 # 300967
MENTAL RETARDATION, X-LINKED, SYNDROMIC 34; MRXS34
Alternative titles; symbols
MENTAL RETARDATION, X-LINKED, SYNDROMIC, MIRCSOF-LANGOUET TYPE;
MRXSML
ORPHA: 466791; DO: 0060817;

Xq13.1 Mental retardation, X-linked, syndromic 34
300967 X-linked 3 NONO 300084

TEXT
A number sign (#) is used with this entry because of evidence that X-linked syndromic mental retardation-34 (MRXS34) is caused by mutation in the NONO gene (300084) on chromosome Xq13.

Description
X-linked syndromic mental retardation-34 is an X-linked recessive neurodevelopmental disordercharacterized by delayed psychomotor development, intellectual disability with poor speech, dysmorphic facial features, and mild structural brain abnormalities, including thickening of the corpus callosum (summary by Mircsof et al., 2015).

Clinical Features
Mircsof et al. (2015) reported 3 unrelated males, aged 15 to 20 years, with syndromic form of intellectual disability. The patients had delayed psychomotor development with poor nasal speech, and a shy, gentle, and cheerful demeanor. They had a slender build, scoliosis or kyphosis, pes planus, and ankylosis of the metacarpophalangeal joint of P1. Facial features included macrocephaly, long face with upslanting palpebral fissures, malar hypoplasia, thin and high nasal root, small open mouth, and narrow high-arched palate with dental crowding. Additional variable features included strabismus, myopia, and hypotonia with poor sucking in infancy, One patient had seizures and 2 had delayed puberty. Brain imaging showed thickening or dysgenesis of the corpus callosum in 2 patients; 1 patient had a Chiari type I malformation and another had a hypoplastic cerebellum.

Reinstein et al. (2016) reported a 17-year-old Ashkenazi Jewish boy of Libyan origin who had developmental delay, macrocephaly, dysmorphic facies, and left ventricular noncompaction (LVNC). At age 1 month, he presented with macrocephaly, axial hypotonia, and head lag. At 8 months, chest x-ray revealed an enlarged cardiac silhouette, and echocardiography showed LVNC. In addition, he exhibited low muscle tone, and all developmental milestones were delayed. At 4 years of age, he was diagnosed with autism and mild intellectual disability, and at age 12, he developed aggressive behavior. Examination at age 16 showed a shy and anxious patient, with verbal dyspraxia, intention tremor, and mild ataxia. He had mild joint laxity, macrocephaly, and dysmorphic features that included long face, prominent nose, wide mouth, thick lips, and short philtrum. Neurologic examination demonstrated general hypotonia, increased patellar and Achilles reflexes without clonus, kyphoscoliosis, and bilateral hallux valgus. Brain imaging showed a thick calvarium, with a short and hypoplastic corpus callosum, but no cerebellar abnormalities. His parents and 2 sibs were healthy.

Scott et al. (2017) studied 3 unrelated Hispanic boys who all exhibited developmental and

intellectual delays, relative macrocephaly, dysmorphic features, and cardiac defects, including LVNC, atrial and ventricular septal defects, patent ductus arteriosus, and patent foramen ovale. MRI of the brain showed corpus callosum defects in 2 of the patients.

Inheritance

The transmission pattern of MRXS34 in one of the families reported by Mircsof et al. (2015) was consistent with autosomal recessive inheritance.

Molecular Genetics

Mircsof et al. (2015) reported 3 different hemizygous mutations in the NONO gene (300084.0001-300084.0003) in 3 unrelated males with MRXS34. One patient inherited the mutation from an unaffected mother; another patient had a de novo mutation and also carried a hemizygous deletion of chromosome 15q13, which may have contributed to the phenotype. The mutations were found by whole-exome sequencing; Western blot analysis of patient cells showed loss of NONO protein. Patient fibroblasts showed increased expression of 2 other splicing genes PSPC1 (612408) and SFPQ (605199), as well as a reduced amplitude of circadian oscillations.

In a 17-year-old Ashkenazi Jewish boy of Libyan origin with developmental delay, macrocephaly, dysmorphism, and LVNC, Reinstein et al. (2016) performed exome sequencing and identified hemizygosity for a de novo splice site mutation in the NONO gene (300084.0004).

Noting that the cardiac phenotype was not reported in the patients described by Mircsof et al. (2015), Reinstein et al. (2016) suggested that LVNC might be part of MRXS34.

By exome sequencing in 2 unrelated Hispanic boys with global developmental delay, relative macrocephaly, dysmorphic features, and cardiac anomalies including LVNC, Scott et al. (2017) identified mutations in the NONO gene, the previously identified 1-bp duplication (300084.0002) and the R365X substitution (300084.0003), respectively. In a similarly affected Hispanic male infant, the authors identified a maternally inherited Xq13.1 deletion that included the first 3 coding exons of the NONO gene. The authors noted that all 6 reported patients with mutations in the NONO gene exhibited relative macrocephaly and intellectual disability and/or global developmental delay, and 5 of the 6 had abnormalities of the corpus callosum; however, other features showed greater variability. Given that 2 of the patients with LVNC carried the identical mutation as previously reported patients without cardiac defects, Scott et al. (2017) suggested that loss of NONO function might predispose males to the development of congenital heart defects and LVNC, with the penetrance of these cardiac-related problems being influenced by genetic, epigenetic, environmental, or stochastic differences that affect the expression or function of other cardiac genes or compensatory mechanisms.

Animal Model

Mircsof et al. (2015) found that mice with disruption of the Nono gene had a small cerebellum, impaired spatial memory performance, and increased anxiety compared to control mice. Mutant mouse brains and neurons showed decreased levels of Gabra2 (137140) associated with altered postsynaptic clustering of gephyrin (GPHN; 603930). Expression of Gabra2 rescued the defect in gephyrin clustering. The findings suggested that Nono can regulate Gabra2 levels and thus has a role in regulating inhibitory synaptic biology in the brain, which can affect behavior.

REFERENCES

Mircsof, D., Langouet, M., Rio, M., Moutton, S., Siquier-Pernet, K., Bole-Feysot, C.,

Cagnard, N., Nitschke, P., Gaspar, L., Znidaric, M., Alibeu, O., Fritz, A.-K., and 18 others. Mutations in NONO lead to syndromic intellectual disability and inhibitory synaptic defects. Nature Neurosci. 18: 1731-1736, 2015. [PubMed: 26571461] [Full Text: https://dx.doi.org/10.1038/nn.4169]
1.
Reinstein, E., Tzur, S., Cohen, R., Bormans, C., Behar, D. M. Intellectual disability and noncompaction
cardiomyopathy with a de novo NONO mutation identified by exome
sequencing. Europ. J. Hum. Genet. 24: 1635-1638, 2016. [PubMed: 27329731] [Full Text: https://dx.doi.org/10.1038/ejhg.2016.72]
2.
Scott, D. A., Hernandez-Garcia, A., Azamian, M. S., Jordan, V. K., Kim, B. J., Starkovich, M.,
Zhang, J., Wong, L.-J., Darilek, S. A., Breman, A. M., Yang, Y., Lupski, J. R., Jiwani, A. K., Das, B., Lalani, S. R., Iglesias, A. D., Rosenfeld, J. A., Xia, F. Congenital heart defects and left ventricular non-compaction in males with loss-of-function variants in NONO. J.
Med. Genet. 54: 47-53, 2017. [PubMed: 27550220] [Full Text: http://jmg.bmj.com
/cgi/pmidlookup?view=long&pmid=27550220]
3.
Contributors: Marla J. F. O'Neill - updated : 06/08/2017
Creation Date: Cassandra L. Kniffin : 2/18/2016
Edit History: carol : 06/08/2017
carol : 02/19/2016
ckniffin : 2/18/2016

Printed: March 23, 2019
® ®
®

OMIM Entry - # 300967 - MENTAL RETARDATION, X-LINKED, SYNDROMIC 34, MRXS34; https://www.omim.org/entry/300967

NON-POU DOMAIN-CONTAINING OCTAMER-BINDING PROTEIN; NONO

NUCLEAR RNA-BINDING PROTEIN, 54-KD; NRB54
p54NRB
p54(NRB)

Other entities represented in this entry:
NONO/TFE3 FUSION GENE, INCLUDED
HGNC Approved Gene Symbol: NONO

Cytogenetic location: Xq13.1 Genomic coordinates (GRCh38): X:71,283,191-71,301,167 (from
NCBI)

Xq13.1 Mental retardation, X-linked, syndromic 34 300967.

Description
The NONO gene encodes a protein that belongs to the highly conserved Drosophila behavior/human splicing (DBHS) protein family. This family includes 3 members in mammals: NONO, PSPC1 (612408), and SFPQ (605199). DBHS proteins are nuclear proteins involved in various aspects of RNA metabolism (summary by Mircsof et al., 2015).

Cloning and Expression
Dong et al. (1993) purified and cloned the cDNA of HeLa cell p54nrb, a nuclear protein with 2 RNA recognition motifs and extensive homology to human splicing factor PSF (SFPQ; 605199) and Drosophila NONA/BJ6. By mass spectrometry of proteins isolated from purified HeLa cell nucleoli, Andersen et al. (2002) identified p54(NRB). By SDS-PAGE, p54(NRB) had an apparent molecular mass of about 55.4 kD. Fox et al. (2002) found that p54NRB colocalized with PSP1 (PSPC1; 612408) and PSP2 (RBM14;612409) in nucleoplasmic structures called paraspeckles, which were adjacent to but distinct
from SC35 (SFRS2; 600813)-containing splicing speckles.
Mircsof et al. (2015) found expression of the Nono gene in several regions of mouse brain, including cortex and hippocampus. Immunostaining was strong in neurons and granule cells, and absent in astrocytes.

Gene Structure
Peters et al. (1997) determined that the NRB54 gene contains 12 exons ranging in size from 40 to 1,227 bp. The start codon is in exon 3 and the stop codon in exon 12.

Mapping
Brown et al. (1997) examined the expression of 33 X-linked genes in 8 mouse/human somatic cell hybrids that contained either the human active (3 hybrids) or inactive (5 hybrids) X chromosome. They found that the p54nrb gene was expressed only in those hybrids with the active human X. Using a megabase scale from pter to qter devised by Nelson et al. (1995), they noted that the approximate physical position of the gene was 70 Mb from pter. Brown et al. (1997) placed it in almost exactly the same position as the CCG1 gene (TAF2A;

313650), which had been mapped to Xq13-q27, and approximately 2 Mb proximal to PHKA1 (311870), which had been mapped to Xq13. Thus, Xq13 is the likely location. Peters et al. (1997) stated that the AFX1 gene (300033) and the NRB54 gene map to a YAC contig of Xq13.1.

Cytogenetics

NONO/TFE3 Fusion Gene

In papillary renal cell carcinoma tissue (RCCX1; 300854), Clark et al. (1997) identified an X-chromosome inversion inv(X)(p11.2;q12) that resulted in the fusion of the NONO gene to the TFE3 gene (314310).

Gene Function

Fox et al. (2002) found that PSP1, PSP2, and p54NRB relocalized from paraspeckles to the perinucleolar cap region upon transcriptional blockade.

Brown et al. (2005) identified 2 PER1 (602260)-associated factors, NONO and WDR5 (609012), that modulate PER activity. The reduction of NONO expression by RNA interference (RNAi) attenuated circadian rhythms in mammalian cells, and fruit flies carrying a hypomorphic allele were nearly arrhythmic. WDR5, a subunit of histone methyltransferase complexes, augmented PER-mediated transcriptional repression, and its reduction by RNAi diminished circadian histone methylation at the promoter of a clock gene.

Using a high-throughput screen, Amelio et al. (2007) found that endogenous NONO interacted with the CREB (123810) coactivators TORC1 (MECT1; 607536), TORC2 (CRTC2; 608972), and TORC3 (608986) in human embryonic kidney cells. RNAi experiments showed that NONO was necessary for cAMP-dependent activation of CREB target genes in vivo. TORC2 and NONO interacted on cAMP-responsive promoters, and NONO acted as a bridge between the CREB/TORC complex and RNA polymerase II (see 180660).

In a screen to identify factors that interacted with Sox9 (608160) to promote chondrocyte differentiation and Col2a1 (120140) expression in the mouse chondrogenic cell line ATDC5, Hata et al. (2008) identified p54nrb. p54nrb physically interacted with Sox9 and enhanced Sox9-dependent transactivation of the Col2a1 promoter. In ATDC5 cells, p54nrb colocalized with Sox9 in nuclear paraspeckle bodies, and knockdown of p54nrb suppressed Sox9-dependent Col2a1 expression and promoter activity. Overexpression of a mutant p54nrb protein lacking the RNA recognition motifs markedly altered the appearance of paraspeckle bodies and inhibited maturation of Col2a1 mRNA in ATDC5 cells. Mutant p54nrb inhibited chondrocyte differentiation of mesenchymal cells and mouse metatarsal explants, and transgenic mice expressing mutant p54nrb in the chondrocyte lineage exhibited dwarfism associated with impaired chondrogenesis.

Liu et al. (2014) identified a long noncoding RNA, lncUSMYCN (MYCNUT; 615968), that was coamplified with MYCN (164840) in a subset of primary neuroblastomas and neuroblastoma cell lines. Knockdown of lncUSMYCN via small interfering RNA reduced MYCN mRNA expression in a human neuroblastoma cell line, and ectopic expression of lncUSMYCN upregulated exogenous MYCN mRNA and induced cell proliferation. Unlike other lncRNAs, lncUSMYCN did not directly modulate MYCN promoter activity, but it bound directly to NONO, which then increased MYCN expression. High lncUSMYCN or NONO expression in neuroblastoma tissue independently predicted poor patient prognosis. Knockdown of lncUSMYCN reduced tumor growth in neuroblastoma-bearing mice. Liu et al. (2014) concluded that lncUSMYCN and NONO play important roles in regulating MYCN expression and neuroblastoma oncogenesis.

Chaoui et al. (2015) found that p54NRB interacted with SOX10 (602229) to enhance

expression of SOX10 target genes. However, p54NRB did not activate SOX10 target gene transcription alone. Overexpression of p54NRB caused redistribution of SOX10 to nuclear bodies.

Molecular Genetics

Mircsof et al. (2015) reported 3 different hemizygous mutations in the NONO gene (300084.0001-300084.0003) in 3 unrelated males with X-linked syndromic mental retardation-34 (MRXS34; 300967). One patient inherited the mutation from an unaffected mother; another patient had a de novo mutation and also carried a hemizygous deletion of chromosome 15q13, which may have contributed to the phenotype. The mutations were found by whole-exome sequencing; Western blot analysis of patient cells showed loss of NONO protein. Patient fibroblasts showed increased expression of 2 other splicing genes, PSPC1 (612408) and SFPQ (605199), as well as a reduced amplitude of circadian oscillations.

In a 17-year-old Ashkenazi Jewish boy of Libyan origin who had developmental delay, macrocephaly, dysmorphism, and left ventricular noncompaction (LVNC), Reinstein et al. (2016) performed exome sequencing and identified hemizygosity for a de novo splice site mutation in the NONO gene (300084.0004).

In 2 unrelated Hispanic boys with global developmental delay, relative macrocephaly, dysmorphic features, and cardiac anomalies including LVNC, Scott et al. (2017) identified mutations in the NONO gene, the previously identified 1-bp duplication (300084.0002) and the R365X substitution (300084.0003), respectively. In a similarly affected Hispanic male infant, the authors identified a maternally inherited Xq13.1 deletion encompassing all of the NONO noncoding exons, 3 coding exons, and at least 19 kb of sequence upstream of the translational start site. Given that 2 of the patients with LVNC carried the identical mutation as previously reported patients without cardiac defects, Scott et al. (2017) suggested that loss of NONO function might predispose males to the development of congenital heart defects and LVNC, with penetrance influenced by additional factors.

Animal Model

Mircsof et al. (2015) found that mice with disruption of the Nono gene had a small cerebellum, impaired spatial memory performance, and increased anxiety compared to control mice. Mutant mouse brains and neurons showed decreased levels of Gabra2 (137140) associated with altered postsynaptic clustering of gephyrin (GPHN; 603930). Expression of Gabra2 rescued the defect in gephyrin clustering. The findings suggested that Nono can regulate Gabra2 levels and thus has a role in regulating inhibitory synaptic biology in the brain, which can affect behavior.

ALLELIC VARIANTS 4 Selected Examples):

.0001 MENTAL RETARDATION, X-LINKED, SYNDROMIC 34

NONO, 1131G-A rs869025343

In a 17-year-old boy (MCCID1) with X-linked syndromic mental retardation-34 (MRXS34; 300967), Mircsof et al. (2015) identified a de novo hemizygous c.1131G-A transition (c.1131G-A,NM_001145408.1) in the last base of exon 10 of the NONO gene, resulting in a splice site defect. The mutation, which was found by whole-exome sequencing and confirmed by Sanger sequencing, was filtered against the dbSNP (build 130), 1000 Genomes Project, and Exome Variant Server databases, as well as an in-house database. Western blot analysis of patient cells showed little or no NONO protein. The patient also carried a de novo heterozygous deletion of chromosome 15q13.3, which may have contributed to the

phenotype.

.0002 MENTAL RETARDATION, X-LINKED, SYNDROMIC 34
NONO, 1-BP DUP, NT1394 rs869025344
In a 15-year-old boy (MCCID2) with X-linked syndromic mental retardation-34 (MRXS34; 300967), Mircsof et al. (2015) identified a hemizygous 1-bp duplication (c.1394dup, NM_001145408.1) in the last coding exon of the NONO gene, resulting in a frameshift and premature termination (Asn466LysfsTer13). The mutation, which was found by whole exome sequencing and confirmed by Sanger sequencing, was filtered against the dbSNP (build 130), 1000 Genomes Project, and Exome Variant server databases, as well as an in-house database. The mutation was inherited from his unaffected mother. Western blot analysis of patient cells showed little or no NONO protein.
In a 5-year-old Hispanic boy with global developmental delay, relative macrocephaly, and cardiac anomalies including left ventricular noncompaction, Scott et al. (2017) identified the c.1394dupC mutation in the NONO gene. The mutation was not found in his unaffected parents or in the Exome Variant Server, 1000 Genomes Project (phase 3), or ExAC (v.0.3) databases.

.0003 MENTAL RETARDATION, X-LINKED, SYNDROMIC 34
NONO, ARG365TER rs869025345
In a 20-year-old man with X-linked syndromic mental retardation-34 (MRXS34; 300967), Mircsof et al. (2015) reported a hemizygous c.1093C-T transition (c.1093C-T, NM_001145408.1) in the NONO gene, resulting in an arg365-to-ter (R365X) substitution in the coiled-coil domain. The patient was part of the Deciphering Developmental Disorders (DDD) study.
In a 10-year-old Hispanic boy with global developmental delay, relative macrocephaly, and cardiac anomalies including left ventricular noncompaction, Scott et al. (2017) identified the R365X mutation in exon 10 of the NONO gene. The mutation was not found in his unaffected parents or in the Exome Variant Server, 1000 Genomes Project (phase 3), or ExAC (v.0.3) databases. Quantitative RT-PCR analysis of patient lymphoblastoid cell lines revealed an 84% reduction in mRNA compared to that of his parents, consistent with nonsense-medicated decay, and Western blot of the same cell lines did not detect any NONO protein.

.0004 MENTAL RETARDATION, X-LINKED, SYNDROMIC 34
NONO, IVS11DS, G-T, +1 rs1114167441
In a 17-year-old Ashkenazi Jewish boy of Libyan origin who had developmental delay, dysmorphism, and left ventricular noncompaction (MRXS34; 300967), Reinstein et al. (2016) identified a de novo c.1171G-T transversion (c.1171G-T, NM_001145408.1) in intron 11 of the NONO gene, predicted to abolish the splice donor site.

REFERENCES

Amelio, A. L., Miraglia, L. J., Conkright, J. J., Mercer, B. A., Batalov, S., Cavett, V., Orth, A.
P., Busby, J., Hogenesch, J. B., Conkright, M. D. A coactivator trap identifies NONO (p54-nrb) as a component of the cAMP-signaling pathway. Proc. Nat. Acad. Sci. 104: 20314-20319, 2007. [PubMed: 18077367] [Full Text: http://www.pnas.org /cgi/pmidlookup?view=long&pmid=18077367]
1.
Andersen, J. S., Lyon, C. E., Fox, A. H., Leung, A. K. L., Lam, Y. W., Steen, H., Mann, M.,

Lamond, A. I. Directed proteomic analysis of the human nucleolus. Curr. Biol. 12: 1-11, 2002. [PubMed: 11790298] [Full Text: https://linkinghub.elsevier.com/retrieve/pii/S0960-9822(01)00650-9]
2.
Brown, C. J., Carrel, L., Willard, H. F. Expression of genes from the human active and inactive X chromosomes. Am. J. Hum. Genet. 60: 1333-1343, 1997. [PubMed: 9199554] [Full
Text: https://linkinghub.elsevier.com/retrieve/pii/S0002-9297(07)64225-6]
3.
Brown, S. A., Ripperger, J., Kadener, S., Fleury-Olela, F., Vilbois, F., Rosbach, M., Schibler, U.
PERIOD1-associated proteins modulate the negative limb of the mammalian circadian oscillator. Science 308: 693-696, 2005. [PubMed: 15860628] [Full Text: http://www.sciencemag.org/cgi/pmidlookup?view=long&pmid=15860628]
4.
Chaoui, A., Kavo, A., Baral, V., Watanabe, Y., Lecerf, L., Colley, A., Mendoza-Londono, R., Pingault, V., Bondurand, N. Subnuclear re-localization of SOX10 and p54NRB correlates with a unique neurological phenotype associated with SOX10 missense mutations. Hum. Molec. Genet. 24: 4933-4947, 2015. [PubMed: 26060192] [Full Text: https://academic.oup.com/hmg/article-lookup/doi/10.1093/hmg/ddv215]
5.
Clark, J., Lu, Y.-J., Sidhar, S. K., Parker, C., Gill, S., Smedley, D., Hamoudi, R., Linehan, W. M., Shipley, J., Cooper, C. S. Fusion of splicing factor genes PSF and NonO (p54-nrb) to the TFE3 gene in papillary renal cell carcinoma. Oncogene 15: 2233-2239, 1997. [PubMed: 9393982] [Full Text: https://dx.doi.org/10.1038/sj.onc.1201394]
6.
Dong, B., Horowitz, D. S., Kobayashi, R., Krainer, A. R. Purification and cDNA cloning of HeLa cell p54(nrb), a nuclear protein with two RNA recognition motifs and extensive homology to human splicing factor PSF and Drosophila NONA/BJ6. Nucleic Acids Res. 21: 4085-4092, 1993. [PubMed: 8371983]
7.
Fox, A. H., Lam, Y. W., Leung, A. K. L., Lyon, C. E., Andersen, J., Mann, M., Lamond, A. I. Paraspeckles: a novel nuclear domain. Curr. Biol. 12: 13-25, 2002. [PubMed: 11790299] [Full
Text: https://linkinghub.elsevier.com/retrieve/pii/S0960-9822(01)00632-7]
8.
Hata, K., Nishimura, R., Muramatsu, S., Matsuda, A., Matsubara, T., Amano, K., Ideda, F., Harley, V. R., Yoneda, T. Paraspeckle protein p54(nrb) links Sox9-mediated transcription with RNA processing during chondrogenesis in mice. J. Clin. Invest. 118: 3098-3108, 2008. [PubMed: 18677406] [Full Text: https://doi.org/10.1172/JCI31373]
9.
Liu, P. Y., Erriquez, D., Marshall, G. M., Tee, A. E., Polly, P., Wong, M., Liu, B., Bell, J. L., Zhang, X. D., Milazzo, G., Cheung, B. B., Fox, A., Swarbrick, A., Huttelmaier, S., Kavallaris,
M., Perini, G., Mattick, J. S., Dinger, M. E., Liu, T. Effects of a novel long noncoding RNA, lncUSMycN, on N-Myc expression and neuroblastoma progression. J. Nat. Cancer Inst. 106: dju113, 2014. Note: Electronic Article. Erratum published online. [PubMed: 24906397] [Full Text: https://academic.oup.com/jnci/article-lookup/doi/10.1093/jnci/dju113]
10.
Mircsof, D., Langouet, M., Rio, M., Moutton, S., Siquier-Pernet, K., Bole-Feysot, C.,

Cagnard, N., Nitschke, P., Gaspar, L., Znidaric, M., Alibeu, O., Fritz, A.-K., and 18 others. Mutations in NONO lead to syndromic intellectual disability and inhibitory synaptic defects. Nature Neurosci. 18: 1731-1736, 2015. [PubMed: 26571461] [Full Text: https://dx.doi.org/10.1038/nn.4169]
11.
Nelson, D. L., Ballabio, A., Cremers, F., Monaco, A. P., Schlessinger, D. Report of the sixth international workshop on X chromosome mapping 1995. Cytogenet. Cell Genet. 71: 308-342, 1995.
12.
Peters, U., Haberhausen, G., Kostrzewa, M., Nolte, D., Muller, U. AFX1 and p54(nrb): fine mapping, genomic structure, and exclusion as candidate genes of X-linked dystonia parkinsonism. Hum. Genet. 100: 569-572, 1997. [PubMed: 9341872]
13.
Reinstein, E., Tzur, S., Cohen, R., Bormans, C., Behar, D. M. Intellectual disability and noncompaction
cardiomyopathy with a de novo NONO mutation identified by exome
sequencing. Europ. J. Hum. Genet. 24: 1635-1638, 2016. [PubMed: 27329731] [Full Text: https://dx.doi.org/10.1038/ejhg.2016.72]
14.
Scott, D. A., Hernandez-Garcia, A., Azamian, M. S., Jordan, V. K., Kim, B. J., Starkovich, M.,
Zhang, J., Wong, L.-J., Darilek, S. A., Breman, A. M., Yang, Y., Lupski, J. R., Jiwani, A. K., Das, B., Lalani, S. R., Iglesias, A. D., Rosenfeld, J. A., Xia, F. Congenital heart defects and left ventricular non-compaction in males with loss-of-function variants in NONO. J. Med. Genet. 54: 47-53, 2017. [PubMed: 27550220] [Full Text: http://jmg.bmj.com /cgi/pmidlookup?view=long&pmid=27550220]
15.
Contributors: Marla J. F. O'Neill - updated : 06/08/2017
Patricia A. Hartz - updated : 2/24/2016
Cassandra L. Kniffin - updated : 2/18/2016
Patricia A. Hartz - updated : 8/27/2014
Cassandra L. Kniffin - updated : 9/13/2011
Patricia A. Hartz - updated : 11/6/2008
Patricia A. Hartz - updated : 4/16/2008
Ada Hamosh - updated : 9/8/2005
Victor A. McKusick - updated : 10/16/1997
Creation Date: Victor A. McKusick : 6/22/1997
Edit History: carol : 06/08/2017
OMIM Entry - * 300084 - NON-POU DOMAIN-CONTAININ...
https://www.omim.org/entry/300084

300967

MENTAL RETARDATION, X-LINKED, SYNDROMIC 34; MRXS34
ORPHA: 466791; DO: 0060817;

INHERITANCE
- X-linked

GROWTH
Other
- Slender build

HEAD & NECK
Head
- Macrocephaly, relative or absolute
Face
- Long face
- Frontal bossing
- Malar hypoplasia
Eyes
- Upslanting palpebral fissures
- Strabismus
- Myopia
Nose
- Thin nasal root
- High nasal root
- Deviated nasal septum (in some patients)
- Prominent nose
Mouth
- Open mouth
- Small mouth
- High narrow palate
- Wide mouth (in some patients)
Teeth
- Crowded teeth
- Widely spaced teeth (in some patients)

CARDIOVASCULAR
Heart
- Left ventricular noncompaction
- Atrial septal defect
- Ventricular septal defect
- Patent ductus arteriosus
- Patent foramen ovale
- Right ventricular hypertrophy

ABDOMEN
Gastrointestinal
- Poor sucking in infancy
- Gastroesophageal reflux (in some patients)

GENITOURINARY
Internal Genitalia (Male)
- Cryptorchidism (in some patients)

SKELETAL
Skull
- Macrocephaly, relative or absolute
- Thickened calvarium
Spine
- Scoliosis
- Kyphosis
Hands
- Ankylosis of the metacarpophalangeal joint of P1
Feet
- Pes planus
- Hallux valgus

MUSCLE, SOFT TISSUES
- Hypotonia, neonatal

NEUROLOGIC
Central Nervous System
- Delayed psychomotor development
- Intellectual disability
- Poor language
- No language
- Seizures (in 1 patient)
- Thickened corpus callosum
- Dysgenesis of the corpus callosum
- Cerebellar hypoplasia (in some patients)
Behavioral Psychiatric Manifestations
- Shy, gentle, cheerful demeanor (in some patients)
- Anxious demeanor (in some patients)
- Aggressive behavior (in some patients)

VOICE
- Nasal speech

ENDOCRINE FEATURES
- Delayed puberty (in some patients)

MISCELLANEOUS
- Three unrelated males have been reported (last curated February 2016)

MOLECULAR BASIS
- Caused by mutation in the non-POU domain-containing octamer-binding protein gene (NONO, 300084.0001)

Contributors: Marla J. F. O'Neill - updated : 06/15/2017
Creation Date: Cassandra L. Kniffin : 2/18/2016

NOTE: OMIM is intended for use primarily by physicians and other professionals concerned with genetic disorders, by genetics
researchers, and by advanced students in science and medicine. While the OMIM database is open to the public, users seeking
information about a personal medical or genetic condition are urged to consult with a qualified physician for diagnosis and for

answers to personal questions.

Printed: March 23, 2019
® ®
®
OMIM Clinical Synopsis - #300967 - MENTAL RETARDATIO...
https://www.omim.org/clinicalSynopsis/300967