SOX3 DUPLICATION: A GENETIC CAUSE TO INVESTIGATE IN FETUSES WITH MYELOMENINGOCELE

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INTRODUCTION

- Majority of NTDs : sporadic, combination of genetic and environmental factors
- 10% of cases : gene disorders or chromosomal anomalies

- *SOX3* (SRY-related HMG-box gene 3) is an X-linked member of the SOX gene family of transcription factors, belonging to the Soxb1 subfamily
- SOXB1 proteins play a crucial role during neurogenesis

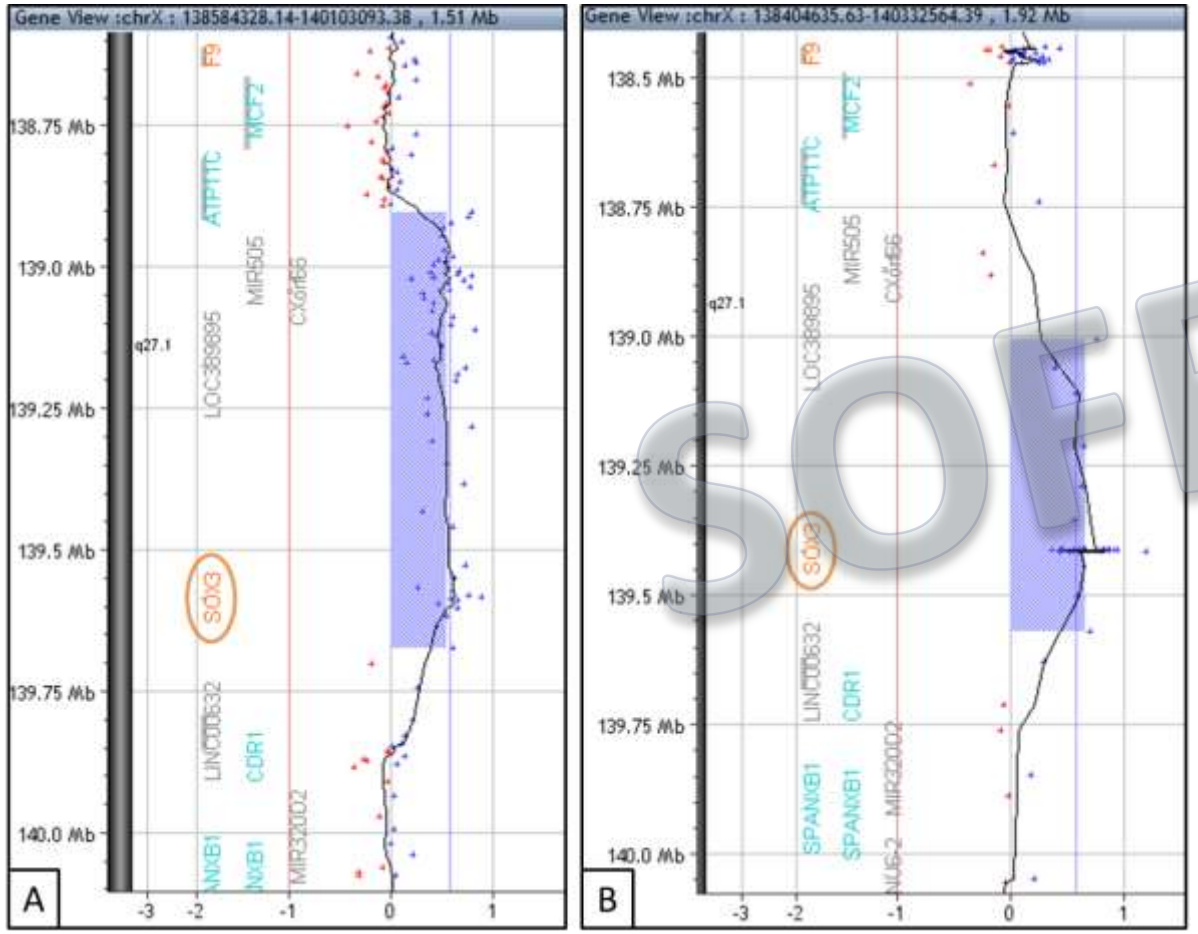
- **In males,** *SOX3* mutations and duplications are associated
  - X-linked hypopituitarism (isolated growth hormone deficiency to panhypopituitarism)
  - Cognitive impairment (learning difficulties to intellectual disability)

- Recently, an association between Xq27.1 duplication encompassing *SOX3* gene and NTDs has been suggested

Ugen A et al. Am J Med Genet A. 2015 Jul;167(7):1676–8
Bauters M et al. Am J Med Genet A. 2014 Aug;164A(8):1947–52

MATERIAL AND METHODS

2 index cases



SOX3 microduplication detected by array CGH in 2 female fetuses with myelomeningocele

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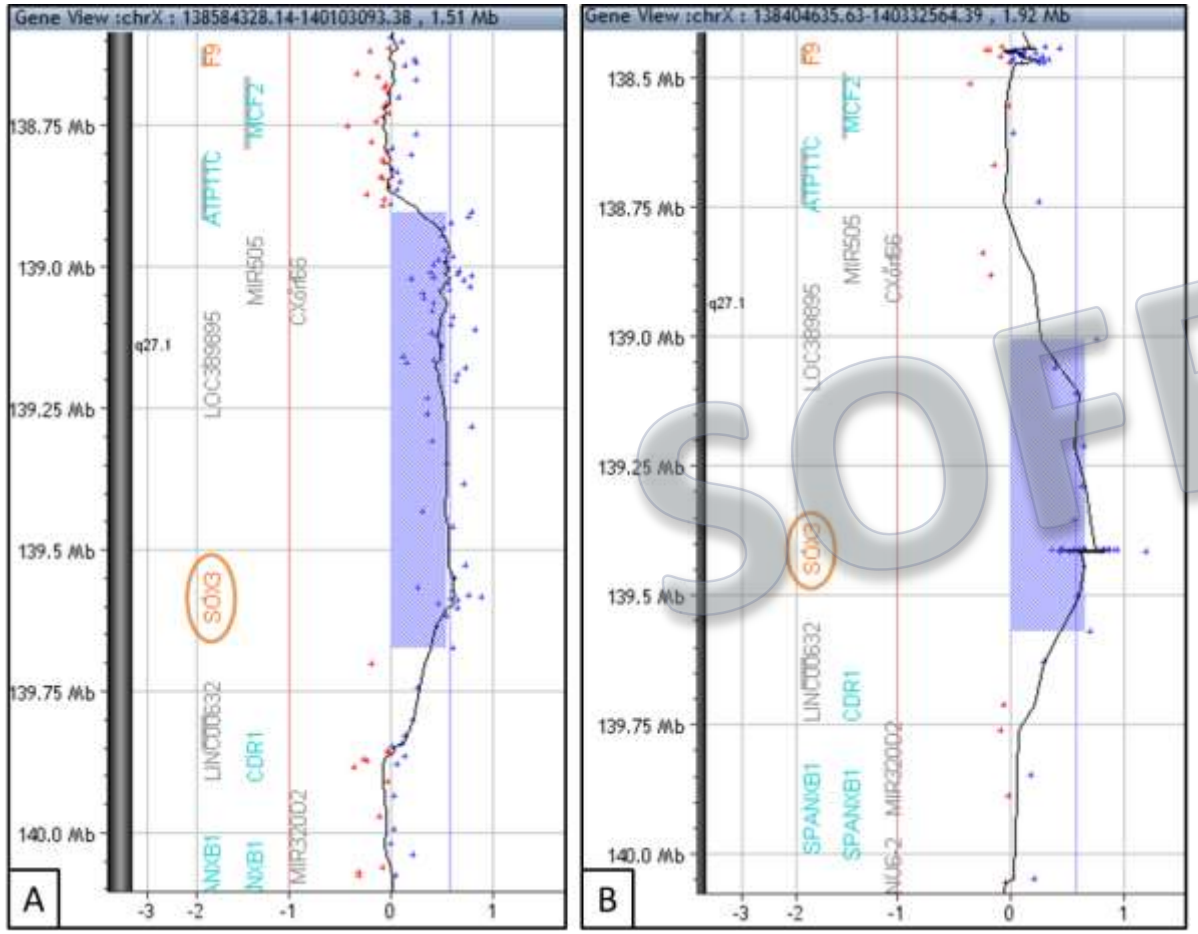


SOX3 microduplication detected by array CGH in 2 female fetuses with myelomeningocele

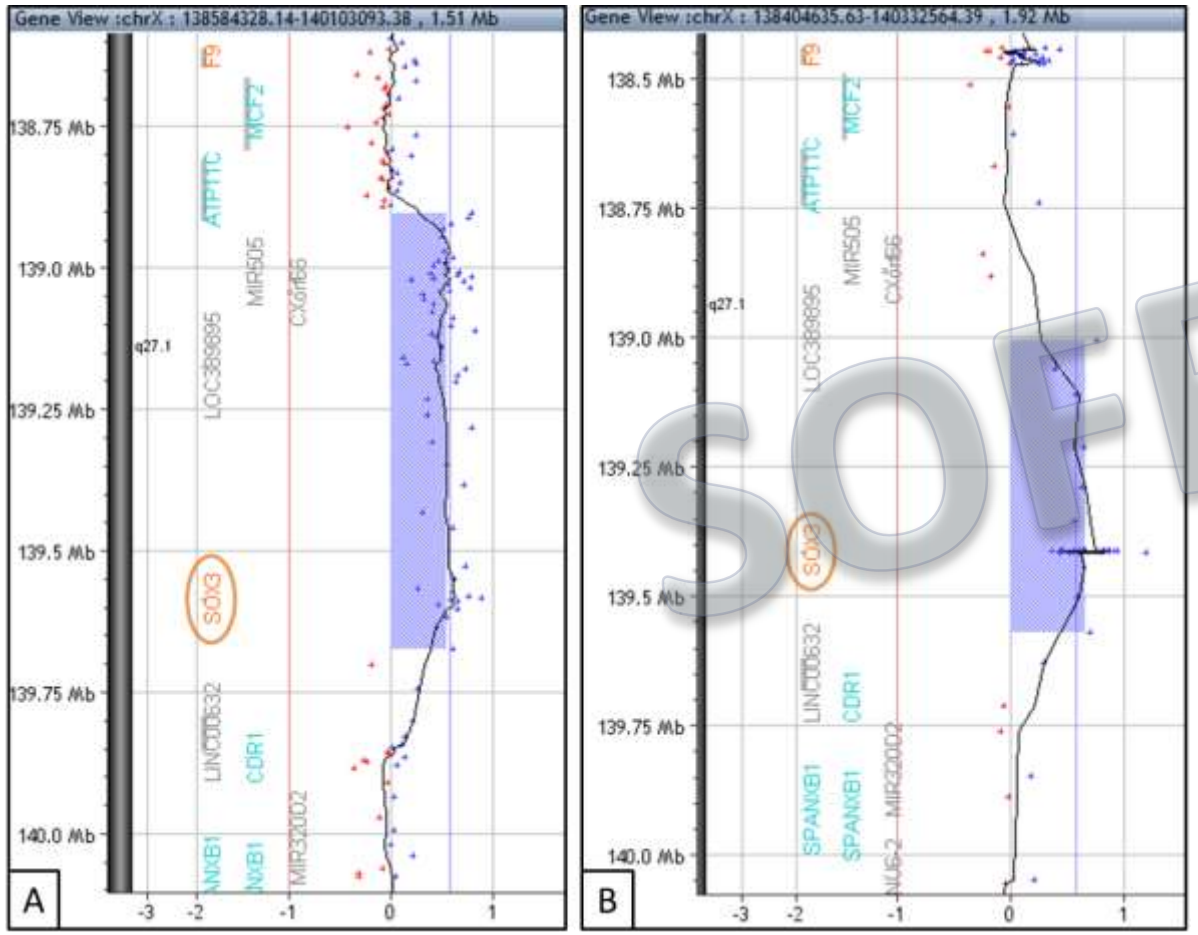
Cohort of **53 fetuses** with **MMC (TOP)**

qPCR targeting *SOX3* gene

***SOX3* gene**

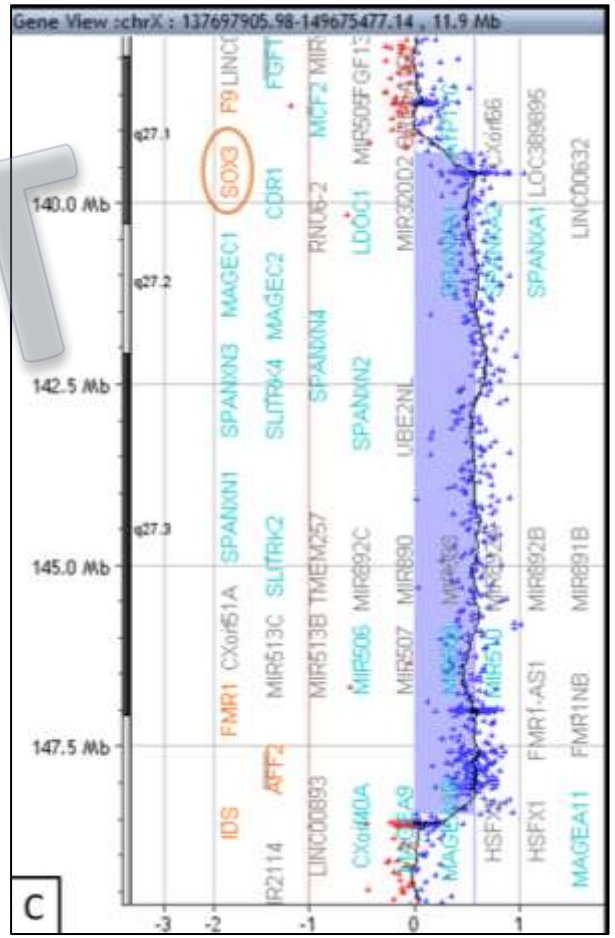
RESULTS

2 index cases



SOX3 microduplication detected by array CGH in 2 female fetuses with myelomeningocele

1/53 cases



Confirmed by array CGH

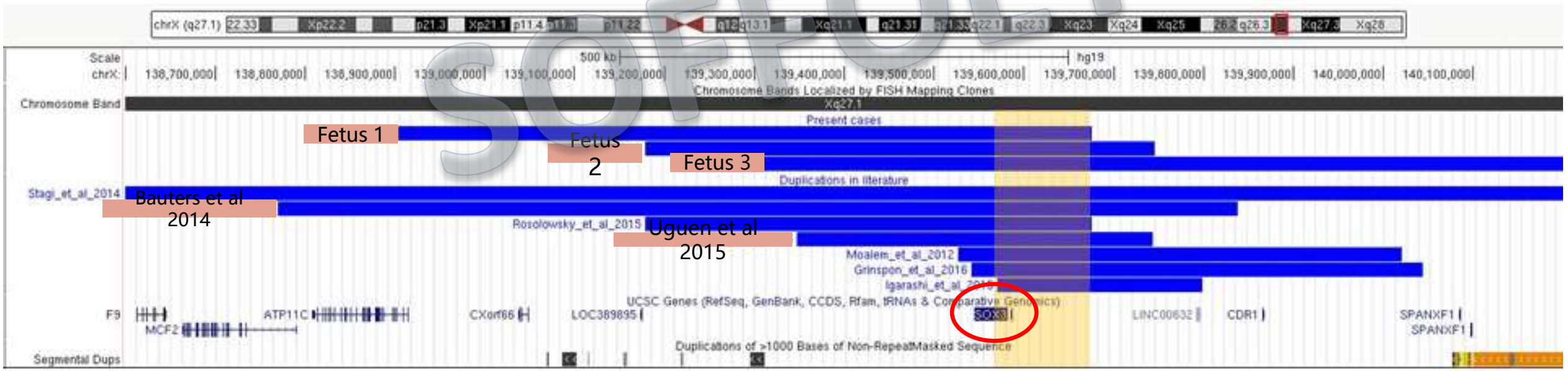
DISCUSSION

- In the literature and with our data → 50 cases with Xq duplication

➢ Size of the duplicated segments : 230 kb to 12.5 Mb

- 8/50 (16%) with NTD

➢ Incomplete penetrance of this condition



Stagi S, et al Hormones 2014 Oct-Dec;13(4):552-60 , Bauters M et al. Am J Med Genet A. 2014 Aug;164A(8):1947–52 , Rosolowsky et al,.J Pediatr Endocrinol Metab 2015 Aug 26. , Ugen A et al. Am J Med Genet A. 2015 Jul;167(7):1676–8 , Moalem S et al._Am J Med Genet A 2012 Jul;158A(7):1759-64, Grinspon RP et al, Clin Endocrinol 2016 Oct;85(4):673-5, Igarashi M et al, Sex Dev 2015;9(3):125-9

SOX3 DUPLICATION & NTD

	Our cases			Literature		
	Fetus 1	Fetus 2	Fetus 3	Uguen	Bauters	Hol
Chromosomal rearrangement	dup Xq27.1 (138903207_139675115)mat	dup Xq27.1 (139178537_139745254x3) pat	dup Xq27.1q28 (139308651_148434114x3)	dup Xq27.1 (139347579_139743254)	dup Xq27.1 (138769764_139837737)	dup Xq26.1q27.3 (no exact genomic position)
Size of the duplicated segment	772 kb	560 kb	9.1 Mb	395 kb	1.1 Mb	12.5 Mb
Duplication *SOX3* carriers	1* F 1 F	1* F 1 M	1* F	2* M (brothers) 1 F	3M 4F including 1F*	2 M (brothers) 2 F (mother & grand mother)
Inheritance	maternal	paternal	NA	maternal	maternal and paternal	maternal
Hypopituitarism	NA	NA	NA	NA	panhypopituitarism (2M)	panhypopitutarism (1M), GH deficiency (1M)
Cognitive fonctions	NA	NA	NA	NA	intellectual disability (1M) learning & social difficulties (1M)	developmental delay 2M
NTD Carriers	1* F	1* F	1* F	2* M	1* F	2 M
Type of NTD	MMC	MMC	MMC	2 MMC	MMC	1 MMC 1 SB occulta

IS *SOX3* DUPLICATION ASSOCIATED WITH SPECIFIC FEATURES OF MMC?

	Our cases			Literature			
	Fetus 1	Fetus 2	Fetus 3	Uguen et al.		Bauters	Hol
IUGR	-	-	-	-	-	-	-
Chiari II	+	+	+	+	NA	+	+
Hydrocephalus	+	-	+	+	NA	+	+
N open vertebrae	5	5	5	NA	NA	NA	NA
Level of the defect	Lumbar	Lumbo-sacral	Lumbo-sacral	Lumbo-sacral	Lumbo-sacral	Lumbo-sacral	Lumbo-sacral
Clubfoot	+	-	+	-	-	-	+
Other		Pituitary anomaly					

DISCUSSION: Pathophysiology

- Overexpression of *SOX3* in Xenopus and chicks expanded the neural plate and inhibited epidermis formation and neurogenesis

- *SOX3* blocks the action of proneural transcription factors, which induce neuronal differentiation

- Overexpression of *SOX3* as a result of the duplication may maintain the neural cell precursors in the undifferentiated state, thus preventing neural tube morphogenesis

Rogers N, et al.Gene Expr Patterns GEP. 2013 Oct;13(7):240–8; Dee CT, et al. Dev Biol. 2008 Aug 1;320(1):289–301; Bylund M, et al. Nat Neurosci. 2003 Nov;6(11):1162–8; Rogers CD et al. Mech Dev. 2009 Feb;126(1–2):42–55.

CONCLUSION

SOX3 **duplication**:

- is involved in the pathogenesis of NTDs in both sexes
- worsens the prognosis in males (developmental delay, panhypopituitarism)

Whole genome analysis by array CGH should be part of routine genetic testing in MMC **with a focus on *SOX3* gene**

Article submitted to Prenatal Diagnosis

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Whole genome analysis **with a focus on *SOX 3*** should be part of routine microarray in MMC

whole genome analysis by array CGH should be part of routine genetic testing in MMC **with a focus on *SOX3* gene**

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