# A syndromic form of Pierre Robin sequence is caused by 5q23 deletions encompassing *FBN2* and *PHAX*

*Ansari et al.*

**Supplementary material**

**Supplementary Table S1.** Genes mapping within the critical region associated with Pierre Robin sequence and congenital contractural arachnodactyly.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Gene | Other names | Function | Mutant phenotype | HI Score | Notes |
| GRAMD3 | NS3TP2 | Unknown | Unknown | 73 | GRAMD3 is highly expressed in the retinal pigment epithelium (Strunnikova et al., 2010). The GRAM domain is around 70 amino acids long and has been identified in a variety of membrane-associated proteins such as glucosyltransferases, Rab-like GTPase activators, and phosphatidyl inositol phosphate (PIP) phosphatases of the myotubularin (MTM) family (Doerks et al., 2000). |
| ALDH7A1 | EPD, PDE, ATQ1 | Aldehyde dehydrogenase | Loss of one copy: none (man) | 22.9 | ALDH7A1 is an enzyme required for lysine catabolism (Mills et al., 2006). Homozygous or compound heterozygous mutations of the ALDH7A1 gene cause pyridoxine-dependent epilepsy (MIM 266100), characterised by neonatal seizures that do not respond to conventional anticonvulsants. In the absence of ALDH7A1, accumulation of lysine catabolites inactivates pyridoxal phosphate (PLP), thus perturbing neurotransmitter metabolism and causing seizures (Mills et al., 2006; Plecko et al., 2007). Individuals with one mutant copy of the gene are asymptomatic. |
|  |  |  | Loss of both copies: pyridoxine-dependent epilepsy (man) |  |  |
| PHAX | RNUXA | Small nuclear RNA export protein | Unknown | Unknown | RNUXA (also called PHAX) is a component of the nuclear protein complex that exports small nuclear and small nucleolar RNAs into the cytoplasm and nucleolus respectively (Mourao et al., 2010) (Suzuki et al., 2010). It is enriched in nuclear subdomains called Cajal bodies which are specialised sites for the assembly of small ribonucleoproteins (Suzuki et al., 2010). |
| LMNB1 | LMN, ADLD, LMN2, LMNB | Component of nuclear lamina | Duplication: demyelinating leukodystrophy (man) | 2.9 | The LMNB1 gene encodes Lamin B1, a structural component of the nuclear lamina that is important for normal nuclear architecture, DNA replication and gene expression (Capell and Collins, 2006). Up-regulation of LMNB1 expression, typically through genomic duplication, is implicated in the aetiology of adult-onset demyelinating leukodystrophy (ADLD, MIM 169500), a progressive form of neuronal degeneration (Padiath et al., 2006). The phenotype associated with loss of human LMNB1 function is unknown. Heterozygous Lmnb1 knockout mice are phenotypically indistinguishable from wild type, but homozygotes have bone and lung defects and die at birth (Vergnes et al., 2004). Lmnb1-/- fibroblasts have misshapen nuclei and undergo premature senescence. |
|  |  |  | Loss of one copy: none (mouse) |  |  |
|  |  |  | Loss of both copies: neonatal lethality (mouse) |  |  |
| MARCH3 | RNF173, MARCH III | Possible endosomal protein | Unknown | 8.9 | MARCH3 is a member of a family of membrane-bound E3 ubiquitin ligases which have a variety of functions including immune regulation, protein degradation and vesicular trafficking (Fukuda et al., 2006). MARCH3 is thought to function in the endosomal recycling pathway (Fukuda et al., 2006). |
| MEGF10 | EMARDD | Homolog of C. elegans CED-1 phagocytic receptor | loss of both copies: congenital myopathy with minicores | 84 | MEGF10 is a plasma membrane protein which has structural and functional similarities to the C. elegans phagocytic cell receptor CED-1 and appears to be involved in the clearance of dead cells and amyloid-b aggregates (Hamon et al., 2006; Singh et al., 2010). It also regulates proliferation and differentiation of muscle satellite cells, which play an important role in skeletal muscle repair (Holterman et al., 2007). Homozygous or compound heterozygous mutations in MEGF10 have been identified in early-onset myopathy, areflexia, respiratory distress, and dysphagia (EMARDD, MIM 614399) (Logan et al., 2011). |
| PRRC1 | FLJ32875 | Unknown | Unknown | 73 | PRRC1 encodes a protein of unknown function which contains an N-terminal domain that is highly enriched in proline (Kamakari et al., 2005). The PRRC1 gene has several splice variants and is expressed in a wide variety of human tissues. At least one PRRC1 protein isoform associates with the Golgi apparatus. |
| CTXN3 | Cortexin 3, KABE | Unknown | Unknown | 14.5 | The CTXN3 gene encodes Cortexin 3, an 81-amino acid polypeptide of unknown function (Wang et al., 2007). It is expressed in kidney and brain. The protein has a predicted transmembrane domain that is highly conserved. |
| SLC12A2 | BSC, BSC2, NKCC1 | Ion transporter | Loss of both copies: deafness and imbalance (mouse) | 46 | The SLC12A2 protein (also called NKCC1) transports sodium, potassium and chloride ions across the basolateral membranes of secretory epithelia (Flagella et al., 1999). Homozygous loss of function of Slc12a2 in mice causes deafness and balance problems due to abnormal production of cochlear endolymph (Flagella et al., 1999; Dixon et al., 1999; Delpire et al., 1999). |
| FBN2 | Fibrillin 2, CCA, DA9 | Component of elastic fibres | Gain of function: CCA (man) | 10.7 | The FBN2 gene encodes fibrillin 2 which is preferentially expressed in elastic fibre-rich extracellular matrices during embryogenesis (Ramirez et al., 2010). Fibrillins are large glycoproteins that are important for elastic fibre structure while also playing a role in tissue morphogenesis by binding and sequestering growth factors such as TGFb (Ramirez et al., 2010). |
|  |  |  | Loss of one copy: CCA (man); none (mouse) |  |  |
|  |  |  | Loss of both copies: unknown (man); syndactyly, weak limbs (mouse) |  |  |

**Supplementary Table S2.** Genes mapping within the critical region associated with talipes equinovarus (TEV).

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Gene | Other names | Function | Mutant phenotype | HI Score | Notes |
| CHSY3 | CSS3, CHSY2, chondroitin sulfate synthase 3 | Glycosyltransferase activity | Unknown | 39.6 | CHSY3 is a glycosyltransferase that has both glucuronyltransferase and N-acetylgalactosaminyltransferase activities, and is ubiquitously expressed in various human tissues (Yada et al., 2003). |
| HINT1 | HINT, NMAN, PKCI-1, PRKCNH1, histidine triad nucleotide binding protein 1 | Hydrolyses adenosine 5'-monophosphoramidate substrates. Also a tumour suppressor | Loss of both copies: no overt phenotype (mouse) | 31.6 | HINT1 encodes a ubiquitously expressed homodimeric purine phosphoramidase which hydrolyzes substrates such as AMP-morpholidate, AMP-N-alanine methyl ester, AMP-alpha-acetyl lysine methyl ester, and AMP-NH2. Additionally, HINT1 has been implicated as a tumour suppressor that participates in several apoptotic pathways. Loss-of-function point mutations have been shown to cause autosomal recessive neuromyotonia and axonal neuropathy (MIM 137200) (Zimon et al., 2012). |
| LYRM7 | MZM1L, LYR motif containing 7 | Mammalian Complex III assembly factor | Unknown | 82.2 | LYRM7 works as a human Rieske Fe-S protein (UQCRFS1) chaperone, binding to this subunit within the mitochondrial matrix and stabilizing it prior to its translocation and insertion into the late Complex III dimeric intermediate within the mitochondrial inner membrane (Sanchez et al., 2013). A disease-segregating homozygous mutation was identified in a proband with early onset, severe encephalopathy, lactic acidosis and profound, isolated cIII deficiency in skeletal muscle (Invernizzi et al., 2013). |
| CDC42SE2 | SPEC2, CDC42 small effector 2 | Probably involved in organisation of actin cytoskeleton | Unknown | 39.5 | The CDC42SE2 protein is widely expressed, with high expression in lymphocytes. It interacts with CDC42 and modulates the actin polymerization, focal complex assembly, and kinase signalling activity of CDC42 (Pirone et al., 2000). |
| RAPGEF6 | RAGEF2, PDZGEF2, KIA001LB, PDZ-GEF2, RA-GEF-2, Rap guanine nucleotide exchange factor 6 | Guanine nucleotide exchange factor | Loss of both copies: enlarged spleen, increased IgE and IgG levels and altered cytokine production (mouse). | 10.7 | RAPGEF6 is a ubiquitously expressed guanine nucleotide exchange factor (GEF) characterised by the presence of a PSD-95/DlgA/ZO-1 (PDZ) domain, a Ras-association (RA) domain and a region related to a cyclic nucleotide binding domain (RCBD). These domains are in addition to a Ras exchange motif (REM) and GEF domain characteristic for GEFs for Ras-like small GTPases. RAPGEF6 exchanges nucleotides of two Ras-like GTPases, Rap1 and Rap2 involved in cell adhesion and proliferation (Kuiperij et al., 2003). |
| FNIP1 | folliculin interacting protein 1 | May be involved in energy and/or nutrient sensing through the AMPK and mTOR signalling | Unknown | 15 | FNIP1 is ubiquitously expressed and interact with FLCN, which is mutated in autosomal dominant Birt-Hogg-Dubé syndrome (MIM 135150), a hamartoma disorder characterized by benign tumours of the hair follicle, lung cysts, and renal neoplasia (Nickerson et al., 2002). FNIP1 interacts with 5' AMP-activated protein kinase (AMPK), a key molecule for energy sensing that negatively regulates mTOR activity (Baba et al., 2006). |
| ACSL6 | ACS2, FACL6, LACS2, LACS5, LACS 6, acyl-CoA synthetase long-chain 6 | Catalyses formation of acyl-CoA from fatty acids, ATP and CoA | Unknown | 93.7 | ACSL6 is highly expressed in the brain and bone marrow, and plays a major role in fatty acid metabolism (Soupene et al., 2010). Three balanced translocations involving ACSL6 were identified in a patient with refractory anaemia with excess blasts (RAEB) with basophilia, a patient with acute myelogenous leukemia (AML) with eosinophilia, and a patient with acute eosinophilic leukemia (AEL) (Yagasaki et al., 1999). |
| IL3 | MCGF, MULTI-CSF, interleukin 3 | Growth promoting cytokine | Unknown | 98.8 | Interleukin-3 is a hematopoietic colony-stimulating factor is mostly expressed in spleen and lymph nodes, and is capable of supporting the proliferation of a broad range of hematopoietic cell types (Chavany et al., 1998). Mice over-expressing IL3 exhibit severe hind limbs paralysis (Chavany et al., 1998). |
| CSF2 | GMCSF, colony stimulating factor 2 | Cytokine activity | Loss of both copies: lung abnormalities with lymphocytic infiltration and accumulation of surfactant lipids. Perinatal mortality (mouse) | 2.7 | CSF2 encodes a granulocyte/macrophage colony-stimulating factor (GM-CSF) which is necessary for the survival, proliferation, and differentiation of hematopoietic progenitor cells |
| P4HA2 | prolyl 4-hydroxylase, alpha polypeptide II | A component of prolyl 4-hydroxylase, a key enzyme in collagen synthesis | unknown | 30.6 | In collagen, P4HA2 catalyses the formation of 4-hydroxyproline, essential for the proper three-dimensional folding of newly synthesised pro-collagen chains |

**Supplementary Table S3.** Sequences of primers used to construct riboprobes for WISH

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Gene/Primer Name | Primer sequence (RNA polymerase binding site in bold) | Polymerase | Target region | Probe size |
| Aldh7a1\_F | **AATTAACCCTCACTAAAGG**GGAAGGTCACTGCTGAGAGG | **T3** | 3' UTR | 414bp |
| Aldh7a1\_R | **TAATACGACTCACTATAGG**TAGTGCAGTGCTGGAGATGG | **T7** |  |  |
| Fbn2\_F | **AATTAACCCTCACTAAAGG**CAAAAAGGGAAACTCGCTTG | **T3** | 3' UTR | 494bp |
| Fbn2\_R | **TAATACGACTCACTATAGG**AGGTGTTCCTGCTCAAAGGA | **T7** |  |  |
| Gramd3\_F | **AATTAACCCTCACTAAAGG**ATCCTGGTCAGCCATCAGAC | **T3** | 3' UTR | 435bp |
| Gramd3\_R | **TAATACGACTCACTATAGG**GCTTTCCGTCCCATGTTAAA | **T7** |  |  |
| Lmnb1\_F | **AATTAACCCTCACTAAAGG**GCGAATCTGATGGCCTTAAT | **T3** | 3' UTR | 472bp |
| Lmnb1\_R | **TAATACGACTCACTATAGG**CTCCATCCAGAGTGCGTACA | **T7** |  |  |
| March3\_F | **AATTAACCCTCACTAAAGG**ATGTGACGAGGCTGACACTG | **T3** | 3' UTR | 410bp |
| March3\_R | **TAATACGACTCACTATAGG**CGCTTTGTTTTCCTCTTTGG | **T7** |  |  |
| Megf10\_F | **AATTAACCCTCACTAAAGG**CAGAGCAGCATAGGGTGTCA | **T3** | 3' UTR | 408bp |
| Megf10\_R | **TAATACGACTCACTATAGG**AGGACTCTACGGGGCAGTTT | **T7** |  |  |
| Prrc1\_F | **AATTAACCCTCACTAAAGG**GGCTCGTTTGAAACCGAATA | **T3** | 3' UTR | 404bp |
| Prrc1\_R | **TAATACGACTCACTATAGG**AAGGCTTGAAAAAGGCAACA | **T7** |  |  |
| Phax\_F | **AATTAACCCTCACTAAAGG**CGAGAAACGTTTGCAAGTGA | **T3** | CDS | 401bp |
| Phax\_R | **TAATACGACTCACTATAGG**AACAGTGGGCTGAACAGAGG | **T7** |  |  |

**Supplementary Table S4.** Previously published cases of constitutional deletion 5q (adapted from Courtens *et* *al*. American Journal of Medical Genetics 77:188-197 (1998)).

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Clinical findings | Courtens et al. [1998] | Silengo et al. [1981] (case 2, Centerwall et al. [1978) | Felding and Kristoffersson [1980] | Harprecht-Beato et al. [1983] | de Michelena et al. [1990] | Silengo et al. [1981] (case 1) | Hastings et al. [2000] | Bennett et al. [1997] | Kadotani et al. [1984] | Rivera et al. [1987] | Rivera et al. [1990] | Kobayashi et al. [1991]; Kadotani et al. [1979]; Katano et al. [1980] | Arens et al. [2004] | Lindgren et al. [1992] (case 2) | Tzschach et al. [2006] |
| Cytogenetic breakpoints (chr5) | q15q31.1 | q15q31 or q13q22 | q15q31 | q15q31 or q13q15 | q15q31 & t(1;11) | 22q31 or q13q15 or q15q22 | q22q23.3 ins(10;5)(q25;q22q23.3) | q22q23.2] | q22q31 | q23.3q31.1 | q22q31.1 | q22.1q31.1 | 5q22.1-5q31.3 Familial Insertion (3;5)(q25.3;q22.1q31.3) | q22.3q31.1 | q23.3q31.2 |
| Molecular cytogenetics | N | N | N | N | N | N | Y | Y | N | N | N | N | Y | N | Y |
| Max size of deletion |  |  |  |  |  |  |  | chr5:117,171,838-128,291,729 |  |  |  |  |  |  | chr5:127,811,207-137,225,025 |
| Boundary probes |  |  |  |  |  |  | APC probe only | D5S494 |  |  |  |  | cCI5-162 probe only |  | RP11-1069N21 to RP11-381K20 |
| Age at assessment/ Follow-up | IU 23 w | 15 m-4y | 0–30 m | 0–14 m | 12–22 m | 6 m | 1 m | 34 y | 28 y | 4 m | 14 m | 15 y | 7y | 8 m | 2.25 y |
| Sex | F | F | F | M | F | M | M | F | M | M | F | M | F | F | M |
| Birth weight (g) | 620 | 2900 | 3640 | 2900 | 2620 | 3300 | 1860 @ 40/40 | 2636 | 3100 | 2800 | 3350 | 3750 | 1820 @ 37/40 | 2750 | 3700 |
| Age Mother/Father (years) | 30/35 | 28/39 | 29/31 | 21/24 | 18/25 | 32/33 | 21/34 | 24/24 | 32/33 | 33/30 | 20/25 | 29/30 | 19/? | NR | 31/38 |
| Failure to thrive | - | + | + | + | + | + | + | ? | NR | + | - | -? | + | + | + |
| Short stature | - | + | NR | + | + | + | + | + | + | + | +/- | +/- | + | + | - |
| Psychomotor retardation | ? | S | S | S | S | + | ? | + (schizophrenia) | S | + | + | + | + | S | + |
| Hypotonia | ? | + | + | - | + | + | - |  | NR | + | NR | + | - | + | NR |
|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Short neck | + | + | + | + | + | + |  | + | + | + | ? | NR | - | + | - |
| Prominent/high forehead | + | + | + | + | + | + |  | - | NR | + | ? | NR | + | + | - |
| Downslanting palpebral fissures | + | - | + | + | + | + | + | + | ? | + | + | + | - | + | - |
| Palpebral fissure aperture |  |  |  | Blepharophimosis |  |  |  | Blepharophimosis | Blepharophimosis | Ptosis |  | Ptosis | Normal |  |  |
| Hypertelorism | + | - | + | . | + | NR |  | + | + | + | ? | + | - | + | + |
| Flat nasal bridge | + | + | + | + | + | + |  | ? | + | NR | + | + | + | + |  |
| Anteverted nostrils | + | + | + | + | + | - | + |  | + | + | ? | + | - | + | + |
| Cleft or high arched palate | - | + | + | + | . | - | + (CP) |  | - | + | + | + | + (CP) | + | + (HAP) |
| Micrognathia | + | - | + | - | + | NR | + | + | NR | + | ? | + | + | + | + |
| Low-set/dysplastic ears | + | + | + | + | unfolded conchae | + | + |  | - | outfolded helix | + | + | - | abnormal folding, pointed | + |
|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Thin limbs | + | NR | NR | NR | NR | + |  | - | ? | + | ? | ? | NR | + | + |
| Arachno/camptodactyly | +(?) | NR | NR | - | - | - | mirror polydactyly, arthrogryposis | tapering digits | NR | NR | NR | - | - | + | + |
| Dislocated hip(s) | + | - | - | + | + | + |  | - | NR | + | ? | - | - | + | - |
| Talipes equinovarus | + | + | NR | + | NR | - | + | - | NR | + | - | - | - | + | - |
| Kyphoscoliosis | - | - | NR | - | NR | - |  | - | + | NR | NR | NR | - | NR | - |
|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Congenital cardiac anomaly | - | - | + | + | NR | NR | ? | - | NR | - | NR | - | - | + | - |
| Urogenital abnormalities | - | + | + | - | ? | - | cryptorchidism | - | + | + | NR | + | - | NR | - |
| Polyposis coli | - | - | - | - | - | - | - | - | NR | NR | NR | + | - | NR | - |

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