REVIEW ARTICLE

Robinow syndrome

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In 1969, Robinow and colleagues described a syndrome of mesomelic shortening, hemivertebrae, genital hypoplasia, and "fetal facies". Over 100 cases have now been reported and we have reviewed the current knowledge of the clinical and genetic features of the syndrome. The gene for the autosomal recessive form was identified as the *ROR2* gene on chromosome 9q22. ROR2 is a receptor tyrosine kinase with orthologues in mouse and other species. The same gene, *ROR2*, has been shown to cause autosomal dominant brachydactyly B, but it is not known at present whether the autosomal dominant form of Robinow syndrome is also caused by mutations in *ROR2*.

In 1969, Robinow *et al*[1] described a new dwarfing syndrome with mesomelic limb shortening, hemivertebrae, and genital hypoplasia. Robinow proposed the term "fetal facies" to describe the characteristic facial appearance and this term has continued to be used. Both autosomal recessive and autosomal dominant inheritance have been described suggesting there is allelic heterogeneity. Recently, the gene for the autosomal recessive Robinow syndrome has been mapped[2] and identified,[3 4] which leads the way to a new understanding of this multisystem developmental disorder.

Medical publications now include over 100 cases and cover most ethnic groups, but relatively few reports have emerged in Afro-Caribbean or Japanese patients. With the autosomal recessive form, clusters have been reported from Turkey,[5] Oman,[6] and Czechoslovakia.[7] This reflects the high degree of consanguinity in these populations.

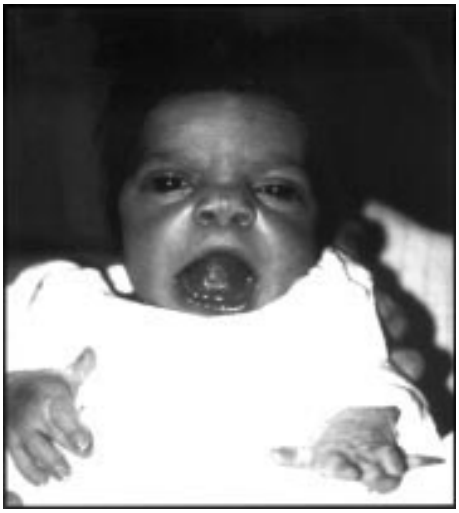

Figure 1 Facial features of Robinow syndrome.

CLINICAL FEATURES

The facial features in early childhood are characteristic (fig 1). There is marked hypertelorism with midfacial hypoplasia and a short upturned nose. The nasal bridge may be depressed or flat. The forehead is broad and prominent. Robinow[8] illustrates the resemblance to a fetal face by emphasising the relatively small face, laterally displaced eyes, and forward pointing alae nasi. The appearance changes with time and the resemblance to "fetal facies" becomes less marked with time. This point is well illustrated in the paper by Saraiva *et al*,[9] which shows the progressive changes with age in a pair of monozygous twin boys. The facial appearance in adult life is not well documented. Bain *et al*[10] illustrate the facial features in an affected father who had two children affected by the autosomal dominant form. The fetal facial proportions have been lost and there is no midfacial hypoplasia, but hypertelorism with a broad nasal root and broad forehead have persisted.

There are a number of specific oral features, which greatly aid in the diagnosis. The upper lip tends to be "tented", that is, to have an inverted V appearance with tethering in the centre. This defect in the lip may expose the incisors and upper gum. Midline clefting of the lower lip has also been reported. In the mouth, gum hypertrophy may be present from birth. A similar pattern of gum hypertrophy at birth may be seen in storage diseases such as I cell disease. Dental crowding and irregular teeth may be seen with both primary and secondary dentition. Another feature commonly seen in the mouth is the presence of ankyloglossia or "tongue tie". When it is marked it may give the appearance of a bifid tongue.

The eyes may be very prominent and give the appearance of exophthalmos. This feature in Robinow syndrome differs from true exophthalmos as the eyes do not protrude from the orbit. Instead there is a deficiency of the lower eyelid that gives the eyes a more prominent appearance. This pseudoexophthalmos may need surgical correction if the eyes cannot close fully. The ears may be low set and simple or have deformation of the pinna. Occasionally there may be a midline capillary haemangioma.

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Abbreviations: TK, tyrosine kinase; RTK, receptor tyrosine kinase; Ig, immunoglobulin-like; CRD cysteine rich domain; KD, kringle domain; BMP, bone morphogenic proteins

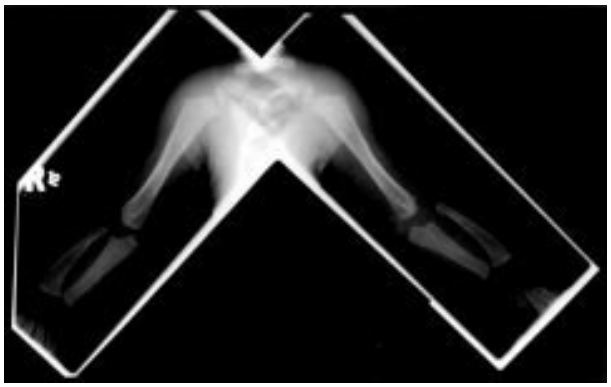

Figure 2 *X* ray showing the mesomelic shortening in the arms.

In most skeletal dysplasias with dwarfism, the limb shortening is rhizomelic. In Robinow syndrome the limb shortening is mesomelic or acromesomelic (fig 2). The shortening of the forearm tends to be more striking than the shortening in the leg. Madelung deformity has been reported. In the hands, there is also brachydactyly with shortening of the distal phalanx and nail hypoplasia or dystrophy. The thumb may be displaced and on occasions there may be a bifid thumb. Partial cutaneous syndactyly occurs in the hands and feet, but does not produce a consistent pattern. In a number of the patients, especially those reported from Turkey, there has been a split hand (ectrodactyly). The dermatoglyphic pattern[5] reflects the underlying maldevelopment of the hands with absent interphalangeal creases, bilateral transverse creases, and a hypothenar whorl pattern. Radiological examination may show fusion of the phalanges and fusion of the carpal bones. One very striking feature is the splitting of one or more distal phalanges.

Spinal abnormalities are frequent and may be severe (fig 3A). Externally there is kyphoscoliosis and chest deformity, but radiologically there is widespread fusion of thoracic vertebrae with frequent hemivertebrae (fig 3B). There may also be fusion of the ribs (fig 3A). The radiological appearance in severe cases may resemble that of Jarcho-Levin syndrome and spondylocostal dysostosis.

Genital abnormalities may be noted at birth and in some cases cause concern regarding gender assignment at birth. In females, the anatomical defect is not always very obvious. There is reduced clitoral size and hypoplasia of the labia minora. One report by Balci *et al*[11] described associated vaginal atresia and haematocolpos. In males, the characteristic pattern is to find a micropenis with normal scrotum and testes (fig 4). There has been some debate about whether this is because of a defect in androgen receptors, as suggested by Schonau *et al*.[12] Lee *et al*[13] found normal androgen receptor activity and 5α reductase activity in genital skin fibroblasts in two patients, and Soliman *et al*[6] showed a good response to prolonged HCG stimulation in three prepubertal boys leading to improvement in penile size. The other significant endocrine finding in the study of Soliman *et al*[5] was the presence of an empty sella in the majority of cases studied. This finding did not appear to be associated with abnormality in the LH or FSH levels. There is relatively sparse information about the onset of puberty, but it appears to take place spontaneously in both males and females. There are also several reports of both male and female patients having children. The reports of normal fertility in affected men have been in families with autosomal dominant inheritance,[10 14] but it is not clear whether there would be reduced fertility in the autosomal recessive cases.

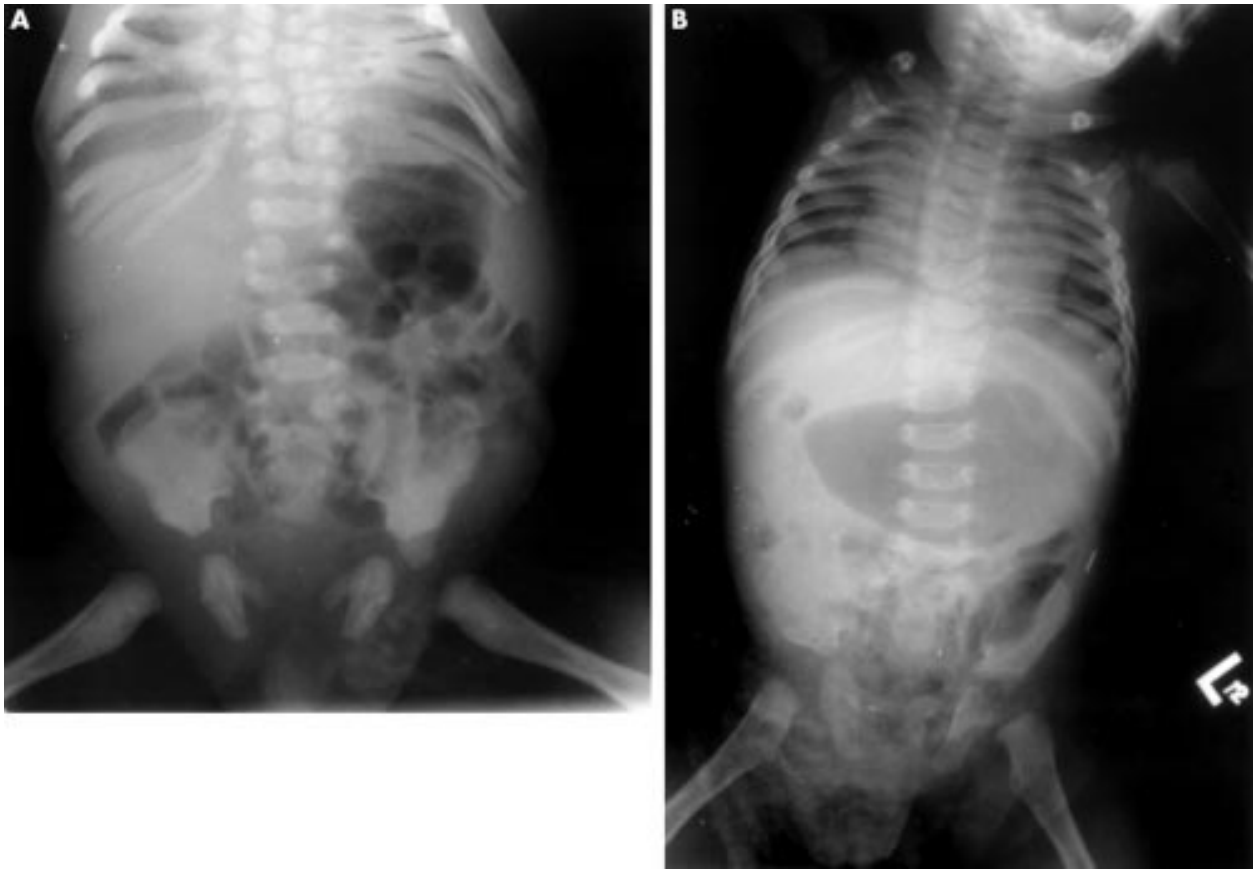

Figure 3 (A) In autosomal recessive Robinow syndrome there may be considerable spinal deformity and rib fusion resembling the features seen in spondylocostal dysostosis. (B) *X* ray of spine showing multiple hemivertebrae.

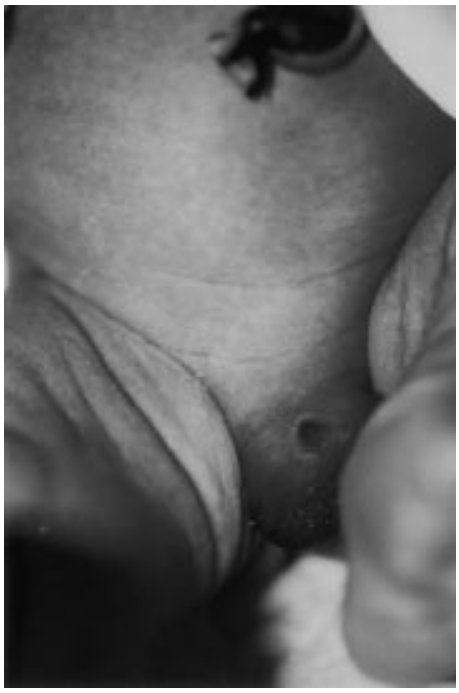

Figure 4 The genital abnormalities in males are micropenis with normal scrotum and testes.

Renal tract abnormalities have been associated with the genital abnormalities. Hydronephrosis is relatively common where it is screened for and might in theory predispose to urinary tract infections. Cystic dysplasia of the kidney has also been reported.[5 15] As would be expected in a syndrome with limb shortening and spinal deformity, there is also reduced stature. Birth length is reduced and in the series of Soliman *et al*[6] the growth was –2.17 SD below the mean. There is a normal growth hormone response and normal levels of insulin-like growth factor (IGF1). Growth hormone should be used with care as there may be a theoretical risk of exacerbating the scoliosis. Short stature has not been universal and normal growth has been reported.[9 10]

A number of reports[16 17] have drawn attention to the association of congenital heart disease in Robinow syndrome. Around 15% of published cases have had a congenital heart defect. Among the abnormalities reported are atrial septal defect, ventricular septal defect, coarctation of the aorta, tetralogy of Fallot, severe pulmonary stenosis or atresia, and tricuspid atresia. It is difficult to recognise any specific pattern in the heart defects but the commonest abnormality appears to be pulmonary stenosis or atresia. It is important to screen for congenital heart defects at birth as they are probably the major cause of mortality in this syndrome in the first years of life.

Intelligence is usually normal but developmental delay occurs in 10-15% of cases. Macrocephaly is commonly found in Robinow syndrome and does not specifically indicate a risk factor for developmental delay. One reported patient with developmental delay has been reported with an MRI brain scan which showed cortical dysplasia.[18] It is not known whether this is the explanation for the developmental delay in other affected children.

A number of complications that have been associated with Robinow syndrome may be coincidental especially if the child comes from a highly consanguineous population. The report by Nazer *et al*[19] of Crigler-Najar syndrome in association with Robinow syndrome is almost certainly explained in this way. Similarly, a report from Kuwait by Sabry *et al*[20] in which cutis laxa and immune deficiencies occur with Robinow syndrome might be coincidental.

Table 1 There is considerable overlap between the autosomal dominant and recessive forms of Robinow syndrome. The recessive Robinow syndrome tends to be more severe as can be seen in the table below (modified from Robinow[8])

Autosomal recessive	Autosomal dominant
Shorter stature –2 SD or less	Height short or normal
Very marked shortening of arms	Slight shortening of arms
Radial head dislocation	No radial head dislocation
Tented upper lip	Normal upper lip
10% mortality	No excess mortality

GENETICS

Genetic counselling in the presence of a family history is relatively easy and prenatal diagnosis may be offered at 19 weeks using fetal ultrasound.[21] The main problem in genetic counselling arises when there is an isolated case, as the phenotypic features for autosomal recessive cases and new autosomal dominant cases are similar. In general terms, the severity tends to be greater in autosomal recessive cases, but table 1 indicates some of the features which may guide genetic counselling in this situation and, in addition, mutation analysis may now resolve the issue.

The gene for autosomal recessive Robinow syndrome was first localised to a 4 cM interval on chromosome 9q22 between markers D9S1836 and D9S1803, with a maximum multipoint lod score of 12.3.[2] This was done using homozygosity (autozygosity) mapping on patients from Oman, Brazil, and Pakistan. The Omani cases shared a common haplotype at this locus (RBNW1), so were considered likely to have originated from a single founder mutation. Mapping to this region has also been described in people of Turkish origin to 4.9 cM.[4] The *ROR2* gene was also located in this region and heterozygous mutations in *ROR2* had been shown to cause the autosomal dominant condition brachydactyly type B.[22] Moreover, homozygous mutations in the mouse *Ror2* gene cause mesomelic dwarfing.[23 24] These reports made *ROR2* a strong candidate gene for autosomal recessive Robinow syndrome. Confirmation of this was reported by Afzal *et al*[3] and van Bokhoven *et al*.[4]

ROR2 belongs to the ROR family of receptor tyrosine kinases (RTKs) closely related to Trk, with at least two structurally very similar members, ROR1 and ROR2, with 58% overall amino acid identity and, more importantly, similar domain structures. *ROR1*, which is located on chromosome 1p31-32,[25] encodes a 3358 bp transcript with a protein product of 937 amino acid. *ROR2* contains nine exons and encodes a 4092 bp transcript. The protein product consists of 943 amino acids and is an orphan receptor tyrosine kinase that binds to an as yet unidentified ligand. It contains distinct motifs including an immunoglobulin-like (Ig) domain, a frizzled-like cysteine rich domain (CRD), and a kringle domain (KD) in the extracellular region, a transmembrane section, and an intracellular region with tyrosine kinase (TK), serine/threonine rich and proline rich structures (fig 5A). The extracellular motifs of the ROR2 protein are known to be involved in protein-protein interactions by analogy with other similar proteins.[26]

ROR2 AND ITS ORTHOLOGUES IN OTHER SPECIES

Orthologues of the ROR family of RTKs have been identified in other species, such as *CAM-1* in *C elegans*,[27] *Dror* and *Dnrk* in *Drosophila melanogaster*,[28 29] and *Ror1* and *Ror2* in rats and mice.[26]

In mice, the *Ror1* and *Ror2* genes are located on chromosome 4 and chromosome 13 respectively. Mouse *Ror1* and *Ror2* have a very similar structure not only at the DNA level but also at the protein level with 58% amino acid identity. Both proteins contain similar conserved domains.

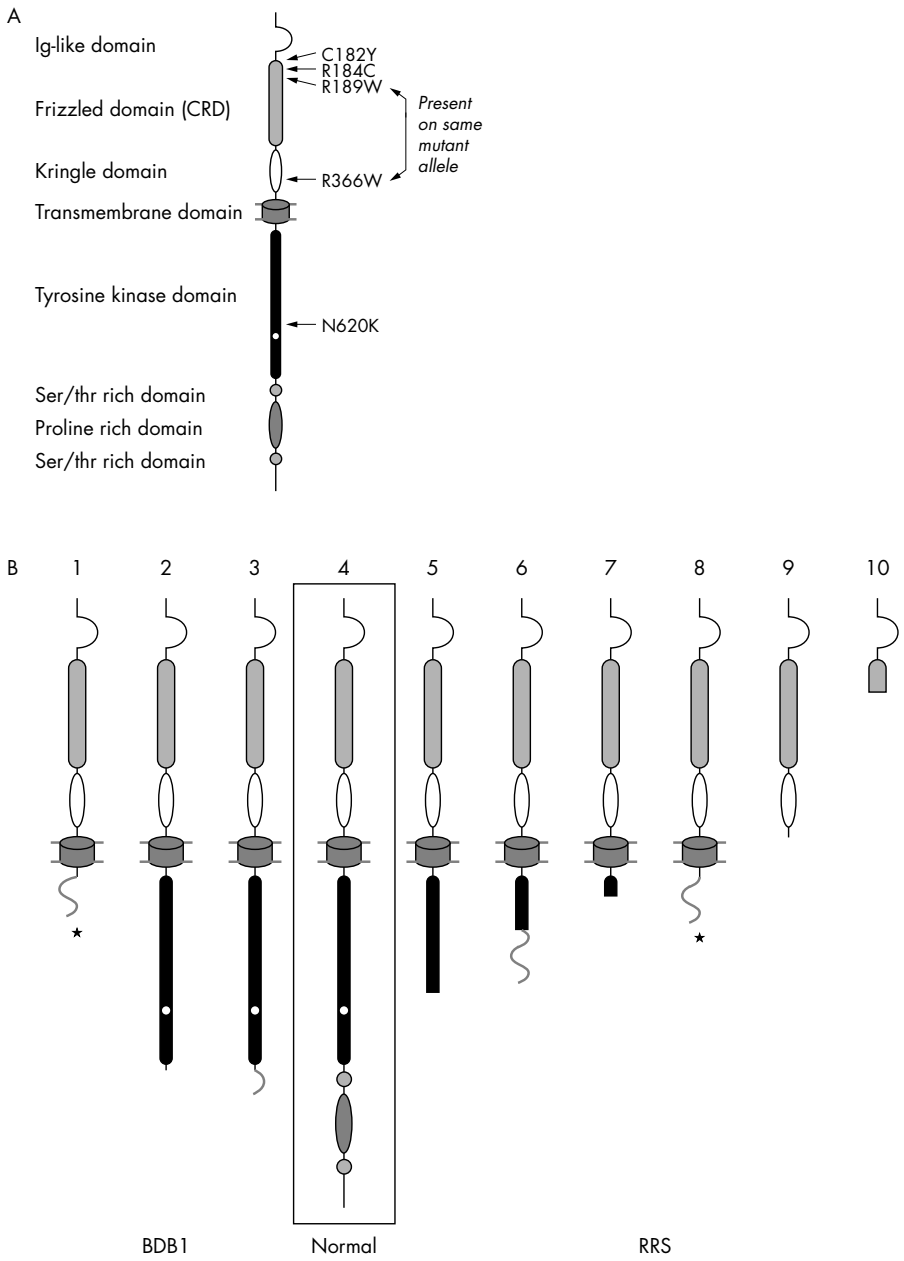

Figure 5 (A) Missense mutations identified in different domains of *ROR2* in recessive Robinow syndrome. The extracellular domain of *ROR*2 contains three distinct motifs all of which are known to be involved in protein-protein interactions. This is consistent with a ligand binding function, although no ligand(s) for *ROR*2 has been reported. Some clustering of missense mutations occurred in the cysteine rich domain, pointing to structurally/functionally important residues of this domain in the *ROR*2 protein. Any changes in the cysteine content in this domain (as in mutations R184C[3] and C182Y[4]) are suggested to affect intramolecular disulphide bonding and protein folding. Moreover, missense mutations in critical residues of this domain such as R189W could cause a defect in a potential glycosylation site (potential binding site of the receptor to the ligand(s)) of this domain.[26] (B) Schematic diagram of the ROR2 protein compares location of terminating mutations discovered in this gene in RRS, with mutations identified in brachydactyly type B (BDB1).[3 4 22 31] Mutations in RRS are scattered throughout the protein. However, mutations in the BDB1 phenotype cause premature termination of the protein only in the intracellular region. The asterisk shows the mutation reported by Schwabe *et al*[31] in a brachydactyly family where one subject was homozygous for the mutation and showed a severe phenotype with similarities to recessive Robinow syndrome. Numbers refer to different mutations as follow: 1 and 8=1321-1325del5(CGGCG),[31] 2=W749X,[22] 3=2249delG,[22] 4=normal,[26] 5=W720X,[4] 6=1740-1774del35,[4] 7=Q502X,[3] 9=R397X,[4] 10=R205X.[4] Mutations Del3(ctc)ins19 at 5′ donor IVS8+ 3-5del3ins19 and 1398-1399insA[31] are in a similar location to number 1.

It has been suggested that Ror2 is necessary for proper proliferation, maturation, motility, and function of chondrocytes, and the resulting normal formation and ossification of the limbs, tail, vertebrae, and ribs, and gives rise to the overall skeletal size.[23 24] In early stages of mouse development both Ror1 and Ror2 are highly expressed in the anterior part of the embryo. However, Ror2 is also expressed in entire regions of the primitive streak. They are both expressed in the developing face, that is, the frontonasal process and branchial arches. Comparatively, Ror2 has a low expression in proximal regions of the limb buds and brain and neither is expressed in the ectoderm. In the later stages, Ror1 is expressed in the anterior and posterior parts of the limbs, whereas Ror2 is expressed in the proliferative chondrocytes of the skeletal system, for example, the perichondrium of the digits and on the margin of the developing limbs. They are both expressed in myocardium, interventricular septum, aortic valve, atrium, and primitive alveoli in the lungs, but not the epicardium. Ror2 alone is

expressed in cortex, hippocampus, and caudate putamen and only Ror1 is expressed in lens epithelium.[26 30]

There are two mouse models for this disease. The first one is produced by replacement of the tyrosine kinase domain of the orthologous *Ror2* with a *lacZ-neo* cassette. This dramatically affects cartilage patterning and growth in pups homozygous for the insertion, and show lethality in the perinatal period.[23] Interestingly, heterozygous mice for this mutant allele were viable, fertile, and appeared normal. The second model produces a similar phenotype in mice homozygous for replacement of the exon encoding the immunoglobulin-like domain of *Ror2* with a PGK-*neo* cassette. In this second model, the pups had severe cyanosis and died within six hours owing to incomplete expansion of alveoli.[24] Interestingly, both mouse models, although showing early lethality, have similar abnormal features to each other and to the human Robinow syndrome. The homozygous knock out model of *Ror2* in the mouse mainly affects all bones that undergo endochondral ossification but not bones that undergo intramembranous ossification. The resulting dwarfism is associated with shortened and deformed limbs, brachydactyly, a short tail, costovertebral segmentation defects, maxillary and mandibular hypoplasia/malformations (cleft palate), and congenital heart anomalies (ventricular septal defect).[23 24] Heterozygous mice show a normal phenotype.

GENOTYPE-PHENOTYPE

Heterozygous terminating mutations in the *ROR2* gene were recently shown to cause the autosomal dominant condition of brachydactyly type B,[22 31] which is characterised by terminal deficiency of fingers and toes.

Autosomal recessive Robinow syndrome is caused by different homozygous missense, nonsense, and frameshift mutations. The reported mutations were mainly in exons 5 and 9 of the gene.[3 4] The mutations can be divided into two groups. The first group contains missense mutations (fig 5A) in cysteine rich, kringle and tyrosine kinase domains. Cysteine rich and kringle domains are known to be involved in protein-protein interactions and are consistent with a ligand binding function, although no ligand or ligands for *ROR2* have been identified. The second group contains terminating mutations, which occurred 3′ to the Ig-like domain, and are predicted to truncate the protein in different regions (fig 5B). At present the phenotypic differences produced by these two groups are being actively studied.

While the heterozygous mutations in *ROR2* in brachydactyly B have been predicted to be associated with gain of function,[22] homozygous mutations in *ROR2* in autosomal recessive Robinow syndrome are likely to cause loss of function. The loss of function hypothesis is supported by the similarity in phenotype between autosomal recessive Robinow syndrome and the homozygous mouse model. It is not clear at the present time whether the autosomal dominant Robinow syndrome is caused by mutations in the *ROR2* gene or whether it is caused by mutations in a different gene. The data so far favour the latter hypothesis.

The occurrence of distinct phenotypes associated with recessive and dominant mutations within a single gene is unusual but not unprecedented. For example, dominant negative mutations of the insulin receptor (another receptor tyrosine kinase) are associated with insulin resistance and recessive mutations with additional growth retardation (leprechaunism).[32] Heterozygous mutations of *GDF5*, a member of the bone morphogenic proteins (BMP) family, cause brachydactyly type C,[33] whereas homozygous mutations are associated with acromesomelic dysplasia Hunter-Thompson type[34] and Grebe syndrome.[35]

The existence of clinically similar cases of Robinow syndrome inherited in an autosomal dominant fashion[8] raises the possibility of further genetic heterogeneity of this disease. It is possible that such patients might harbour mutations in the genes for the ligand or other components of the ROR2 pathway and, if this were the case, the discovery of these other loci would greatly assist accurate genetic counselling.

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ECHO

Cystatin C gene and exudative age related macular degeneration are linked

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Exudative age related macular degeneration (ARMD) is linked with the *CST3* gene, a study in Germany has found. The condition—an advanced stage of ARMD—is a leading cause of blindness among elderly western Europeans. There is evidence for a genetic cause but no consensus about a candidate gene.

Zurdel *et al* chose as a potential candidate the cystatin C gene—*CST3*—coding for a protease inhibitor common in tissues and body fluids which strongly inhibits cathepsins, including cathepsin S, and results in debris accumulating around retinal pigment epithelial cells. Extracellular deposits beneath the retinal pigment epithelium are one characteristic of early ARMD.

They characterised 167 patients with exudative ARMD and 517 unrelated controls for *CST3* genotypes A/A, A/B, B/B by PCR and restriction endonuclease analysis. The controls were from Germany, Switzerland, Italy, and the United States to cover regional or ethnic differences in frequency of *CST3* alleles.

CST3 genotype counts were significantly different for patients over controls, especially for *CST3* B/ B genotype (odds ratio 2.97; 95% confidence interval 1.28 to 6.86). Allele frequencies A and B were similar between patients and controls and among controls from all locations. *CST3* B/B was significantly linked with ARMD as shown by Kaplan-Meier analysis, with mean disease free survival time in pooled men and women for genotype A/A or A/B of 85 years and B/B 76 years.

CST3 B/B carries increased risk of exudative ARMD, conclude Zudel *et al*; cystatin C is therefore implicated in the disease process, though its exact role remains to be determined.

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