Publication date**

2010

**Document Version**

Final published version

**Published in**

Heart

[Link to publication](#)

**Citation for published version (APA):**

van Engelen, K., Topf, A., Keavney, B. D., Goodship, J. A., van der Velde, E. T., Baars, M. J. H., Snijder, S., Moorman, A. F., Postma, A. V., & Mulder, B. J. M. (2010). 22q11.2 Deletion Syndrome is under-recognised in adult patients with tetralogy of Fallot and pulmonary atresia. *Heart*, 96(8), 621-624. <https://doi.org/10.1136/hrt.2009.182642>

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# 22q11.2 Deletion Syndrome is under-recognised in adult patients with tetralogy of Fallot and pulmonary atresia

Klaartje van Engelen,<sup>1,2,6</sup> Ana Topf,<sup>3</sup> Bernard D Keavney,<sup>3</sup> Judith A Goodship,<sup>3</sup> Enno T van der Velde,<sup>4</sup> Marieke JH Baars,<sup>2</sup> Simone Snijder,<sup>2</sup> Antoon F Moorman,<sup>5</sup> Alex V Postma,<sup>5</sup> Barbara JM Mulder<sup>1,6</sup>

<sup>1</sup>Department of Cardiology, Academic Medical Center, Amsterdam, The Netherlands

<sup>2</sup>Department of Clinical Genetics, Academic Medical Center, Amsterdam, The Netherlands

<sup>3</sup>Institute of Human Genetics, Newcastle University, Newcastle upon Tyne, UK

<sup>4</sup>Department of Cardiology, Leiden University Medical Center, Leiden, The Netherlands

<sup>5</sup>Heart Failure Research Center, Department of Anatomy and Embryology, Academic Medical Center, Amsterdam, The Netherlands

<sup>6</sup>Interuniversity Cardiology Institute of the Netherlands, Utrecht, The Netherlands

## Correspondence to

Dr K van Engelen, Department of Cardiology, Academic Medical Center, Meibergdreef 9, 1105 AZ Amsterdam, The Netherlands; [k.vanengelen@amc.uva.nl](mailto:k.vanengelen@amc.uva.nl)

Accepted 21 December 2009

## ABSTRACT

**Background** Three quarters of patients with 22q11.2 Deletion Syndrome (22q11.2DS) have congenital heart disease (CHD), typically conotruncal heart defects. Although it is currently common practice to test all children with typical CHD for 22q11.2DS, many adult patients have not been tested in the past and therefore 22q11.2DS might be under-recognised in adults.

**Objectives** To determine the prevalence of 22q11.2DS in adults with tetralogy of Fallot (TOF) and pulmonary atresia (PA)/ventricular septal defect (VSD) and to assess the level of recognition of the syndrome in adult patients.

**Methods** Patients were identified from CONCOR, a nationwide registry for adult patients with CHD. Inclusion criteria were diagnosis of TOF or PA/VSD and the availability of DNA. Patients with syndromes other than 22q11.2DS were excluded. Multiplex ligation-dependent probe amplification was used to detect 22q11.2 microdeletions.

**Results** 479 patients with TOF and 79 patients with PA/VSD (56% male, median age 34.7 years) were included and analysed. Twenty patients were already known to have 22q11.2DS. A 22q11.2 microdeletion was detected in a further 24 patients. Thirty-one patients with TOF (6.5%) had 22q11.2DS, whereas 13 patients with PA/VSD had 22q11.2DS (16.5%). Of all 22q11.2 microdeletions, 54% (24/44) were unknown before this study.

**Conclusion** This study shows that although the prevalence of 22q11.2DS in adults with TOF and PA/VSD is substantial, it is unrecognised in more than half of patients. As the syndrome has important clinical and reproductive implications, a diagnostic test should be considered in all adult patients with TOF and PA/VSD.

22q11.2 Deletion Syndrome (22q11.2DS) is the most common microdeletion syndrome in humans, with an estimated prevalence of at least one in 4000.<sup>1,2</sup> The features associated with 22q11.2DS include congenital heart disease (CHD), cleft palate, velopharyngeal insufficiency with hypernasal speech, hypocalcaemia, dysmorphic facial features and mild to moderate mental retardation, with a high variability in the number and severity of associated features (reviewed in Kobrynski and Sullivan).<sup>2</sup> CHD is present in approximately 75% of patients with 22q11.2DS, and typically constitutes conotruncal malformations such as interrupted aortic arch type B, truncus arteriosus communis, tetralogy of Fallot (TOF) and pulmonary atresia (PA) with ventricular septal defect (VSD).<sup>3,4</sup>

Psychiatric disorders, most notably schizophrenia, develop in up to two thirds of adults with 22q11.2DS.<sup>4–6</sup> Individuals with 22q11.2DS have a 50% chance of transmitting the deletion to his or her offspring.

In the early 1990s of the last century fluorescence in situ hybridisation became widely available as a diagnostic test for 22q11.2DS and it is currently common practice to test all children with typical CHD for 22q11.2DS. However, such a diagnostic test was not available at the time that many adult patients with CHD were children. Some adult patients will have been tested as the phenotype was defined and a diagnostic test became available, but this was not undertaken in a systematic way. The variable phenotype can make it difficult to recognise the syndrome, which may contribute to under-recognition in adults.<sup>5,7</sup> As more and more patients with CHD reach adulthood due to improved surgical techniques,<sup>8</sup> adult cardiologists will encounter an increasing number of patients with 22q11.2DS. Recognition of the syndrome is important, as it has significant clinical and reproductive implications for the patient.

The aim of this study was to determine the prevalence of 22q11.2DS in adult patients with TOF and PA/VSD and to assess the level of recognition of the syndrome in these patients.

## PATIENTS AND METHODS

Patients were selected from the CONCOR national registry database and DNA bank, which has been described in detail previously.<sup>9</sup> In short, CONCOR aims to facilitate research on the aetiology of CHD and its outcome. In August 2009, 10 942 patients with CHD aged 16 years and older had been included in the registry. Patients are contacted through their cardiologist or advertisements in the local media. Approximately 75% of registered patients originate from tertiary referral centres. Diagnoses, procedures and clinical events are classified with the use of the European Paediatric Cardiac Code short list coding scheme. DNA is isolated from peripheral blood and stored for research purposes.

For this study, we selected all patients registered with TOF and PA/VSD for whom DNA was available. Patients with known syndromes associated with CHD, other than 22q11.2DS, were excluded. Other extracardiac symptoms were not considered. We employed multiplex ligation-

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dependent probe amplification (MLPA) to detect 22q11.2 deletions, using the SALSA MLPA P250-A1 DiGeorge kit (MRC Holland, Amsterdam, The Netherlands) containing 30 probes in the 22q11 region.<sup>10</sup>

In the case of detected 22q11.2 deletions, the medical charts of the patients for whom the deletion was not recorded in CONCOR were reviewed, to clarify whether the diagnosis had indeed not been made previously.

For statistical analyses, SPSS 16.0 for Windows was used. *p* Values less than 0.05 were considered statistically significant. The data regarding age are presented as median with range because of a skewed distribution. Comparison of discrete variables (ie, gender and cardiac diagnosis) between patients in whom 22q11.2DS was known and patients in whom 22q11.2DS was not known before this study was performed using Fisher's exact test. Comparison of continuous variables (ie, age) between groups were made by the Mann–Whitney U test.

### RESULTS

At 1 January 2007, 993 patients with diagnoses of interest to this study had been registered in the CONCOR registry (total number of registered patients at that time 7503), with DNA available for 577 patients. Fifteen patients were excluded because they had a recognised syndrome other than 22q11.2DS, leaving 562 patients eligible for the study. The main cardiac diagnosis was TOF in 483 of these patients and PA/VSD in 79 patients. MLPA was successful in 479 patients with TOF and in all 79 patients with PA/VSD. Therefore, analysis was performed on 558 patients (56% male; median age 34.7 years, range 19.8–82.8).

Twenty patients had already been diagnosed with 22q11.2DS before this study. We detected a 22q11.2 deletion in an additional 24 patients. Therefore, a total of 44 out of 558 (7.9%, 95% CI 5.9 to 10.4) patients had 22q11.2DS. Thirty-one of 479 (6.5%, 95% CI 4.6 to 9.1) patients with TOF had a 22q11.2 deletion and 13 of 79 (16.5%, 95% CI 9.7 to 26.3) patients with PA/VSD had a 22q11.2 deletion (table 1). Of the patients with 22q11.2DS, 22 were men and 22 were women.

In 24 of 44 (54%) patients with 22q11.2DS, the deletion was not known to be present before this study. Patients with unknown 22q11.2DS were significantly older than patients with known 22q11.2DS (median age 37.4 and 28.5 years, respectively, *p*=0.03). No significant differences were present between patients with known 22q11.2DS and unknown 22q11.2DS with regard to gender or cardiac diagnosis (TOF or PA/VSD).

### DISCUSSION

In this study we found that 6.5% of adult patients with TOF and 16.5% of adult patients with PA/VSD had 22q11.2DS and, importantly, that more than half of the patients with 22q11.2DS had not been diagnosed before this study, reflecting the under-recognition of the syndrome.

Two smaller studies reported on the prevalence of 22q11.2DS among adults with TOF and PA/VSD. Beauchesne *et al*<sup>7</sup> found

prevalence rates of 3.8% in adults with TOF and 8.7% in PA/VSD, which have overlapping confidence intervals with the rates in our study. In another study that included 377 adult patients with TOF, only the patients with TOF plus additional features suggestive of 22q11.2DS (*n*=103) were screened and a prevalence of 29.1% was found, which translated to a minimum prevalence of 6.6% in the whole group.<sup>11</sup> The prevalence data in our study and these two other studies in adult patients are lower than generally reported in paediatric studies (TOF 6–26%, PA/VSD 24–46%).<sup>12–20</sup> This might be explained by the cardiac and extracardiac complications associated with 22q11.2DS, decreasing survival into adulthood. Differences in ascertainment may also contribute. We used a national registry, which provided the opportunity to review a group of patients with CHD without knowledge of additional characteristics of the patients. However, most patients (75%) in the CONCOR registry originate from tertiary referral centres, which might have led to an overrepresentation of patients with complex heart defects and extracardiac disorders and therefore to an overestimated prevalence of 22q11.2DS.

In our study, less than half of the patients with 22q11.2DS had been diagnosed before this study, reflecting the under-recognition of the syndrome in adult patients. The highly variable phenotype of the syndrome and difficulties in recognising the associated manifestations of the syndrome may contribute to the under-recognition in adult patients.<sup>7</sup> The facial features (box 1) are often subtle if present at all in adults.<sup>21</sup> In addition, the lack of awareness of the high prevalence and the lack of knowledge among adult cardiologists about the availability of molecular testing may play a role. With regard to recognition of the presence of 22q11.2DS, no differences in gender and cardiac diagnosis of the patients were present. However, patients in whom 22q11.2DS was not known to be present before this study were significantly older than the patients with known 22q11.2DS. Some of the younger patients in this study may have routinely been tested when they were still children or adolescents because of the availability of a test. In addition, the syndrome might be easier to recognise in younger patients.

Nevertheless, recognition of 22q11.2DS has important implications in directing immediate and long-term clinical management. Patients with TOF and 22q11.2DS more frequently have additional cardiovascular abnormalities, including right aortic arch, aberrant right subclavian artery and major aortopulmonary collateral arteries, than patients with TOF without a deletion.<sup>12 14 17 22</sup> The postoperative morbidity and mortality of 22q11.2DS patients is higher than in other patients due to the presence of these associated cardiac anomalies as well as the extracardiac anomalies of the syndrome.<sup>12 14 23</sup> In addition, individuals with 22q11.2DS who survive childhood have an increased risk of sudden death and diminished life expectancy, which cannot be attributed to a single factor.<sup>24</sup> Many of the associated extracardiac conditions are treatable once detected, emphasising the importance of follow-up in a coordinated multidisciplinary setting.<sup>5 25</sup> In children, features requiring attention besides CHD are velopharyngeal insufficiency

**Table 1** Prevalence of 22q11.2DS in patients with TOF and PA/VSD

Main cardiac diagnosis	Total	No of patients with 22q11.2DS	% of patients with 22q11.2DS (95% CI)	No of patients with unknown 22q11.2DS	% of patients with unknown 22q11.2DS (95% CI)
TOF	479	31	6.5 (4.6 to 9.1)	18	58 (41 to 74)
PA/VSD	79	13	16.5 (9.7 to 26.3)	6	46 (23 to 71)
Total	558	44	7.9 (5.9 to 10.4)	24	54 (40 to 68)

PA, pulmonary atresia; TOF, tetralogy of Fallot; 22q11.2DS, 22q11.2 Deletion Syndrome; VSD, ventricular septal defect.

**Box 1 Features that should raise clinical suspicion of 22q11.2DS in adults<sup>5 21 26</sup>**

- ▶ Typically associated CHD\*
  - Interrupted aortic arch (type B)
  - PA/VSD
  - TOF
  - Isolated arch anomalies
  - Truncus arteriosus
- ▶ Extracardiac features
  - Mental retardation/learning disability
  - Psychiatric history
  - Typical facial features†
  - Hypernasal speech
  - History of cleft palate
  - Hypocalcaemia
- ▶ Family history of CHD or extracardiac features

\* Especially in the presence of additional cardiovascular abnormalities such as right aortic arch, aberrant right subclavian artery and major aortopulmonary collateral arteries.

† Facial features are often absent or subtle in adults, but include: long face, prominent nasal root, full nasal tip, small mouth and chin, squared off external ears, narrow palpebral fissures.‡ Facial features are often less prominent in adults, but include: long face, prominent nasal root, full nasal tip, small mouth and chin, squared off external ears, narrow palpebral fissures.

and feeding difficulties, immunodeficiency, hypocalcaemia and developmental delay, among others.<sup>2</sup> Specific problems in adolescents and adults are autoimmune and endocrinological disorders, including thyroid dysfunction.<sup>5</sup> In addition, psychiatric disorders are reported in up to 58% of patients, with schizophrenia being especially common (18–24%),<sup>4–6</sup> although other disorders such as anxiety and mood disorders and attention deficit disorders also occur frequently.<sup>5 26 27</sup> Hypocalcaemia due to hypoparathyroidism, common in the neonatal period, may also occur in adulthood,<sup>5 26</sup> and renal abnormalities may also lead to complications in adults. Recurrent respiratory tract infections are often present.<sup>5 26</sup> If treating physicians are aware of these problems, early intervention can take place, which may significantly reduce morbidity. Another important issue is the heredity of 22q11.2DS; the deletion arises as a de novo event in approximately 90% of patients, but an affected individual has a 50% chance of transmitting the deletion to his or her offspring. Appropriate (preconception) genetic counselling is important for these patients.

Nonetheless, the majority of patients in our study were found to be negative for 22q11.2DS. Several other genetic disorders are known to underlie TOF and PA/VSD; there is a subset of patients that have other known cytogenetic abnormalities leading to syndromic CHD, for example, trisomy 21 (Down syndrome). Other syndromic patients have single gene disorders such as Holt–Oram syndrome, caused by mutations in *TBX5*. Patients with known syndromes were excluded from our study. The greater proportion of patients with TOF and PA/VSD have isolated, non-syndromic TOF. Recently, Greenway *et al*<sup>28</sup> identified copy number variations other than 22q11.2 deletions at nine loci in 15 of 512 patients with isolated TOF, although their significance has yet to be determined. Moreover, they also found 22q11.2 deletions in two patients with isolated TOF, as well as in one of 2265 control subjects. Mutations in several genes,

including the transcription factor genes *NKX2.5*<sup>29</sup> and *GATA4*,<sup>30</sup> and transmembrane receptor *NOTCH1*<sup>31</sup> and its ligand *JAG1*,<sup>32</sup> are also known to be implicated in a small subset of isolated TOF. Such single gene mutations and copy number variations may also underlie the heart defects in some of our patients.

It remains controversial which adults should be screened for 22q11.2DS.<sup>7 13 33</sup> Given the high prevalence, the variable phenotype and the difficulties in recognising the often subtle features, we believe that testing for the deletion should be performed in all adults with selected conotruncal heart defects, including TOF, PA/VSD, interrupted aortic arch (type B), isolated aortic arch anomalies and truncus arteriosus communis; also in patients who apparently do not have extracardiac features. Although this might not be feasible due to practical and/or financial reasons; at the very least, testing should be performed in patients with extracardiac features of the syndrome, as well as in patients with additional heart defects, such as major aortopulmonary collateral arteries, right aortic arch and aberrant right subclavian artery. Clinical features that should raise the suspicion of 22q11.2DS are listed in box 1. Fung *et al*<sup>11</sup> determined a model for the prediction of the presence of 22q11.2DS in adults with CHD in a brief encounter with the patient. A combination of three out of four features (global dysmorphic face, voice abnormalities, learning difficulties and age <30 years) yielded the highest sensitivity and discriminant ability. Education about the syndrome for physicians managing adult patients with CHD would contribute to a greater awareness and recognition of the syndrome.

In conclusion, this study shows that although the prevalence of 22q11.2DS in adult patients with TOF and PA/VSD is substantial (6.5% and 16.5%, respectively), it is unrecognised in more than half of patients. This reinforces the need for cardiologists' awareness of the syndrome. As the syndrome has important implications for surveillance and reproduction, screening should be considered in these patients, especially in the presence of extracardiac symptoms of 22q11.2DS.

**Funding** Funding for this study was provided under the European Community's Sixth Framework program contract (HeartRepair LSHM-CT-2005-018630).

**Competing interests** None.

**Ethics approval** The CONCOR national registry obtained approval from a Central Medical Ethics Committee in the Netherlands for research studies performed on medical data and DNA of registered patients. No additional approval for this specific study was applied for.

**Provenance and peer review** Not commissioned; externally peer reviewed.

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*Heart* 2010 96: 621-624

doi: 10.1136/hrt.2009.182642

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