12q21 deletion syndrome: narrowing the critical region down to 1,6 Mb including *SYT1* and *PPP1R12A*

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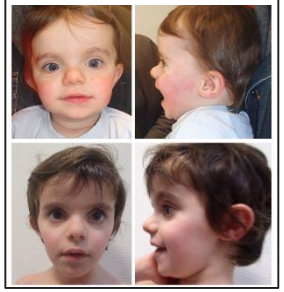
Background: Interstitial deletions of the long arm of chromosome 12 have rarely been reported. To date, deletions including the 12q21 region were reported in only 11 patients. Interestingly, these patients share common specific developmental features, suggesting the existence of a microdeletion syndrome[1-2].

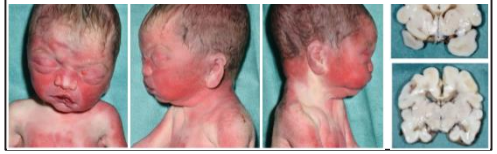
Patient 1
2 years-old (top) and 4 years-old (bottom)

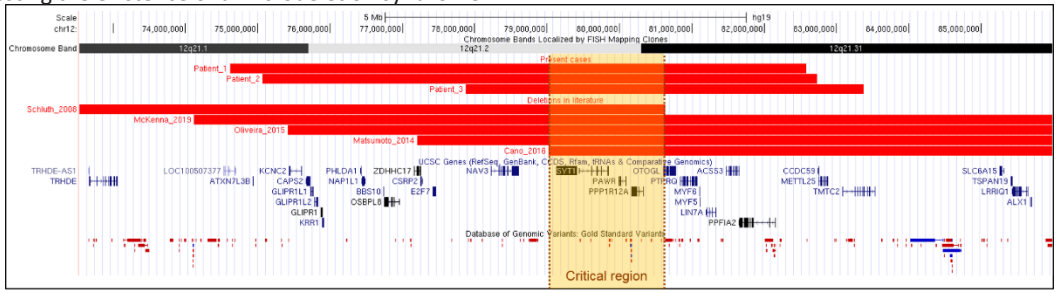


Patients and Methods

We report 3 new patients with deletions of the 12q21 region, including the smallest deletion of this region reported to date as well as the first patient with a microdeletion characterized in prenatal by array CGH. A review of the literature identified 11 other patients with overlapping deletions.

Patient 2
autopsy at 27 gestational weeks ; brain coronal sections showing ventriculomegaly





Map of the 12q21 region using UCSC Genome Browser (GRCh37)

Table 1: Clinical features of patients with 12q21 deletions

Patients	1	2	3	McKenna 2019	Cano 2016	Oliveira 2015	Matsumoto 2014	Schluth 2008	Klein 2005	James 2005	Rauen 2002	Rauen 2000	Brady 1999	Watson 1989	Ratio
Gender	M	M fœtus	M	M	F	F	M	F	M	F	M	F	F	F	M/F 1:1
Growth retardation	-	-	-	+	+	+	-	+	-	+	-	+	+	-	7/14
Developpemental delay	+	uk	+	+	+	+	+	+	+	+	+	+	+	+	13/13
Large thorax / pectus excavatum	+	-	+	uk	-	-	-	+	-	-	-	+	+	-	5/13
Large anterior fontanel	-	-	-	uk	uk	+	-	-	+	-	-	+	-	-	3/12
Facial dysmorphism	+	+	+	+	+	+	+	+	+	+	+	+	+	+	14/14
Proeminent forehead	+	+	+	+	uk	+	+	+	+	-	+	+	+	+	12/13
Hypertelorism	-	-	+	-	-	+	-	+	+	-	-	+	+	-	6/14
Short upturned nose / nostril hypoplasia	+	+	+	+	+	+	+	+	+	+	+	+	-	+	13/14
Low set ears / dysplasia	+	+	+	+	uk	+	+	+	+	+	+	+	+	+	13/13
Microretrognathia	-	+	-	-	-	+	+	+	-	-	+	+	+	uk	7/13
Pterygium / excess nuchal skin	-	+	-	+	-	+	-	-	+	-	-	-	+	-	5/14
Syndactyly 2-3 toe	-	-	-	+	+	+	-	+	+	-	+	-	-	+	7/14
Single palmar crease	-	+	-	+	-	+	-	-	+	-	+	-	-	-	5/14
Cardiac anomaly	uk	+	-	+	uk	-	uk	+	+	-	+	+	-	uk	6/10
Ectodermal abnormalities	+	+	+	+	+	+	+	+	+	+	+	+	+	+	14/14
Sparse eyebrows / hair	-	+	+	+	-	+	+	+	+	+	+	+	+	+	12/14
Xerosis / hyperkeratosis	-	-	+	-	-	+	-	-	+	+	+	+	-	-	6/14
Strabism / hypermetropia	+	uk	-	+	+	+	+	+	+	+	-	+	-	-	9/13
Hydronephrosis / reflux / horse-shoe kidneys	+	+	-	-	uk	+	uk	uk	+	uk	+	-	uk	uk	5/8
Cerebral anomaly on MRI	+	+	-	+	-	+	+	uk	+	uk	-	+	uk	uk	7/10
Ventriculomegaly / hydrocephaly	+	+	-	+	-	+	+	uk	+	uk	-	+	uk	uk	7/10
Hypoplasia of corpus callosum	+	-	-	-	-	+	+	uk	-	uk	-	-	uk	uk	3/10
Axial hypotonia / spastic diplegia	+	uk	-	uk	uk	+	+	+	+	-	+	-	-	-	6/11

Results & discussion

Clinical features shared by the patients are detailed in table 1.

Those patients allowed us to narrow the critical region to a 1,6 Mb region containing 4 genes: *SYT1*, *PAWR*, *PPP1R12A* and *OTOGL*. Among them, *SYT1* and *PPP1R12A* are predicted to be highly intolerant to haploinsufficiency (ExAC, gnomAD, DOMINO). According to the known function and consequences of a reported loss of function SNV in *SYT1*[3] we link this gene to the neurodevelopmental defect. *PPP1R12A* has never been described in human pathology. It is proposed to play major roles in multiple cellular processes including embryonic development[4].

Conclusion

12q21 deletions are associated with a variable phenotype but include specific recurrent clinical findings, as ectodermal abnormalities, growth retardation, ventriculomegaly or hydrocephalus, congenital heart and genitourinary defects. We propose the haploinsufficiency of *SYT1* as responsible for the neuro-developmental disorders and the *PPP1R12A* gene as the main candidate for the malformative part of the phenotype.

References

1. Klein *et al.* (Am J Med Genet A, 2005) ; 2. Oliveira *et al.* (Am J Med Genet A, 2015)
3. Baker *et al.* (Brain, 2018) ; 4. Kiss *et al.* (Mol Cell Res, 2019)