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Short clinical report

# Haploinsufficiency of SOX5, a member of the SOX (SRY-related HMG-box) family of transcription factors is a cause of intellectual disability

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ABSTRACT

Intellectual disability (ID) is a clinically and genetically heterogeneous condition; the cause is unknown in most non-specific and sporadic cases. To establish an etiological basis in those patients represents a difficult challenge. Over the last years it has become apparent that chromosomal rearrangements below the detection level of conventional karyotyping contribute significantly to the cause of ID.

We present three patients with non-specific intellectual disability who all have overlapping microdeletions in the chromosomal region 12p12.1. *De novo* occurrence of the deletion could be proven in the two cases from which parental samples were available. All three identified deletions have different breakpoints and range in size from 120 kb to 4.9 Mb. The smallest deletion helps to narrow down the critical region to a genomic segment (chr12:23,924,800-24,041,698, build 37/hg19) encompassing only one gene, *SOX5*. *SOX5* is a member of the SOX (SRY-related HMG-box) family of transcription factors shown to play roles in chondroblast function, oligodendrocyte differentiation and migration, as well as ensuring proper development of specific neuronal cell types. Because of these biological functions, mutations in *SOX5* are predicted to cause complex disease syndromes, as it is the case for other *SOX* genes, but such mutations have not yet been identified. Our findings indicate that haploinsufficiency of *SOX5* is a cause of intellectual disability without any striking physical anomalies.



## 1. Introduction

Over the last years it has become apparent that chromosomal rearrangements below the detection level of conventional karyotyping contribute significantly to the cause of intellectual disability (ID) accounting for 14–18% of unselected ID-cases [1–4]. Interpreting the clinical significance of non-recurrent variants can be challenging, so several criteria are used to determine if a variant is a benign CNV (copy-number variant) or disease causing. *De novo* occurrence of a CNV is widely accepted to have great significance as an indicator for causality [1]. Apart from that the strongest evidence for causality is the identification of further patients with a similar variant and a similar clinical phenotype. Recurrent overlapping CNVs are often associated with similar clinical phenotypes and have led to the definition of new syndromes [5,6]. Subtle deletions have repeatedly revealed genes for monogenic forms of ID [7].

Here, we present detailed clinical and genomic characterization of three unrelated patients with overlapping microdeletions in the chromosomal region 12p12.1. Patient 2 and 3 were identified due to a search of the DECIPHER database after the microdeletion was detected in patient 1 (DECIPHER; http://decipher.sanger.ac.uk). Clinical similarities, *de novo* occurrence and biological functions of the involved gene *SOX5* suggest that the overlapping deletions in chromosome 12p12.1 are causative for the phenotype of these three patients. Informed consent was obtained to publish the patient's photographs.

## 2. Patient reports

### 2.1. Patient 1

The 2 year 5 months old boy was the first child of a non-consanguineous, healthy couple of German origin. At the time of

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birth both parents were 27 years old, and family history was unremarkable. The mother was treated with Citalopram during the first months of pregnancy because of a depression disorder. Because of a prenatally detected nuchal oedema, amniocentesis and prenatal cytogenetic analysis was performed showing a normal male karyotype. The patient was born after 41 weeks of gestation with a body length of 48 cm (10–25th centile), weight of 3250 g (25–50th centile) and a head circumference of 33 cm (5–10th centile). No malformations or dysmorphisms were apparent. In the second half of his first year a delayed psychomotor development became obvious. He learnt to sit without support at the age of 12 months and walked independently at 21 months. His speech development was also delayed. He spoke his first words around the age of 24 months and had an active vocabulary of 10 words at the age of 29 months. Receptive language skills appeared to be less delayed.

On examination at the age of 2 years and 5 months, his height was 88 cm (3–10th centile) and his head circumference was 48 cm (3–10th centile). Slight facial dysmorphisms such as down-slanting palpebral fissures, epicanthal folds, a broad nasal bridge, an upturned nose with a bulbous tip, accentuated prominent philtral ridges and an open mouth appearance were noted. Moreover the patient showed strabismus, mild muscular hypotonia, flat feet and diastasis recti (Fig. 1).

### 2.2. Patient 2

The patient was the firstborn of a non-consanguineous, healthy couple of white British origin. The mother was 26 years old and the father 27, at the time of his birth. Family history was non-contributory. He was born at term of an uneventful pregnancy, with normal, vaginal delivery. Birth weight was 3720 g (75th centile) and head circumference was 34.5 cm (25th centile). He had two episodes of bronchiolitis, at the age of 8 and 16 weeks. He walked at 17 months and failed to develop speech. He had grommets inserted at 2 years of age. Hearing was normal. Eye examination showed a squinting and myopia. At 2 years and 10 months, his weight and height were on the 50th centile and his OFC between the 50th and 75th centiles. He was noted to have down-slanting palpebral fissures, a slightly thin upper lip with notched nares and a drooping lower lip and a double crown. His reflexes were normal; he had a slightly unsteady gait. Although there were no major behaviour problems, he clapped his hands loudly or hit himself or banged doors when frustrated. He had poor sleep and was started on melatonin. At 4 years 9 months he was diagnosed with global developmental delay; he had only 4 single words and was not toilet trained. He presented with a number of rituals i.e. related to manual rotation of the washing machine and had no imaginative play. He was waking five times a night despite treatment with melatonin. His growth was normal; OFC was on the 25th centile, and his weight and height on the 50th. He was now noted to have a high forehead and chubby cheeks with a pointed chin, an open mouth appearance with distinct philtrum margins and prominent upper median incisors (Fig. 1). He also had 5th finger clinodactyly. By 9 years of age he had constipation. He was attending special school and had showed considerable speech progress with regular speech therapy sessions. His cognitive skills were comparable to when he was 4–5 years old. A brain MRI scan showed no abnormalities.

### 2.3. Patient 3

This is a 7-year-old female referred by the Immunology service secondary to a chromosome abnormality detected by array CGH. She was seen by Immunology because of frequent respiratory infections and ear infections. She was subsequently diagnosed with immunoglobulin A (IgA) deficiency. Her pregnancy was complicated by low-grade fever and malaise, treated with ibuprofen during the first trimester but otherwise normal. She was born full term by spontaneous vaginal delivery, birth weight was 3200 g. Medical history is

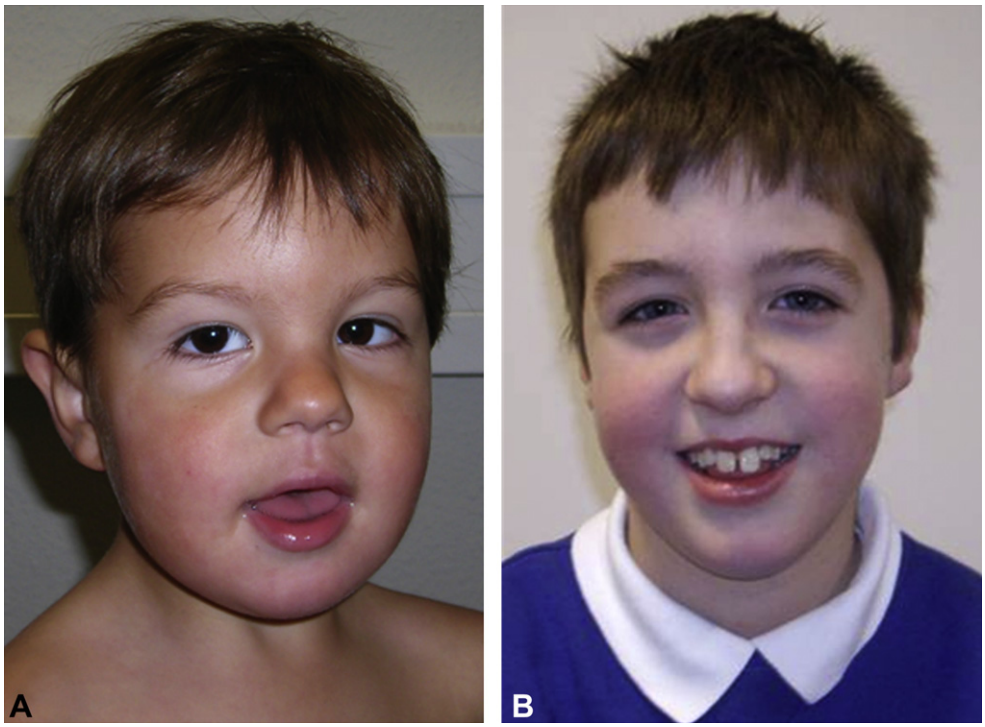


**Fig. 1.** (A) Patient 1 at the age of 29 months. (B) Patient 2 at the age of 9 years. Both patients show minor facial dysmorphic features including down-slanting palpebral fissures, a broad nasal bridge, accentuated, prominent philtral ridges and an open mouth appearance.

significant for frequent respiratory infections and reactive airway disease. She was also evaluated by gastroenterology because of abdominal pain. Upper CI endoscopy and biopsies were consistent with gastritis. She had a history of intermittent constipation. She had delays in achieving her milestones, sitting up at 1 year, standing at 1 ½ years and walking at 2 years. She started saying words at 3 years and putting words together after 5 years. She was toilet trained at 4 years. At the time of evaluation she was attending first grade but planned to be held back one year due to her delays. At school she receives support for mathematics, reading and speech. She also receives private speech therapy twice a week. Physical exam showed a height at 112.1 cm (3.88th centile), weight 21.4 kg (30th centile). FOC was not recorded. There were no apparent dysmorphic features noted. The chest was narrow with flaring of the lower costal cage. Nipples were inverted bilaterally. Hands showed bilateral shortening of middle fingers. Toes 2–5th were shortened with internal deviation of the 1st toe.

## 3. Genetic analysis

### 3.1. Microarray

Genomic DNA was extracted from lymphocytes using standard protocols. Microarray analysis was performed on patient 1 using an Affymetrix genome-wide human SNP 6.0 array (Santa Clara, CA, USA), on patient 2 using an OGT CytoSure ISCA 8 × 60 k oligonucleotide microarray (Agilent Technologies, Santa Clara, CA, USA), and on patient 3 using a 180,000 oligonucleotide array by Baylor College of Medicine (BCM) microarray version 8.0. (BCM, Houston, Texas, USA.) This is a custom made array with an Agilent platform (Agilent Technologies, Santa Clara, CA, USA). Experimental procedures were performed according to the manufacturer's instructions. Image data were analysed with the Affymetrix Genotyping console 4.1 and the Chromosome Analysis Suite V.1.2 for the Affymetrix array, with the Cytosure Interpret v3.4.3 analysis software for the Agilent array and with the BCM v 8.0 array with a custom made analytical software to assist in identifying each targeted-DNA sequence and copy number variations. Results were interpreted using external and internal data resources. External resources include the Database of Genomic Variants (DGV), DECIPHER, Ensembl, and OMIM.

### 3.2. Method of confirmation

The deletion in patient 1 was confirmed by MLPA analysis using a self-designed probe in exon 3 of *SOX5* (chr12:23,998,976-23,999,069, build 37/hg19). The MLPA probe was designed according to the instructions of MRC-Holland, and the reaction was performed using the SALSA MLPA reagents EK5 (MRC-Holland, Amsterdam, Netherlands). The *SOX5*-probe was added to the SALSA MLPA P300 Human DNA reference-2 probemix (MRC Holland, Amsterdam, Netherlands) which contains 15 reference probes. Copy number values were calculated using values from four healthy control individuals and the Seqpilot software (JSI Medical Systems, Kippenheim, Germany).

The deletion in patient 2 was confirmed by FISH using the BAC probe RP11-313H21, obtained from the Genome Resource Facility at the Centre for Applied Genomics (www.tcag.ca). Parental samples were also assayed for the abnormal region detected by aCGH in the proband, using FISH, and they showed no abnormal results.

The deletion in patient 3 was also confirmed by FISH. Unfortunately the parents of this patient did not follow through further confirmation studies, so there is no data available regarding *de novo* occurrence or inheritance.

## 4. Results

In patient 1, molecular karyotyping revealed a 2.26 Mb heterozygous deletion in chromosome 12p12.1 [arr12p12.1(22,421,865-24,678,035)x1, build 37/hg19] containing four genes: *ST8SIA1*, *KIAA0528*, *ETNK1* and *SOX5*. This deletion was confirmed using MLPA analysis with a self-designed probe in *SOX5*. MLPA revealed no evidence for the deletion in any parent, indicating that it has occurred *de novo*.

In patient 2, oligonucleotide-based array CGH revealed a heterozygous approximately 0.1–0.3 Mb deletion in chromosome 12p12.1 [arr12p12.1(23,924,800-24,041,968)x1, build 37/hg19] containing only exon 3 of the *SOX5*-gene. FISH analyses were done for the patient and his parents. We could confirm the deletion in the patient whereas the parents showed normal results.

In patient 3, oligonucleotide array CGH showed a 4.93 Mb deletion in chromosome 12p12.1 [arr12p12.1(22,609,919-27,538,360)x1, build 37/hg19]. Within this deletion in total 23 genes are annotated. FISH analyses were done to confirm the deletion in the patient. Parental samples could not be done as they did not follow through.

## 5. Discussion

Here we report a 29 months old patient with a heterozygous *de novo* deletion of 2.26 Mb in the chromosomal region 12p12.1 (Fig. 2). Patients 2 and 3, with overlapping microdeletions, were identified through data obtained through the DECIPHER database. All three deletions range in size from 120 kb to 4.9 Mb. The deletion in patient 2 delineates the critical region to a genomic segment (chr12:23,924,800-24,041,698, build 37/hg19) encompassing only exon 3 of the *SOX5* gene (Fig. 2). The breakpoints of the deletions are non-recurrent.

Clinical similarities between the three patients described here include developmental delay and intellectual disability especially concerning active language development (Table 1). Despite a strongly varying size of the deletions, the level of cognitive impairment was about the same in these patients, indicating that other genes around the critical region defined by the smallest deletion do not contribute significantly to the phenotype. Although congenital malformations and severe dysmorphisms are not part of the presentation, these children share some minor facial dysmorphic features including down-slanting palpebral fissures, a broad nasal bridge, accentuated, prominent philtral ridges and an open mouth appearance (Fig. 1). A recent study reports 16 patients with deletions including the *SOX5* gene, one patient with a translocation breakpoint within *SOX5*, 8 patients with intragenic deletions and 7 patients with large deletions containing further genes [8,9]. Major features described in all patients were developmental delay and prominent speech delay. The authors noticed some minor dysmorphic features with the only common feature of frontal bossing and skeletal anomalies in some cases. Among the major features of the reported cases are behaviour problems, which are described in the patients with intragenic as well as in the patients with larger deletions. In contrast, in our cohort only patient 2 with the deletion of exon 3 of *SOX5* showed some behavioural anomalies.

*SOX5* is a member of the family of sex-determining region (Sry)-related transcription factors. *SOX5* together with *SOX6* and *SOX13* are representing group D of SOX-genes, which are shown to play a role in multiple developmental pathways, including cartilage formation as well as development of central nervous system [10–14]. Mouse studies have shown on the one hand a role in chondrogenesis for *SOX5* and *SOX6* and on the other hand demonstrated expression of *SOX5* in the brain and thus support a role in the development of central nervous system [11,12,15,16]. *SOX5* ensures proper development of specific neuronal cell types and

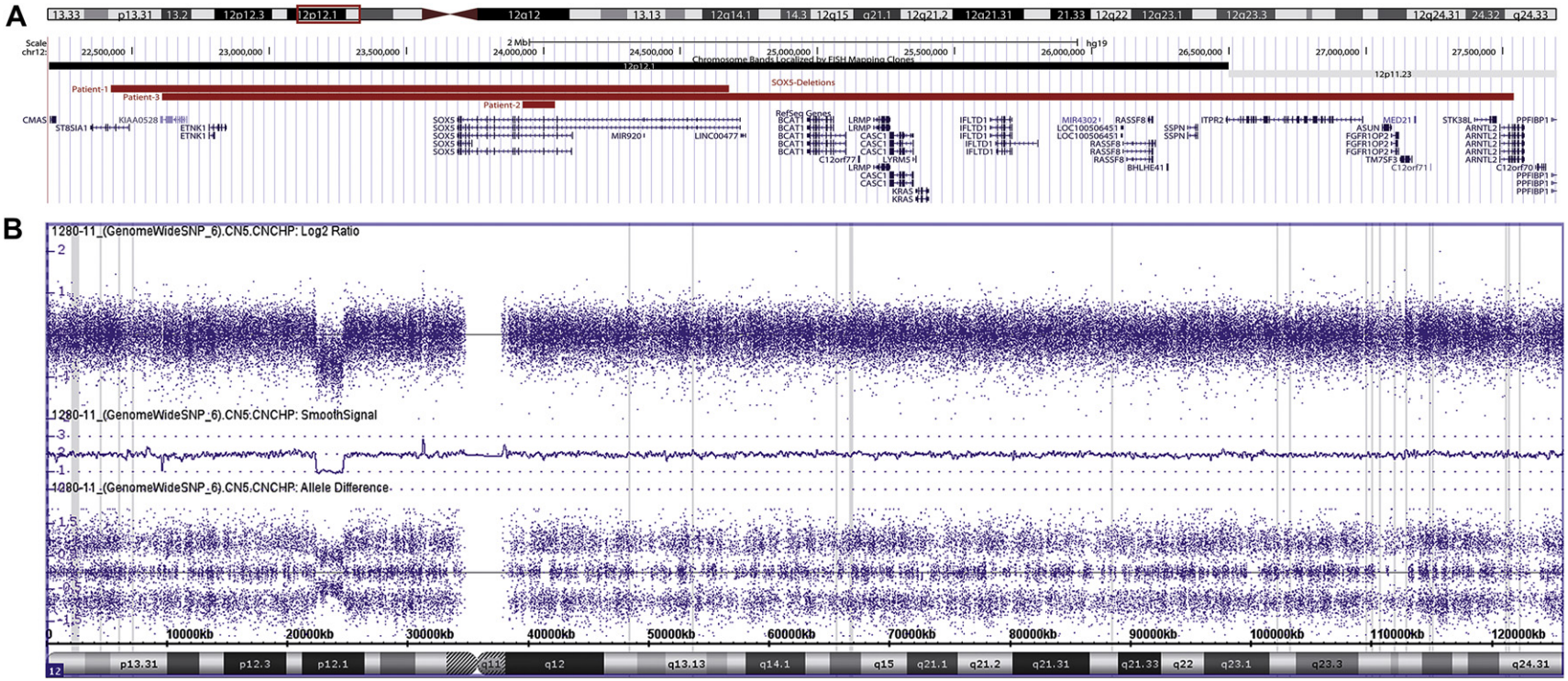


**Fig. 2.** (A) Map of the deletions in the chromosomal region 12p12.1 with an overview of the genes involved (parts of the figure were composed with UCSC Human genome Browser). Deletions of the three patients reported here are depicted in red. (B) Result of microarray analysis of patient 1 using an Affymetrix genome-wide human SNP 6.0 array showing the deleted region, according to ISCN 2009: arr12p12.1 (22,421,865-24,678,035)x1, build 37/hg19. Upper panel: log2 Ratio of the total fluorescence intensity; middle panel: smoothed signal of log2 Ratio; lower panel: allele difference showing loss of heterozygosity (LOH) in the region of the deletion.

**Table 1**
Clinical information for patients 1–3 compared to the patients described by Lamb et al. [8].

| | Patient 1 | Patient 2 | Patient 3 | Lamb et al. alterations limited to *SOX5* |
|---|---|---|---|---|
| Gender | Male | Male | Female | |
| Age | 2.5 years | 9 years | 7 years | |
| Deletion coordinates[a] | 22,421,864-24,678,010 | 23,924,800-24,041,968 | 22,609,919-27,538,360 | |
| Deletion size | 2.26 Mb | 120 kb | 4.93 Mb | |
| Number of genes | 4 | 1 (*SOX5*) | 23 | |
| Inheritance | *De novo* | *De novo* | Unknown | |
| *Growth* | | | | |
| Birth parameters | Normal | Normal | Normal | |
| Height centile | 3–10th | 50th | 4th | |
| Weight centile | | 50th | 30th | |
| OFC centile | 3–10th | 25th | | |
| *Neurological features* | | | | |
| Motor development | Moderate delay; walked at 21 m | Moderate delay; walked at 17 m | Moderate delay; walked at 20 m | Delay 9/9 |
| Cognitive | Mild ID | Mild to moderate ID | Mild ID | Mild to severe 9/9 |
| Speech | Delayed; first words at 24 m | Delayed; 4 words at 4 9/12 years | Delayed; first words at 3 years | Delay 8/9 |
| Behavioural anomalies | – | + | – | 5/9 |
| Hypotonia | Mild | – | – | 4/9 |
| Seizures | – | – | – | 2/9 |
| Other features | – | Unsteady gait, sleep disorder | | Brain malformations 2/5 |
| Dysmorphic features | | High forehead | | 6/9 |
| | Down-slanting palpebral fissures | Down-slanting palpebral fissures | | |
| | Epicanthal folds | | | |
| | | Chubby cheeks | | |
| | Broad nasal bridge | | | |
| | Upturned nose | | | |
| | Bulbous nasal tip | | | |
| | | Notched nares | | |
| | Prominent philtral ridges | Prominent philtral ridges | | |
| | Open mouth appearance | Open mouth appearance | | |
| | | Thin upper lip, drooping lower lip | | |
| | | Pointed chin | | |
| | | Prominent upper median incisors | | |
| Malformations | – | – | | Brain, heart, genital |
| Musculoskeletal anomalies | Flat feet | 5th finger clinodactyly | Short 3rd phalanges | Flat feet |
| | | | Brachydactyly 2–5th toes | |
| | | | Narrow chest | |
| | | | Flaring of anterior ribs | Scoliosis |
| Other features | Diastasis recti | Chronic constipation | Intermittent chronic constipation | Chronic constipation |
| | Strabismus | Myopia and strabismus | IgA deficiency | Strabismus 3/9 |
| | | Episodes of bronchiolitis | | |

Abbreviations: +, feature present; –, feature absent; DD, developmental delay; ID, intellectual disability; m, months; OFC, occipitofrontal circumference.
[a] Chromosomal coordinates based on build 37/hg19.

postmitotically regulates the migration, differentiation, and subcortical projections of neocortical neurons [11]. For the pathophysiology of several forms of ID a 'synapse-based' hypothesis has been proposed. Deregulation of specific pathways and cellular processes, defects in synaptic structure and/or function as well as alterations in neuronal connectivity may hamper the ability of the brain to process information resulting in ID [17]. Because of the essential roles of the *SOXD* genes in multiple biological processes and their highly conserved domains it is assumed that alterations of *SOX5* have impact in human disease. Furthermore haploinsufficiency for *SOX5* and *SOX6* is predicted by Huang et al. using a new model which is able to annotate 12,443 genes with their predicted probability of being haploinsufficient [18]. According to this prediction, the intragenic deletion of exon 3 in patient 2 is leading to a premature stop of protein synthesis (c.241_451del; p.Glu81LysfsX28) and is assumed to result in mRNA decay. Moreover intragenic deletions of *SOX5* in the subjects presented by Lamb et al. are predicted to result in loss of the primary DNA-binding domain also leading to haploinsufficiency [8,9].

Patients 2 and 3 of this series as well as two patients presented by Lamb et al. are presenting with constipation [8]. This is a presentation feature of another genetic syndrome caused by mutations in a SOX protein, Waardenburg syndrome type 4, caused by mutations in *SOX10* [19]. *SOX5* has been implicated in neuronal development and migration and the constipation could be a result of a defect of neuronal development or migration in the embryonic gut [12].

In conclusion we report three further patients with heterozygous deletions including the *SOX5* gene resulting in intellectual disability, speech delay and similar but only slightly abnormal facial appearance. Compared to the recently reported cases, the patients of this series showed about the same level of cognitive impairment (mild ID) and behavioural anomalies were no frequent finding. In contrast to the mouse studies showing a role in chondrogenesis for *SOX5* and *SOX6*, haploinsufficiency of human *SOX5* results in no obvious skeletal phenotype. The only minor skeletal anomalies in the presented patients are flat feet and 5th finger clinodactyly. Maybe this is due to the fact that *SOX6* is able to compensate *SOX5*-haploinsufficiency in chondrogenesis in contrast to neurodevelopment. Further investigations are required to better understand how reduced expression of *SOX5*, a gene involved in many developmental processes, contributes to impaired brain function.

Our observations confirm that haploinsufficiency of *SOX5* is the phenocritical mechanism of small deletions affecting this region. Despite the broad expression pattern and multiple proposed functions of *SOX5*, disruption of one allele obviously results in a mainly neurodevelopmental phenotype. *SOX5* is therefore established as a gene for monogenic forms of non-syndromic intellectual disability, and the existence of disease-causing point mutations has to be anticipated.

## References


[1] K. Buysse, B. Delle Chiaie, R. Van Coster, B. Loeys, A. De Paepe, G. Mortier, F. Speleman, B. Menten, Challenges for CNV interpretation in clinical molecular karyotyping: lessons learned from a 1001 sample experience, Eur. J. Med. Genet. 52 (2009) 398–403.

[2] R. Hochstenbach, J.E. Buizer-Voskamp, J.A. Vorstman, R.A. Ophoff, Genome arrays for the detection of copy number variations in idiopathic mental retardation, idiopathic generalized epilepsy and neuropsychiatric disorders: lessons for diagnostic workflow and research, Cytogenet. Genome Res. 135 (2011) 174–202.

[3] D.J. McMullan, M. Bonin, J.Y. Hehir-Kwa, B.B. de Vries, A. Dufke, E. Rattenberry, M. Steehouwer, L. Moruz, R. Pfundt, N. de Leeuw, A. Riess, O. Altug-Teber, H. Enders, S. Singer, U. Grasshoff, M. Walter, J.M. Walker, C.V. Lamb, E.V. Davison, L. Brueton, O. Riess, J.A. Veltman, Molecular karyotyping of patients with unexplained mental retardation by SNP arrays: a multicenter study, Hum. Mutat. 30 (2009) 1082–1092.

[4] L.E. Vissers, B.B. de Vries, J.A. Veltman, Genomic microarrays in mental retardation: from copy number variation to gene, from research to diagnosis, J. Med. Genet. 47 (2010) 289–297.

[5] D.A. Koolen, A.J. Sharp, J.A. Hurst, H.V. Firth, S.J. Knight, A. Goldenberg, P. Saugier-Veber, R. Pfundt, L.E. Vissers, A. Destree, B. Grisart, L. Rooms, N. Van der Aa, M. Field, A. Hackett, K. Bell, M.J. Nowaczyk, G.M. Mancini, P.J. Poddighe, C.E. Schwartz, E. Rossi, M. De Gregori, L.L. Antonacci-Fulton, M.D. McLellan 2nd, J.M. Garrett, M.A. Wiechert, T.L. Miner, S. Crosby, R. Ciccone, L. Willatt, A. Rauch, M. Zenker, S. Aradhya, M.A. Manning, T.M. Strom, J. Wagenstaller, A.C. Krepischi-Santos, A.M. Vianna-Morgante, C. Rosenberg, S.M. Price, H. Stewart, C. Shaw-Smith, H.G. Brunner, A.O. Wilkie, J.A. Veltman, O. Zuffardi, E.E. Eichler, B.B. de Vries, Clinical and molecular delineation of the 17q21.31 microdeletion syndrome, J. Med. Genet. 45 (2008) 710–720.

[6] D.R. Stewart, A. Huang, F. Faravelli, B.M. Anderlid, L. Medne, K. Ciprero, M. Kaur, E. Rossi, R. Tenconi, M. Nordenskjold, K.W. Gripp, L. Nicholson, W.S. Meschino, E. Capua, O.W. Quarrell, J. Flint, M. Irons, P.F. Giampietro, D.B. Schowalter, C.A. Zaleski, M. Malacarne, E.H. Zackai, N.B. Spinner, I.D. Krantz, Subtelomeric deletions of chromosome 9q: a novel microdeletion syndrome, Am. J. Med. Genet. A 128A (2004) 340–351.

[7] C. Zweier, M.M. Peippo, J. Hoyer, S. Sousa, A. Bottani, J. Clayton-Smith, W. Reardon, J. Saraiva, A. Cabral, I. Gohring, K. Devriendt, T. de Ravel, E.K. Bijlsma, R.C. Hennekam, A. Orrico, M. Cohen, A. Dreweke, A. Reis, P. Nurnberg, A. Rauch, Haploinsufficiency of TCF4 causes syndromal mental retardation with intermittent hyperventilation (Pitt–Hopkins syndrome), Am. J. Hum. Genet. 80 (2007) 994–1001.

[8] A.N. Lamb, J.A. Rosenfeld, N.J. Neill, M.E. Talkowski, I. Blumenthal, S. Girirajan, D. Keelean-Fuller, Z. Fan, J. Pouncey, C. Stevens, L. Mackay-Loder, D. Terespolsky, P.I. Bader, K. Rosenbaum, S.E. Vallee, J.B. Moeschler, R. Ladda, S. Sell, J. Martin, S. Ryan, M.C. Jones, R. Moran, A. Shealy, S. Madan-Khetarpal, J. McConnell, U. Surti, A. Delahaye, B. Heron-Longe, E. Pipiras, B. Benzacken, S. Passemard, A. Verloes, B. Isidor, C. Le Caignec, G.M. Glew, K.E. Opheim, M. Descartes, E.E. Eichler, C.C. Morton, J.F. Gusella, R.A. Schultz, B.C. Ballif, L.G. Shaffer, Haploinsufficiency of SOX5 at 12p12.1 is associated with developmental delays with prominent language delay, behavior problems, and mild dysmorphic features, Hum. Mutat. 33 (2012) 728–740.

[9] J.A. Rosenfeld, B.C. Ballif, B.S. Torchia, T. Sahoo, J.B. Ravnan, R. Schultz, A. Lamb, B.A. Bejjani, L.G. Shaffer, Copy number variations associated with autism spectrum disorders contribute to a spectrum of neurodevelopmental disorders, Genet. Med. 12 (2010) 694–702.

[10] M. Aza-Carmona, D.J. Shears, P. Yuste-Checa, V. Barca-Tierno, A. Hisado-Oliva, A. Belinchon, S. Benito-Sanz, J.I. Rodriguez, J. Argente, A. Campos-Barros, P.J. Scambler, K.E. Heath, SHOX interacts with the chondrogenic transcription factors SOX5 and SOX6 to activate the aggrecan enhancer, Hum. Mol. Genet. 20 (2011) 1547–1559.

[11] K.Y. Kwan, M.M. Lam, Z. Krsnik, Y.I. Kawasawa, V. Lefebvre, N. Sestan, SOX5 post mitotically regulates migration, post migratory differentiation, and projections of subplate and deep-layer neocortical neurons, Proc. Natl. Acad. Sci. U. S. A. 105 (2008) 16021–16026.

[12] T. Lai, D. Jabaudon, B.J. Molyneaux, E. Azim, P. Arlotta, J.R. Menezes, J.D. Macklis, SOX5 controls the sequential generation of distinct corticofugal neuron subtypes, Neuron 57 (2008) 232–247.

[13] V. Lefebvre, The SoxD transcription factors-Sox5, Sox6, and Sox13-are key cell fate modulators, Int. J. Biochem. Cell Biol. 42 (2010) 429–432.

[14] V. Lefebvre, P. Li, B. de Crombrugghe, A new long form of Sox5 (L-Sox5), Sox6 and Sox9 are coexpressed in chondrogenesis and cooperatively activate the type II collagen gene, EMBO J. 17 (1998) 5718–5733.

[15] E.A. Kiselak, X. Shen, J. Song, D.R. Gude, J. Wang, S.L. Brody, J.F. Strauss 3rd, Z. Zhang, Transcriptional regulation of an axonemal central apparatus gene, sperm-associated antigen 6, by a SRY-related high mobility group transcription factor, S-SOX5, J. Biol. Chem. 285 (2010) 30496–30505.

[16] P. Smits, P. Li, J. Mandel, Z. Zhang, J.M. Deng, R.R. Behringer, B. de Crombrugghe, V. Lefebvre, The transcription factors L-Sox5 and Sox6 are essential for cartilage formation, Dev. Cell 1 (2001) 277–290.

[17] J. Chelly, M. Khelfaoui, F. Francis, B. Cherif, T. Bienvenu, Genetics and pathophysiology of mental retardation, Eur. J. Hum. Genet. 14 (2006) 701–713.

[18] N. Huang, I. Lee, E.M. Marcotte, M.E. Hurles, Characterising and predicting haploinsufficiency in the human genome, PLoS Genet. 6 (2010) e1001154.

[19] A. Chaoui, Y. Watanabe, R. Touraine, V. Baral, M. Goossens, V. Pingault, N. Bondurand, Identification and functional analysis of SOX10 missense mutations in different subtypes of Waardenburg syndrome, Hum. Mutat. 32 (2011) 1436–1449.