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The use of two different MLPA kits in 22q11.2 deletion syndrome

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ABSTRACT

22q11.2 deletion syndrome (22q11DS) is one of the most common recurrent copy-number variant disorder, caused by a microdeletion in chromosome band 22q11.2 and occurring with a population prevalence of 1 in 2000. Until today there has been no evidence that the size of the deletion has an influence on the clinical phenotype. Most studies report that 22q11DS is associated with mild or borderline intellectual disability. There are a limited number of reports on 22q11DS subjects with moderate or severe intellectual disability.

In this study we describe 63 adult patients with 22q11DS, including 22q11DS patients functioning at a moderate to severe intellectual disabled level. Deletion size was established with an experimental Multiplex ligation-dependent probe amplification (MLPA) mixture (P324) in addition to the commonly used MLPA kit (P250). We compared deletion size with intellectual functioning and presence of psychotic symptoms during life. The use of the experimental MLPA kit gives extra information on deletion size, only when combined with the common MLPA kit. We were able to detect eleven atypical deletions and in two cases the deletion size was shorter than all other "typical ones". We conclude that the use of the experimental kit P324 gives extra information about the deletion size, but only when used together with the standard P250 kit. We did not found any relation of deletion size with intelligence or presence of psychosis.

1. Introduction

22q11.2 deletion syndrome (22q11DS) is one of the most common recurrent copy-number variant disorders caused by a microdeletion in chromosome band 22q11.2. Characteristic clinical features include palatal and cardiac anomalies, hypo- or aplasia of the thymus, hypoplasia of the parathyroid, and typical facial features. The physical appearance is known to be highly variable (McDonald-McGinn et al., 1999; Shprintzen et al., 2005). Its prevalence and birth incidence is still under debate. Because of the strong variance in phenotype some patients with a deletion are not immediately identified or diagnosed at birth. Therefore in the literature differences in birth incidence are reported, ranging from 1 in 2000 (Shprintzen, 2008b) to 1 in 6000 (Botto et al., 2003). Recently Grati et al. (Grati et al., 2015) reported a birth incidence of 1:992 in a cohort of over 9.500 pregnancies, which indicates that reported prevalence rates are often underestimations of the incidence during pregnancy. As some of the physical abnormalities of 22q11DS are not compatible with life, prevalence rates will be lower, but because of the variability of penetrance of the deletion, some patient with a deletions will remain undiscovered until adulthood. The microdeletion can be diagnosed with e.g. fluorescence in situ hybridization (FISH) (Miller, 2008), multiplex ligation-dependent probe amplification (MLPA) (Jalali et al., 2008) or array comparative genomic hybridization (aCGH) analysis (Bittel et al., 2009).

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Table 1
Combined MLPA results with two Salsa kits (P250 and P324).

LCR22 region						Start A-region												Start B-region
Gene\ patient (gender)/IQ	BID[a,b]	MICAL3[a]	USP18[a]	GGT3P[b]	PRODH[b]	GSC2[b]	CLTCL1[a]	HIRA[a]	CDC45L[a]	CLDN5[a]	GP1BB[a]	TBX1[a,b]	GNB1L[b]	KIAA1652[a]	COMT[b]	ARVCF[b]	DGCR8[a]	ZNF74[a]
1 ♀/24[c]					X	X	X	X	X	X	X	X	X	X	X	X	X	X
2 ♂/7[c]				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
3 ♀/17				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
4 ♀/24[c]				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
5 ♂/37[c]				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
6 ♂/32[c]				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
7 ♂/20				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
8 ♂/35				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
9 ♀/37[c]				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
10♀/37[c]				X	X	X	X	X	X	X	X	X	X	X	X	X	X	
11♀/13[c]				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
12♀/30[c]				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
13♂/38[c]				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
14♂/41[c]				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
15♂/23[c]				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
16♂/18[c]				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
17♀/24[c]				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
18♂/41[c]				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
19♂/33				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
20♂/24[c]				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
21♀/31[c]				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
22♂/41				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
23♂/34				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
24♂/22				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
25♀/31[c]				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
26♂/32[c]				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
27♂/30[c]				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
28♀/26					X	X	X	X	X	X	X	X	X	X	X	X	X	X
29♂/37				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
30♀/33[c]				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
31♀/10[c]				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
32♀/36				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
33♀/35[c]				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
34♀/79				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
35♀/86				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
36♂/60[c]				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
37♀/74[c]				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
38♀/71[c]				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
39♀/80[c]				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
40♀/78				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
41♂/77				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
42♀/62				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
43♂/89[c]				X	X	X	X	X	X	X	X	X	X	X	X	X	X	
44♂/88[c]				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
45♀/–				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
46♀/73[c]				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
47♂/66				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
48♂/59				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
49♀/72				X	X	X	X	X	X	X	X	X	X	X	X	X	X	
50♀/74[c]				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
51♀/69[c]				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
52♀/87				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
53♀/83				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
54♀/70				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
55♂/75				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
56♀/89[c]				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
57♀/70				X	X	X	X	X	X	X	X	X	X	X	X	X	X	
58♀/96[c]				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
59♂/–				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
60♀/90				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
61♂/79				X	X	X	X	X	X	X	X	X	X	X	X	X	X	
62♂/82[c]				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
63♂/75				X	X	X	X	X	X	X	X	X	X	X	X	X	X	

Blanc: two copies; X: One copy deleted (hemizygous deletion); +: duplication (three copies present).
[a] Genes covered by the P250 kit.
[b] Genes covered by the P324 kit.
[c] Suffered from psychotic problems during life.