Premature death in adults with 22q11.2 deletion syndrome

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Abstract

Background—22q11.2 deletion syndrome (22q11.2DS) is a multisystem disease with a prevalence of 1/4000. Variable expression of congenital and later onset features contributes to its under-recognition. Longevity in those surviving childhood is believed to be normal but data are limited.

Methods—We prospectively followed 264 subjects; 102 adults (>17 years) with 22q11.2DS (44 male (M), 58 female (F); mean (SD) age 33.6 (10.9) years) and their 162 unaffected siblings (77 M, 85 F; mean age 36.1 (12.2) years). We compared survival between groups using Kaplan–Meier estimates.

Results—Twelve (11.8%; 4 M, 8 F) individuals with 22q11.2DS and no siblings died ($p<0.0001$). Survival to ages 40 and 50 years was 89.9% and 73.9%, respectively. Median age at death was 41.5 (range 18.1–68.6) years. Deaths included two (7.7%) of 26 subjects with neither major congenital heart disease (CHD) nor schizophrenia. Four of six sudden and unexpected deaths occurred in individuals with no major CHD. There was no evidence of cancer or coronary artery disease or family history of sudden death in the 12 patients who died, six of whom had autopsies.

Discussion—Individuals with 22q11.2DS who survive childhood have diminished life expectancy and increased risk of sudden death not attributable to any single factor. Some sudden and/or premature deaths observed in the general population may represent undiagnosed 22q11.2DS. Increased recognition of the syndrome by family doctors, specialists and coroners will be essential to facilitate the tissue studies needed to determine underlying mechanisms.

22q11.2 deletion syndrome (22q11.2DS) (MIM 188400/192430) is a multisystem disorder associated with hemizygous chromosome 22q11.2 interstitial deletions which arise as de novo mutations in >90% of cases. 22q11.2DS occurs at an estimated prevalence of 1/4000 live births when ascertained through associated major congenital anomalies.^{1, 2} Characteristics identified early in childhood include congenital heart disease (CHD), most commonly conotruncal abnormalities and intracardiac shunts, velopharyngeal insufficiency, and other birth defects. However, many features are not recognisable until later, including learning difficulties and endocrine and psychiatric disorders.^{3–5} The phenotype is highly variable in number and severity of associated features, contributing to its under-recognition, particularly in adults.^{3, 6} Identifying patients with this syndrome is important for both the patient and their family. Anticipatory care can reduce morbidity, and transmission to offspring is 50%.^{3, 6, 7}

Infant mortality is elevated in rare, severe forms of 22q11.2DS such as complete DiGeorge syndrome.⁸ Paediatric mortality is also elevated in 22q11.2DS in association with CHD and related complications.^{9–13} There is a belief that longevity after childhood in 22q11.2DS is normal¹⁴ but adult mortality data are limited. We hypothesised that 22q11.2DS may decrease longevity in adults, independent of the presence of CHD.

METHODS

We prospectively studied adults with 22q11.2DS and their unaffected siblings. Informed consent was obtained in writing, and the study was approved by the research ethics boards of the University of Toronto, Centre for Addiction and Mental Health, and University Health Network.

Subjects with 22q11.2DS

For the present study we included all subjects with 22q11.2DS who were followed for 2 months or more and were 17 years or older by last follow-up. All met clinical criteria for 22q11.2DS¹⁵ and were confirmed to have a chromosome 22q11.2 deletion by standard methods using fluorescence in situ hybridisation (FISH) techniques and a probe, most commonly TUPLE1 (Vysis) or N25 (ONCOR), from the commonly deleted 22q11.2 region.^{16, 17} The majority were ascertained for the study because of a psychiatric disorder or CHD, as previously described.³ Deaths of three subjects were briefly mentioned in a report of common clinical features of 22q11.2DS³ and three others in a detailed neuropathologic study.¹⁸

Siblings

We included all full and half siblings of the subject group who had survived to age 17 years or older at last follow up and were unaffected with 22q11.2DS. Twelve younger siblings from nine families were excluded. Six subjects with 22q11.2DS had no siblings and four were adopted with no information about biological siblings. Available parents of affected subjects had FISH testing for 22q11.2 deletions. As expected, negative results confirmed a de novo deletion in most subjects with 22q11.2DS.¹⁹ We excluded 26 (living) siblings from eight families where the subject with 22q11.2DS was known to have inherited a 22q11.2

deletion or where parental deletion status was unknown. We included siblings from these families only if the sibling had negative FISH results and/or did not meet clinical screening criteria for 22q11.2DS.¹⁵

Evaluations

Death from any cause was the primary outcome measure. All subjects and siblings were adults, therefore survival was defined as years since age 17.0 years. Age was recorded to the nearest 0.1 year as at 31 January 2008 or death, or date at last contact for families lost to follow-up. To establish cause of death, we obtained medical records and postmortem results where available. Sudden cardiac death was defined as a natural death from a presumed cardiac cause, occurring within a short period of time in a person without any prior condition that would appear fatal.²⁰

As previously described,^{3, 21, 22} we have comprehensive medical and psychiatric data on our cohort of subjects with 22q11.2DS. All but one subject with 22q11.2DS had echocardiograms and/ or cardiac catheterisation to evaluate their cardiac status. We classified major CHD by structural complexity.²³ In this series, major CHD included tetralogy of Fallot, pulmonary atresia or an absent pulmonary valve. Simple CHD included subjects with repaired ventricular septal defects (VSDs) or atrial septal defects (ASDs) who should have good long term outcome.^{24, 25} All patients with major CHD were followed regularly at a specialty clinic for adults with CHD, most at the Toronto Congenital Cardiac Centre for Adults.

We confirmed DSM-IV lifetime diagnoses of schizophrenia, schizoaffective disorder or psychotic disorder not otherwise specified (collectively termed schizophrenia in this study) in subjects with 22q11.2DS using standard methods.²¹ A DSM-IV diagnosis of mental retardation was determined for subjects with 22q11.2DS from functioning and IQ testing results.²⁶

Extensive family history data from multiple sources and regular updates from family contacts provided information on the demographics and health status, including mortality and presence of major congenital cardiac defects and psychotic illness, of first degree relatives.

Statistical analysis

All analyses were performed using SAS 9.1.3 (SAS Institute, Cary, North Carolina, USA). χ^2 or two tailed Fisher's exact tests and Student's t tests were used to compare variables. The Kaplan–Meier method was used to compare survival between adults with and without 22q11.2DS. Two subjects with 22q11.2DS and their siblings from one family lost to follow-up were censored at the age of last contact. Because there were no deaths in the sibling group, a multivariate (Cox proportional hazard) model could not be created. Values of $p < 0.05$ were considered significant.

RESULTS

A total of 264 subjects from 96 families were included in the study: 102 subjects with 22q11.2DS (44 male (M), 58 female (F)) and 162 unaffected siblings (77 M; 85 F) comprising 144 full and 18 (8 maternal, 10 paternal) siblings. Twelve subjects with 22q11.2DS were related to one another: five parent-offspring pairs and one half-sibling pair. Ethnicity was: 94 (92.2%) Caucasian, 2 black, 2 Asian, and 4 other. Table 1 summarises demographic and clinical variables. Two siblings had psychotic illnesses and none had major CHD, consistent with population prevalence expectations.

Mortality in adults with 22q11.2DS

Twelve (11.8%; 4 M, 8 F) patients with 22q11.2DS died at a median age of 41.5 (range 18.1–68.6) years. Table 2 shows age, cause of death, and accompanying features. Ten (83%) deaths were coroner's cases; six of these had postmortem examinations. All 12 were receiving treatment under the care of family doctors and/or consultants.

Most commonly, death in 22q11.2DS was sudden and unexpected. Of the 12 deaths, six (50%) were considered sudden cardiac deaths²⁰: two in patients with no CHD, two in patients with repaired simple CHD, and two in patients with major CHD (cases 9 and 11, 7 and 8, 3 and 5, respectively, table 2). Three had postmortem examinations. These showed: (1) a morphologically normal heart in a 56-year-old woman, with a history of successfully treated atrial flutter and no CHD (case 11); (2) mild ventricular hypertrophy and mild aortic atherosclerosis that were not believed to be the cause of death in a 44-year-old man with a completely repaired ASD (case 7); and (3) the complex CHD that was likely the major factor in the sudden death of a 23-year-old man (case 3). Case 5, a 33-year-old man, also had a repaired, major CHD that likely contributed to his death. However, his death was considered sudden and unexpected because he had been extensively assessed 17 months before death by his cardiologist, and had been clinically stable and retired to bed with no signs of any cardiac worsening the night before his death.^{27–29} Postmortem examinations were not conducted in this or two other cases of sudden death, in women aged 45 and 48 years (cases 8 and 9).

Causes of death in the other six cases were mixed: one case each of complications of an elective investigation, suicide, pneumonia and stroke (cases 1, 6, 10 and 12, respectively), and complications of major CHD (cases 2 and 4). Notably, case 10 was the only death where infection was documented to have played a role. Autopsy showed only scattered areas of bronchopneumonia, so although death was sudden it was not considered unexpected. Detailed examination showed no neuropathologic cause of death in cases 2, 7, 10 and 11.¹⁸ To the best of our knowledge, individuals who died were taking prescribed medications and supplements, none were using recreational drugs, and none had toxic drug levels reported by coroners. In all cases caregivers or relatives saw them only hours before death.

Examination of possible effects of the major ascertainment groups showed that crude mortality rates were not significantly different (*p* values ranging from 0.45 to 1.0) between patients with schizophrenia (6 of 37, 16.2%), those with major CHD (3 of 30, 10.0%), both (1 of 9, 11.1%) and neither condition (2 of 26; 7.7%). Only one of the seven deaths in adults

with 22q11.2DS and schizophrenia (2 males, 5 females; aged 18.1–56.2), a suicide (case 6), could be attributed directly to the psychiatric disease. Three of the deaths (cases 6, 9 and 12) were in subjects originally diagnosed with 22q11.2DS as transmitting parents—that is, after routine genetic testing because an offspring had been diagnosed with 22q11.2DS. This included a 68-year-old woman who died of a stroke (case 12) whose 76-year-old unaffected brother with atherosclerosis is still living.

The median age of death (41.5 years) was not significantly older than the median age at last follow-up of the 90 living subjects with 22q11.2DS (median 31.0, range 17.3–57.5 years, $Z = 1.22$, $p = 0.22$). We observed a trend in living subjects for the 35 with major CHD to be younger than the 55 with no major CHD (28.9, range 20.2–56.0 years vs 32.6, range 17.3–54.7 years; $Z = -1.96$, $p = 0.05$). Low survival of generations before advances in cardiac surgery would predict a relatively young CHD cohort. As expected, death occurred at a significantly younger median age in the four patients with major CHD (25.8; range 22.9–33.2 years) than the eight with no major CHD (47.3; range 18.1–68.6 years; $Z = -2.35$, $p = 0.02$).

We also examined family history of premature death in unaffected parents of subjects with 22q11.2DS. Of 17 parents who had died age <70 years, 10 died of malignancies at median age 57.5 years, four of pre-existing cardiovascular disease (median 58.5 years) and three of other known causes (median 51 years). There was no case of sudden unexpected death in these parents, nor in a more extended family history of the six subjects with 22q11.2DS and sudden unexpected death.

Survival in adults with 22q11.2DS

Figure 1 shows Kaplan–Meier survival curves for subjects with 22q11.2DS subjects and their siblings. Survival at ages 30, 40 and 50 years was 95.2%, 89.9% and 73.9%, respectively, for subjects with 22q11.2DS and was significantly different from that of their siblings ($p < 0.0001$), none of whom had died. Survival curves for the 102 subjects with 22q11.2DS showed non-significant findings when stratified by sex ($p = 0.48$), major CHD ($p = 0.25$) or schizophrenia ($p = 0.60$).

DISCUSSION

This is the first study to examine late mortality in adults with 22q11.2DS. The results demonstrate that individuals with 22q11.2DS who survive to adulthood are at elevated risk of premature death when compared with their unaffected siblings. Calculating an odds ratio for 22q11.2DS is hampered by the empty cell for sibling deaths. An estimate calculated by artificially attributing one death to the sibling group shows an odds ratio of 21.5 (95% confidence interval 2.7 to 167.8). Notably, deaths in 22q11.2DS occurred at average age 41.5 years overall (47.3 years in those with no major CHD), much earlier than Canadian general population expectations: age 80.4 (both sexes); 78.0 (males); 82.7 (females) years.³⁰ Indeed, the 11.8% mortality rate we observed for a relatively young adult cohort with 22q11.2DS is somewhat higher than that reported for infants (8%), predominantly related to CHD.⁹ This association between 22q11.2 deletions and early mortality in adults has not been previously described.

The causes of premature death in adults with 22q11.2DS are likely multifactorial and both cardiac and non-cardiac in origin. Table 2 shows no unifying cause or single factor that adequately account for all deaths or all six sudden unexpected deaths. In the general adult population, premature death is often due to malignancy but there was no evidence from history or on autopsy of cancer in our sample. Despite its frequency as a lifetime feature of 22q11.2DS, only one death was attributed to infectious disease. Also, surgery for palatal abnormalities and obesity are common in 22q11.2DS, raising the possibility of sleep apnoea, but there was no direct evidence this was involved in the deaths. Neuropsychiatric disease and learning difficulties are common in 22q11.2DS and may interfere with obtaining appropriate medical care and maintaining compliance with recommended management. However, all of the patients in our cohort who died were in active medical follow-up in the Canadian universal health care system. Adults with major CHD have reduced life expectancy,²⁵ but the oldest age at death in our study of 22q11.2DS (33.2 years) is younger than the median age for individuals surviving to adulthood with comparable CHD complexity at our centre, even though patients with genetic syndromes like 22q11.2DS would have been included. While major CHD is an important determinant of mortality in 22q11.2DS, we found that carrying a 22q11.2 deletion was the strongest predictor of mortality in adults, suggesting factors other than major CHD must be involved.

Strikingly, the most common cause of death observed was unexplained sudden death in six (6%) of 102 subjects. This uses a definition of sudden cardiac death that includes the provision that while prior conditions may be present they are not conditions that would appear fatal.²⁰ An alternative view is to consider several of these six deaths sudden but in some way expected because of features associated with possible arrhythmogenicity—for example, atrial flutter, prolonged QT interval, major CHD—or because postmortem results were unavailable and thus there is uncertainty with respect to coronary artery disease. Taking such a conservative approach, and considering only one of these six a sudden unexpected death, the estimated rate would be 29 per 100 000 person-years in this 22q11.2DS cohort. In comparison, rates of sudden adult death syndrome (SADS) in the general population are estimated at 0.13–1.38 per 100 000 person-years.²⁹ The fact that four of these six individuals had no major CHD suggests that, even for sudden unexpected deaths, gross underlying cardiac defects are an insufficient explanation in this cohort.

Studies of target tissue will be essential to determine possible mechanisms. Looking to the general population for clues, however, there are several plausible causes of sudden death to consider. Ventricular arrhythmias in the setting of structural coronary artery disease (CAD)³¹ are most common but none of the six 22q11.2DS patients with sudden unexpected deaths, including the three with postmortem results, had evidence of CAD. The unexpected and sudden nature of these deaths (including death during sleep) without any prior condition that would appear fatal makes other arrhythmic aetiologies a consideration.²⁰ In the general population, familial ion channel abnormalities or cardiomyopathies are rare causes of SADS. However, there was no family history of sudden unexpected death in our sample and no evidence of cardiomyopathy clinically or on postmortem. Electrolyte disturbances (low calcium, magnesium and potassium) and the use of antipsychotics and other medications may be associated with a potential proarrhythmic state. Hypoxia, associated with respiratory disease and/or sleep apnoea, is another possible risk factor. As in general population

samples,²⁹ however, there was no direct evidence linking these factors to sudden death in 22q11.2DS. All 46 patients with schizophrenia and 22q11.2DS were treated with various antipsychotic medications. Six died of natural causes, three with sudden unexpected death, only one of whom had QT >460 ms. However, neither ECGs nor echocardiograms were performed on an annual basis and timing of the studies relative to the sudden unexpected deaths were variable. Serial studies may be helpful to identify the mechanism of death. Schizophrenia itself is known to be associated with sudden unexpected death^{28, 29, 32} and with increased mortality in general, mostly from suicide.³³ The average age at natural death is older and mortality rates much lower³² than we observed in 22q11.2DS schizophrenia (44.8 years; 16%, respectively), however. Impaired autonomic activity has been reported postoperatively in two children with 22q11.2DS³⁴ and, as for the general population,^{27–29} should be considered as another possible mechanism predisposing to sudden death.

Study limitations

The 22q11.2DS phenotype is highly variable in severity and accompanying features.^{3, 6} In this study, we ascertained adults with 22q11.2DS, some of whom had been diagnosed relatively early and many of whom were not identified until they were adults. Adults with schizophrenia were present at about twice the expected rate.³ Like many samples of 22q11.2DS, the rate of major CHD (38.2%) in our sample may be higher than that of an ideal epidemiological sample. Subjects not studied would include individuals with 22q11.2 deletions who died before age 17 and the many who have never been diagnosed with this under-recognised syndrome. Our results would be expected to pertain to individuals with 22q11.2DS identified largely because of characteristic features of 22q11.2DS,^{15, 35} but may be important even for adults not yet identified as having a 22q11.2 deletion. Larger samples would be needed to determine if patients with milder expression have significantly more favourable survival. We note, however, that 25% (cases 6, 9, 12 at ages 38.2, 48.8, 68.8 years) of the patients who died, including one of the six with sudden unexpected death, were initially found to have 22q11.2DS as transmitting parents. The mean age of adults with 22q11.2DS included in this study was relatively young, with the oldest subjects 68.6 and 57.5 years old. Thus, the long term outcome of older individuals with 22q11.2DS remains largely unknown.

Despite the involvement of coroners, only half of the subjects received postmortem examinations and thus pathologic causes of sudden death could not be assessed in three cases. All cases of sudden unexpected death require more detailed examination of cardiac conduction and right ventricular areas than is common in standard autopsies.²⁹ Studies following larger numbers of patients with 22q11.2DS prospectively over decades will provide more details about clinical risk factors for death as an outcome of the syndrome, including possible effects of associated medical and psychiatric illnesses, medications, lifestyle and other factors. Detailed genome-wide molecular studies, under way at several centres including ours, will be needed to determine what role genetic variants play in mortality, both those within the 22q11.2 deletion region and its more than 45 genes, and in other regions of the genome.⁷ Our recent results suggest that genome-wide copy number variants do not appear to play a role but further studies are required.¹⁹

Implications

This study provides an initial overview of premature mortality in predominantly young to middle-aged adults with 22q11.2DS. 22q11.2DS is under-recognised, particularly in adults, has variable expressivity, commonly occurs as a spontaneous mutation, and has an estimated population prevalence of 1 in 4000.³ These features and the mortality results in this study suggest that some of the sudden unexpected deaths observed in general population samples²⁹ may represent undiagnosed individuals with 22q11.2DS. Addition of 22q11.2 deletion studies to the molecular autopsy could clarify this.

For patients with 22q11.2DS, the results have implications for genetic counselling and long term follow-up, reinforcing the need for specialty clinics using a multidisciplinary approach.^{3–5, 36} In addition to suggested preliminary guidelines for the assessment and follow-up of adults with 22q11.2DS³ including calcium and magnesium monitoring, our results suggest that consideration should be given on a research basis to additional cardiac investigations—for example, serial ECGs or Holter monitoring. Further investigations of other systems could also shed light on additional possible causes of premature mortality. The results predict that rates of 22q11.2DS may be lower in older patient populations—for example, as observed in tetralogy of Fallot.³⁵ As for all cases of premature death, the importance of autopsies cannot be overemphasised. Increased case recognition and tissue samples will be essential for elucidating the underlying pathogenesis both of 22q11.2DS itself and its associated excess mortality.

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Figure 1.

Survival curves of adults with 22q11.2DS and their unaffected siblings. Kaplan–Meier curves comparing survival as a proportion in 102 adults with 22q11.2DS and their 162 unaffected siblings. Crosses (22q11.2DS subjects) and vertical lines (siblings) indicate censored data (last follow-up). For ease of interpretation, we have converted years of adult life since age 17 to age in years.

Table 1
Demographics and clinical factors in 102 adult subjects with 22q11.2DS and 162 unaffected siblings

	Subjects with 22q11.2 DS (n = 102)		Unaffected siblings (n = 162)		Analyses	
	n	%	n	%	Statistic	p Value
Sex (% male)	44	43.1	77	47.5	$\chi^2 = 0.49$	1 0.49
Major CHD (%)	39	38.2	0	–	$\chi^2 = 72.7$	1 <0.0001
Schizophrenia (%)	46	45.1	2	1.2	$\chi^2 = 81.0$	1 <0.0001
Mean (SD) age at last follow-up of living (years) *	32.7 (9.9)		36.1 (12.2)		t = 2.36	217 0.02

CHD, congenital heart disease.

* n = 90 subjects with 22q11.2DS.

Table 2

Details of deaths and cardiac and neuropsychiatric findings in 12 adults with 22q11.2 deletion syndrome, listed by age at death

Details of death *				Cardiac findings *					Neuropsychiatric				
Case	Sex	Age (years)	Cause	ECG					SZ	MR	Seizure disorder	Comments	
				CHD	History of arrhythmia	Findings	QTc (ms)	QRS (ms)					Medications †
1	F	18.1	Shock secondary to acute pancreatitis after ERCP	None	No	Normal rhythm	Normal ‡	Normal ‡	Quetiapine Sertraline Ethosuximide Lamotrigine	Yes	No	Yes	
2	M	22.9	Severe congestive heart failure, pulmonary haemorrhage	Major: Unrepaired TOF/PA, severe AS (mean gradient 41 mm Hg), moderate AR, moderately reduced RV dysfunction, O ₂ saturations 80%	No	Sinus tachycardia	488	104	Quetiapine Citalopram ASA Allopurinol	Yes	Mild	No	
3	M	23.7	Sudden, presumed arrhythmia	Major: Repaired TOF, hypoplastic right heart, pulmonary homograft and cavopulmonary shunt, residual severe PR, moderate TS (mean gradient 7 mm Hg)	Atrial flutter	Sinus rhythm	471	160	Digoxin Aldactazide Coumadin	No	No	No	Collapsed
4	F	27.8	Heart failure	Major: Repaired TOF/absent PV, pulmonary xenograft and modified cavopulmonary shunt, preserved biventricular systolic function, residual moderate PR, mean	No	Sinus tachycardia	547	154	Fluoxetine Domperidone Divalproex	No	Mod-severe	No	

Details of death *				Cardiac findings *				Neuropsychiatric					
Case	Sex	Age (years)	Cause	CHD	History of arrhythmia	ECG			Medications †	SZ	MR	Seizure disorder	Comments
						Findings	QTc (ms)	QRS (ms)					
5	M	33.2	Sudden, presumed arrhythmia	pulmonary valve gradient 31 mm Hg, moderate AS (mean gradient 25 mm Hg) Major: Repaired TOF/PA, RV to pulmonary artery conduit, repair of left PS, mild LV systolic dysfunction, mild PR, mean conduit gradient 19 mm Hg	No	Sinus rhythm	417	86	ASA Ramipril	No	No	No	Mild HTN Found dead in bed
6	F	38.2	Suicide	None	No	N/A	N/A	N/A	Risperidone Bupropion L-thyroxine	Yes	No	No	
7	M	44.8	Sudden, unexpected	Repaired ASD, no residual RV dilation or systolic dysfunction	No	Sinus rhythm	469	115	Clozapine Risperidone Gabapentin Diltiazem Furosemide L-thyroxine Clopidogrel Salbutamol Montelukast Rabeprazole	Yes	No	No	Smoking, asthma, HTN. Found dead beside bed
8	F	45.8	Sudden, unexpected	Repaired ASD, no residual RV dilation or systolic dysfunction	No	Sinus rhythm	440	80	Omeprazole Salbutamol	Yes	No	No	Smoking, asthma. Found dead in bed
9	F	48.8	Sudden, unexpected	None	No	N/A	N/A	N/A	L-thyroxine Cimetidine	No	No	No	Smoking, asthma. Found dead in bed

Details of death *				Cardiac findings *				Neuropsychiatric					
Case	Sex	Age (years)	Cause	CHD	History of arrhythmia	ECG			Medications †	SZ	MR	Seizure disorder	Comments
						Findings	QTc (ms)	QRS (ms)					
10	F	52.5	Sudden, attributed to acute bronchopneumonia	Secundum ASD (0.2 cm)	Supra-ventricular arrhythmia	Sinus rhythm	411	76	Loxapine Clonazepam Benztropine Diltiazem Oxybutynin Salbutamol Advair	Yes	Mild	No	Smoking, asthma. Found dead in bed in hospital 1 h after admission for respiratory distress
11	F	56.2	Sudden, unexpected	None	Atrial flutter	Sinus rhythm	401	78	Risperidone Benztropine Metoprolol Carbidopa/levodopa Pulmicort	Yes	Mild	No	Found dead in bed. Asthma
12	F	68.6	Stroke	None	No	LVH Sinus rhythm	N/A	N/A	Nitropaste Felodipine Prazosin Amitriptyline L-thyroxine	No	No	No	

AR, aortic regurgitation; AS, aortic stenosis; ASD, atrial septal defect; ERCP, endoscopic retrograde cholangio-pancreatogram; HTN, hypertension; LV, left ventricular; LVH, left ventricular hypertrophy; MR, mitral regurgitation; N/A, not available; PA, pulmonary atresia; PR, pulmonary regurgitation; PS, pulmonary artery stenosis; PV, pulmonary valve; RV, right ventricular; SZ, schizophrenia; TOF, tetralogy of Fallot; TS, tricuspid stenosis; VSD, ventricular septal defect.

^{*} Cases 1, 2, 3, 5, 6, 7, 8, 9, 10 and 11 were coroner's cases. Cases 2, 3, 6, 7, 10, and 11 had autopsies, none of which showed evidence of coronary artery disease.

[†] All patients were taking calcium and vitamin D supplements recommended for 22q11.2DS.

^{*} No ECG was available for review but a clinical note from a cardiologist stated the ECG was normal.