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Report

Six Novel Missense Mutations in the LDL Receptor-Related Protein 5 (*LRP5*) Gene in Different Conditions with an Increased Bone Density

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Bone is a dynamic tissue that is subject to the balanced processes of bone formation and bone resorption. Imbalance can give rise to skeletal pathologies with increased bone density. In recent years, several genes underlying such sclerosing bone disorders have been identified. The LDL receptor-related protein 5 (*LRP5*) gene has been shown to be involved in both osteoporosis-pseudoglioma syndrome and the high–bone-mass phenotype and turned out to be an important regulator of peak bone mass in vertebrates. We performed mutation analysis of the *LRP5* gene in 10 families or isolated patients with different conditions with an increased bone density, including endosteal hyperostosis, Van Buchem disease, autosomal dominant osteosclerosis, and osteopetrosis type I. Direct sequencing of the *LRP5* gene revealed 19 sequence variants. Thirteen of these were confirmed as polymorphisms, but six novel missense mutations (D111Y, G171R, A214T, A214V, A242T, and T253I) are most likely disease causing. Like the previously reported mutation (G171V) that causes the high–bone-mass phenotype, all mutations are located in the aminoterminal part of the gene, before the first epidermal growth factor–like domain. These results indicate that, despite the different diagnoses that can be made, conditions with an increased bone density affecting mainly the cortices of the long bones and the skull are often caused by mutations in the *LRP5* gene. Functional analysis of the effects of the various mutations will be of interest, to evaluate whether all the mutations give rise to the same pathogenic mechanism.

Maintenance of skeletal integrity requires a dynamic balance between bone formation and bone resorption that is fine tuned by a complex network of systemic hormones and local factors. Imbalance can lead to an extended number of skeletal pathologies, including the sclerosing bone dysplasias, a heterogeneous group of disorders with a generalized increase in skeletal mass. Some of these sclerosing bone dysplasias have an increased trabecular bone density (osteosclerosis), whereas others have a cortical bone thickening (hyperostosis) (Whyte 1999).

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Major breakthroughs have been made in recent years toward understanding of the molecular basis of some sclerosing disorders. Impaired bone resorption, as seen in the various forms of osteopetrosis, can be due to mutations in a subunit of the vacuolar H^+ pump (*TCIRG1* gene) (Frattini et al. 2000; Kornak et al. 2000) or to mutations in the chloride channel *CLCN7* gene (Cleiren et al. 2001; Kornak et al. 2001). On the other hand, increased bone formation or an imbalance between bone formation and bone resorption can also result in sclerosing bone disorders. Recently, missense mutations in the gene encoding the inorganic pyrophosphate channel ANK (Nürnberg et al. 2001; Reichenberger et al. 2001) have been shown to cause craniometaphyseal dysplasia (CMDD [MIM 123000]), and increased TGF-β signaling (Janssens et al. 2000; Kinoshita et al. 2000) results in Camurati-Engelmann disease (CED [MIM 131300]).

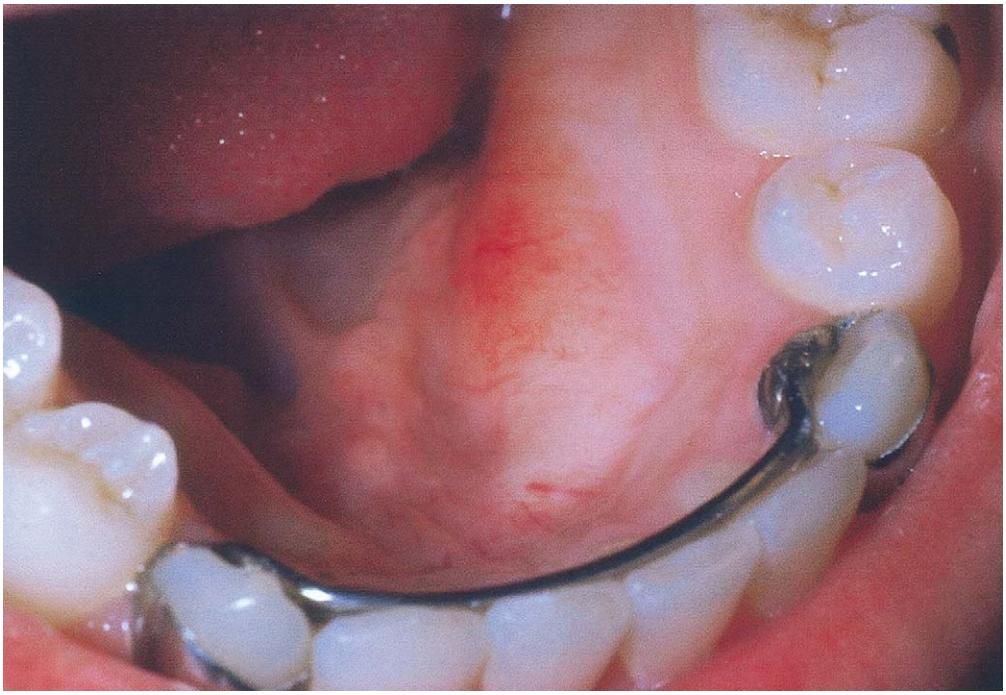

Figure 1 Photo of hard palate of a patient from family C, demonstrating the bony prominence (torus palatinus) and associated dental alterations.

Table 1

Families or Isolated Patients with an LRP5 Mutation

Family	Origin	Original Diagnosis	Radiological Features
A	Portland	Endosteal hyperostosis	Cortical thickening of the long bones with no alteration in external shape, remarkable resistance of the bone to fractures, elongated mandible, decreased gonial angle, torus palatinus, increased bone density of the calvarium, mandible, and endosteal surface of the long bones (Beals 1976)
B	Portland	Endosteal hyperostosis	Cortical thickening of the long bones with no alteration in external shape, remarkable resistance of the bone to fractures, elongated mandible, decreased gonial angle, torus palatinus, increased bone density of the calvarium, mandible, and endosteal surface of the long bones (Beals et al. 2001)
C	Portland	Endosteal hyperostosis	Cortical thickening of the long bones with no alteration in external shape, remarkable resistance of the bone to fractures, elongated mandible, decreased gonial angle, torus palatinus, increased bone density of the calvarium, mandible, and endosteal surface of the long bones. (Beals et al. 2001)
D	Sardinia	Van Buchem disease	Enlarged mandible, increased thickness of the skull and the cortices of the long bones (Scopelliti et al. 1999)
E	England	Autosomal dominant osteosclerosis	Enlarged mandible and an increased gonial angle, thickened cortical bone (Renton et al. 2002)
F	Belgium	Osteopetrosis	Thickened cortical bone with no alteration in external shape, dense cranial basis
G	France	Osteopetrosis	Diffuse osteosclerosis of the trabecular and cortical bone, osteosclerosis of the skull with enlargement of the cranial vault
H	Argentina	Osteopetrosis	Osteopetrosis of the cranium with loss of the diploe, enlarged mandible, increased thickness of the cortices of long bones
I	Denmark	Autosomal dominant osteopetrosis type I	Generalized sclerosis, most pronounced at the cranial vault, not associated with an increased fracture rate (Bollerslev and Andersen 1988)
J	Denmark	Autosomal dominant osteopetrosis type I	Generalized sclerosis, most pronounced at the cranial vault, not associated with an increased fracture rate (Van Hul et al. 2002)

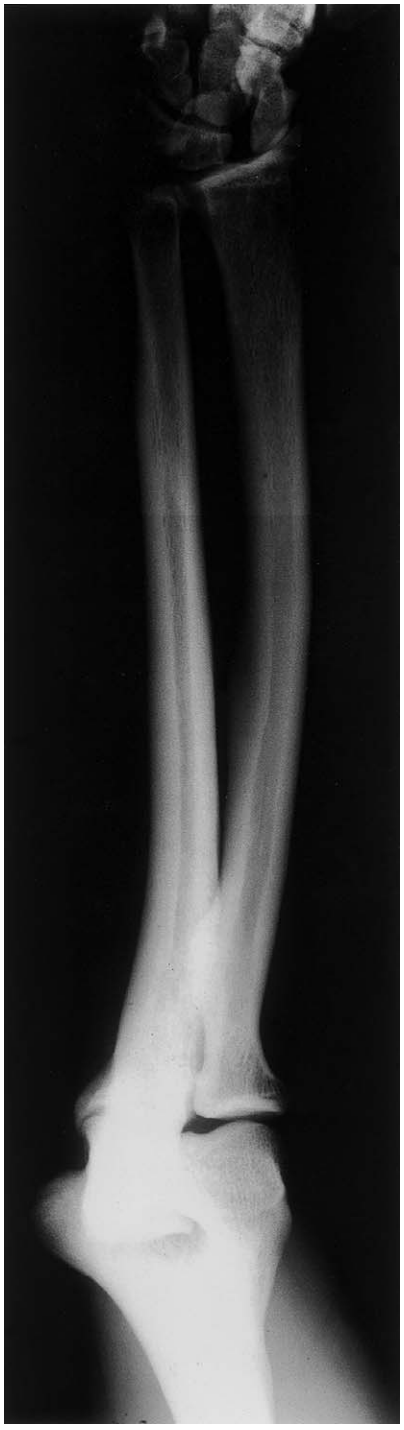

Figure 2 X-ray of forearm of patient from family F, demonstrating thickened cortical bone with no alterations in external shape.

The increased bone formation in sclerosteosis (SOST [MIM 269500]) and in Van Buchem disease (VBCH [MIM 239100]) turned out to be due to loss-of-function mutations of the *SOST* gene, most likely increasing bone morphogenetic protein signaling (Balemans et al. 2001, 2002; Brunkow et al. 2001). Further, it was recently shown that the gene encoding the low-density lipoprotein receptor–related protein 5 (LRP5) is one of the regulators of peak bone mass in vertebrates. The autosomal recessive osteoporosis pseudoglioma syndrome (OPPG [MIM 259770]), a disorder causing both skeletal and eye abnormalities, is due to inactivating mutations in the *LRP5* gene (Gong et al. 2001). Besides the neonatal blindness, children with OPPG have a very low bone mass and are very sensitive to fractures and skeletal deformities. Collagen synthesis appears normal, differentiating it from the severe osteogenesis imperfecta it resembles. Of interest, obligate carriers of OPPG mutations show an increased incidence for osteoporotic fractures, indicating a dominant effect of this gene on bone mass (Gong et al. 1996). Targeted disruption of the *LRP5* gene in mice also produces osteoporosis postnatally (Kato et al. 2002). On the other hand, in a family that includes phenotypically normal individuals with exceptionally dense bones (high bone mass [HBM] [MIM 601884]), a gain-of-function mutation (G171V) in the *LRP5* gene has been described (Little et al. 2002). The same mutation was found in another kindred with other phenotypic abnormalities, such as torus palatinus and a wide, deep mandible in addition to high bone density (Boyden et al. 2002). LRP5 acts as a coreceptor for Wnt proteins and is expressed in osteoblasts, where it is required for the osteoblast proliferation and functions in a Cbfa1-independent manner (Kato et al. 2002). This all illustrates that the LRP5 signaling pathway plays an important role in the regulation of bone mass in vertebrates.

We performed mutation analysis of the *LRP5* gene in

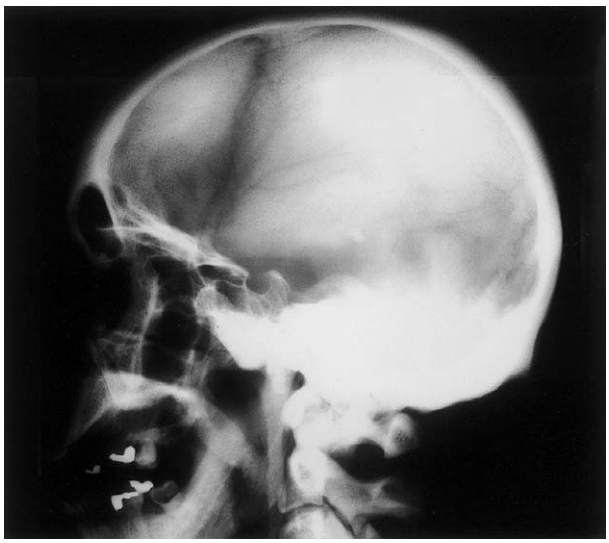

Figure 3 Radiograph of the skull of an affect member of family F, showing the very dense aspect of bone.

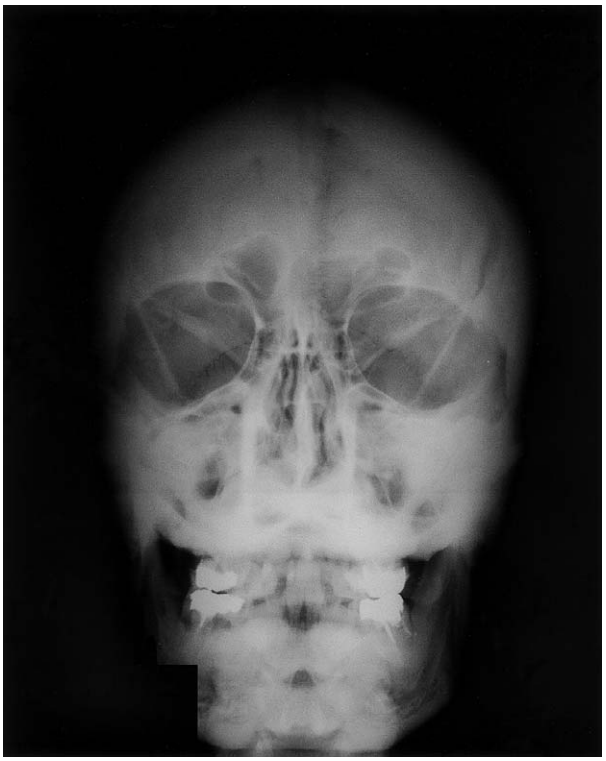

Figure 4 Radiograph of the skull of an affected member of family G, demonstrating a diffuse osteosclerosis.

families or isolated patients with conditions with an increased bone density (figs. 1–7; table 1), including endosteal hyperostosis (families A–C), Van Buchem disease (family D), autosomal dominant osteosclerosis (family E), and autosomal dominant osteopetrosis type I (families F–J). The three kindreds A (described by Beals [1976]), B, and C (both described by Beals et al. [2001]) originate from Portland, OR, and have autosomal dominant endosteal hyperostosis (MIM 144750), a rare generalized bone dysplasia. This condition is characterized by a cortical thickening of the long bones, with no alteration in external shape, and a remarkable resistance of the bone to fracture. The skeleton is normal in childhood; the affected patients have a normal height, proportion, intelligence, and longevity. Facial metamorphoses occur in adolescence, as the forehead flattens, the mandible becomes elongated, and the gonial angle decreases. An enlarging osseous prominence (torus palatinus) develops in the hard palate, which may lead to malocclusion or loss of teeth (fig. 1). Changes apparent on radiographs include increased density of the calvarium, mandible, and endosteal surface of the long bones. With advancing age, the cancellous bone becomes radiographically more involved with areas of increased bone density. The clinical and radiographic features of the affected members of families A, B, and C resemble closely those of the kindred described by Boyden et al. (2002), where a G171V mutation in the *LRP5* gene was identified.

At least five members from family D, originating from Sardinia, including the mother of the reported patient, the grandmother, and two siblings, are proven to be affected (Scopelliti et al. 1999). They all have an osteosclerosis of the skull and an enlarged mandible. The autosomal dominant inheritance of the disease in this family is clearly in contrast with the diagnosis of autosomal recessive Van Buchem disease made elsewhere (Scopelliti et al. 1999).

Patient E, originating from England, is a 20-year-old woman with an enlarged mandible (Renton et al. 2002). Histological examination showed thickened cortical bone not involving the underlying trabeculae. She was diagnosed with autosomal dominant osteosclerosis. The patient's father had an enlarged mandible, but there were no other clinical signs, and the radiographic appearance of the skull was within normal limits (Renton et al. 2002).

At least three members in the Belgian family (F) have been diagnosed with autosomal dominant osteopetrosis type I (Van Gaal et al. 1978). The father suffers from severe headaches, and x-rays show very dense bones of the skull. His daughter has a very dense cranial basis and a cortical thickening of the vertebrae and long bones with normal development (fig. 2). The son presents with x-rays showing a very dense aspect of bone, mainly of the skull (fig. 3).

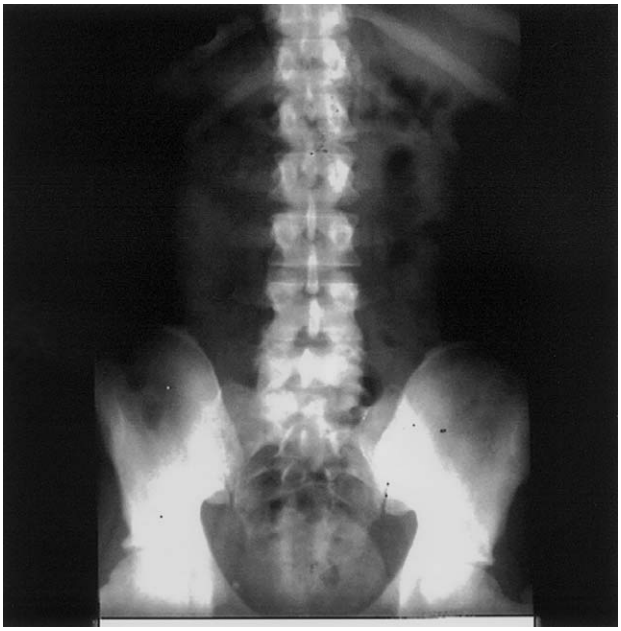

Figure 5 Radiograph of lumbar spine and pelvis of an affected member of family G, demonstrating a diffuse osteosclerosis.

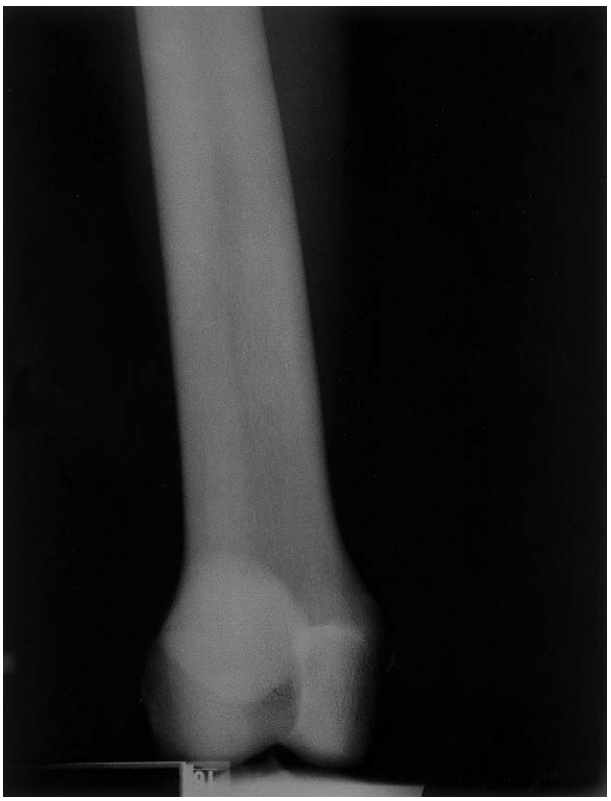

Figure 6 X-ray of a femur of an affected member of family H, demonstrating an increased thickness of the long bones and narrowing of the medullary canals.

Next, an affected member of the French family (G) has an osteomyelitis of the jaw and hearing problems because of small auditory canals. His affected brother has the same clinical features. X-rays show a diffuse osteosclerosis of the trabecular and cortical bone and an osteosclerosis of the skull with enlargement of the cranial vault (figs. 4 and 5). There is an autosomal dominant inheritance in this family diagnosed with osteopetrosis type I.

Patient H is a 17-year-old female from Argentina who presents with a diagnosis of osteopetrosis. She was asymptomatic until age 14, when she presented with a complaint of mandibular pain, severe headaches, and extremity pain (figs. 6 and 7).

The patients of families I and J (Bollerslev and Andersen 1988; Van Hul et al. 2002), originating from the county of Fyn in Denmark, were diagnosed with autosomal dominant osteopetrosis type I, on the basis of the presence of osteosclerosis on x-rays and on bone mineral density measurements. These families were described in detail elsewhere (Bollerslev and Andersen 1988; Van Hul et al. 2002) and were used to localize the ADOI gene to chromosome 11q12–13 (Van Hul et al. 2002). The control subjects who were included in this mutation analysis are of Belgian origin and without any indication of abnormal bone mineral density.

The *LRP5* gene contains 23 exons and spans >100 kb. Direct sequencing of the PCR products spanning all the exons and exon-intron boundaries (primer sequences and conditions are available from the authors) revealed 19 sequence variants, of which 13 are probably polymorphisms (table 2). Eight variants in the coding region involve third codon positions and do not introduce an amino acid change (D111D, T534T, F549F, E644E, N740N, D1099D, V1119V, and T1596T). This makes it very unlikely that they have any effect on the functioning of the protein. Three other polymorphisms do generate an amino acid change (Q89R, V667M, and A1330V). Two of them (V667M and A1330V) were also found in control samples and could, therefore, not be disease-causing variants. We could not find the Q89R variation in 100 control samples. However, this polymorphism is described elsewhere, with an allele frequency of 8% for 89R in the Japanese population (Okubo et al. 2002). The two remaining polymorphisms are located in exon 1, more exactly, in the leucine stretch of the signal peptide of the LRP5 protein. One variant (L20dup) is an in-frame duplication of three nucleotides (CTG), which results in an insertion of one leucine. In the other variant

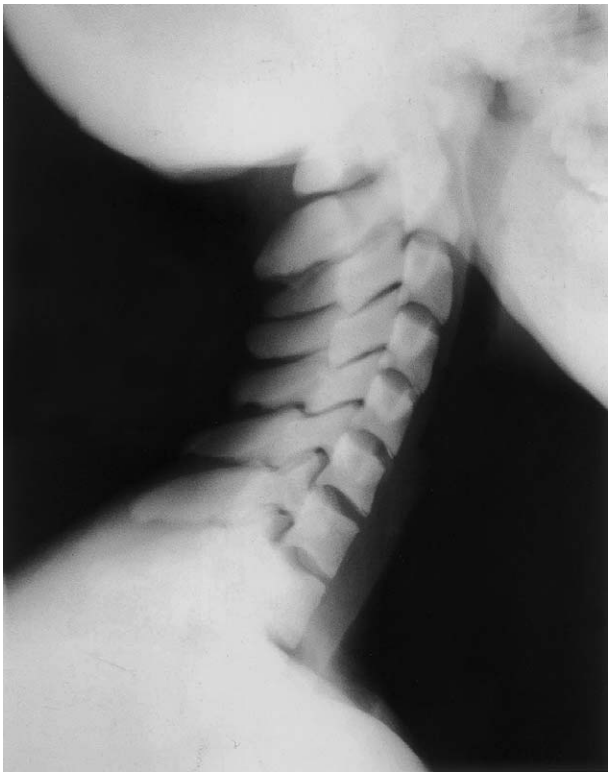

Figure 7 X-ray of the cervical spine of an affected member of family H, showing an increased bone density.

Table 2

Polymorphisms in the Coding Region of the LRP5 Gene

Sequence Change	Protein Change	Exon	Allele Frequency in Controls (%)
52-60delCTGCTGCTG	L18-L20del	1	$(Leu)_6$:1 $(Leu)_9$:99
60-61dupCTG	L20dup	1	$(Leu)_9$:95 $(Leu)_{10}$:5
266A→G	Q89R[a]	2	A:100 G:0
333C→T	D111D	2	C:100 T:0
1602G→A	T534T	8	G:100 A:0
1647C→T	F549F	8	C:94 T:6
1932G→A	E644E	9	G:95 A:5
1999G→A	V667M	9	G:95 A:5
2268C→T	N740N[a]	10	C:86 T:14
3297C→T	D1099D	15	C:100 T:0
3357A→G	V1119V[a]	15	A:73 G:27
3989C→T	A1330V[a]	18	C:91 T:9
4788C→T	T1596T	23	C:97 T:3

[a] Polymorphism identified by Okubo et al. (2002).

(L18-L20del), an inframe deletion of nine nucleotides (CTGCTGCTG) occurred, which resulted in a deletion of three leucines. Both variants are most likely caused by an unequal crossover within the leucine stretch. Both L20dup and L18-L20del are also found in control samples (table 2), indicating that they are not disease causing.

Recently, a gain-of-function mutation (G171V) in the *LRP5* gene was described in two kindreds with an enhanced bone density (Boyden et al. 2002; Little et al. 2002). The glycine at amino acid position 171 lies in the fourth blade of the first propeller of the LRP5 protein, exactly 2 amino acids beyond the YWTD sequence, and is highly conserved (fig. 8). It is remarkable that the family described by Little et al. (2002) has no features other than very dense bones, whereas patients from the other kindred also suffer from a wide, deep mandible and a torus palatinus. Therefore, the same mutation (G171V) is associated with different phenotypic features in the two families. We have now identified a new mutation (G171R) in the Belgian family F (table 3) involving the

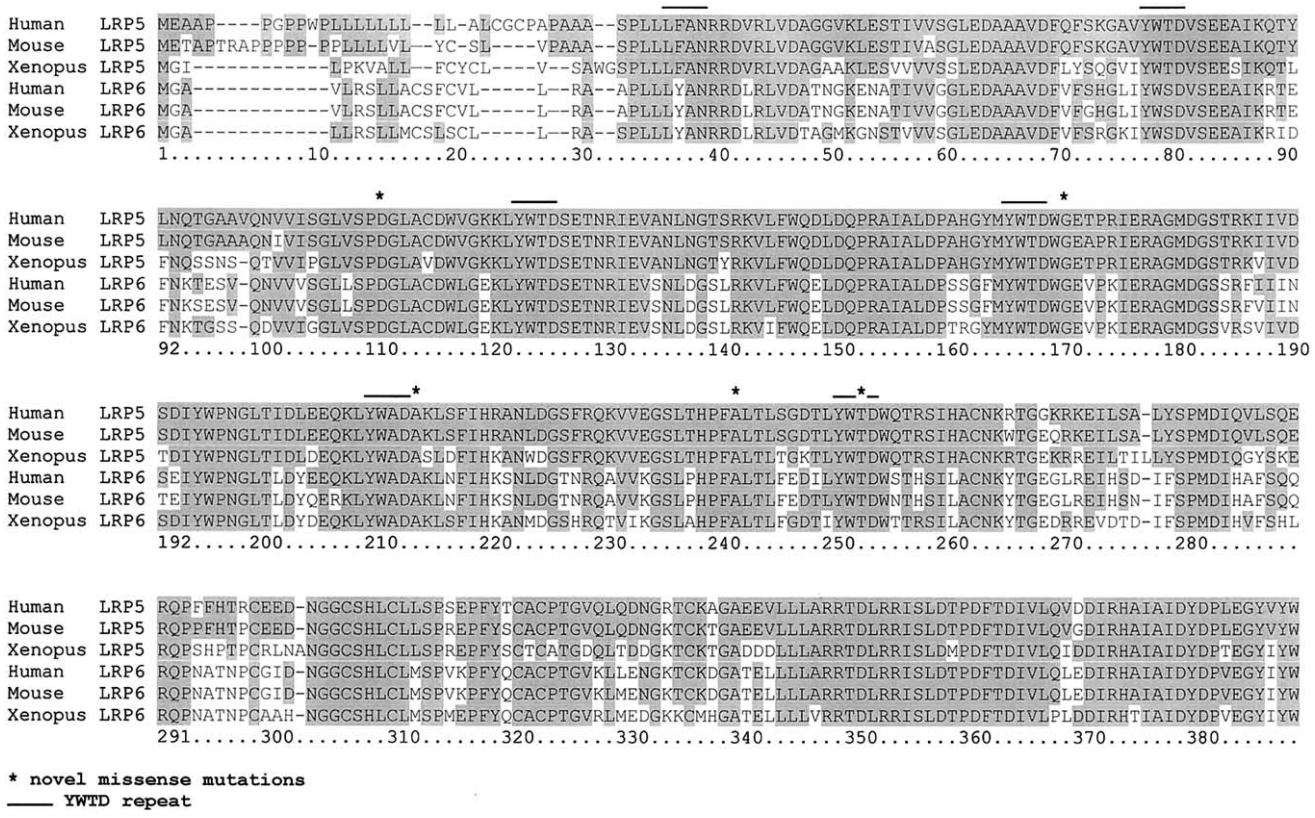

Figure 8 Alignment of the aminoterminal part of the LRP5 protein with its most closely related homologue, LRP6, in human, mouse, and *Xenopus*. The signal peptide, one LDLR repeat with its six YWTD repeats (indicated with a line), and the following EGF repeat are shown. The numbering of the amino acid sequence is based on the human LRP5. The positions of the six novel missense mutations are indicated with an asterisk (*). These residues are highly conserved in human, mouse, and *Xenopus* LRP5 as well as in human, mouse, and *Xenopus* LRP6.

same amino acid. The clinical and radiological features of family F closely resemble those of the family described by Little et al. (2002), since they do not suffer from an enlarged mandible and a torus palatinus.

Next, we identified two mutations in exon 3 changing the same amino acid at position 214. This alanine 214 is located within the fifth YWTD repeat of the first YWTD/EGF domain of the LRP5 protein. In family C, a A214T missense mutation was found in the five affected individuals, whereas an A214V mutation was found in patient E. Despite the fact that family C was diagnosed with endosteal hyperostosis and family E was diagnosed with osteosclerosis, the clinical and radiological features are similar.

Another mutation was found in the sixth YWTD repeat of the first propeller of the LRP5 protein. A C→T transversion at cDNA position 758 resulted in a threonine-to-isoleucine amino acid change (T253I) in families I and J. Families I and J both originate from the county of Fyn in Denmark. Comparison elsewhere of the haplotypes cosegregating with the disease in these families has suggested that these families are related (Van Hul et al. 2002). This is in line with the current finding of a shared mutation. Further, a missense mutation (D111Y) in exon 2 of the *LRP5* gene was found in patient H. This aspartic acid on position 111 is conserved between the LRP5 and LRP6 proteins in human, mouse, and *Xenopus* (fig. 8).

We identified another mutation (A242T) in exon 4 of the *LRP5* gene in families A, B, D, and G (table 3). This highly conserved alanine residue is also located in the first propeller of the LRP5 protein. Analysis of intragenic SNPs (table 2) and of markers intragenic or close to the *LRP5* gene (D11S1917, D11S4087, D11S1337, and D11S4187) have shown that families A, B, D, and G do not have a common haplotype and are, therefore, not related, which suggests that the mutations have arisen independently (data not shown). A possible explanation for the recurrence of this mutation might be that the mutation is caused by a spontaneous deamination of the cytosine being part of a CpG dinucleotide on the complementary strand. This mutation is also associated with slightly different phenotypic features, since the affected members of families A, B, and D all have an enlarged mandible, whereas the affected members of family G suffer from an osteomyelitis of the jaw. We believe that the six missense mutations described are disease causing, as we did not find them in 100 control chromosomes; neither did others (Boyden et al. 2002; Little et al. 2002; Okubo et al. 2002). Moreover, the mutations involve conserved amino acids and are all located within the first propeller of the LRP5 protein.

Our results indicate that gain-of-function mutations in the *LRP5* gene not only cause the high–bone-mass phenotype but are also underlying related sclerosing bone dysplasias. Cases presenting with an autosomal dominant mode of inheritance and diagnosed with osteosclerosis, endosteal hyperostosis, Worth disease, or osteopetrosis type I turned out to have a high risk of being caused by missense mutations in the *LRP5* gene. All such cases share an increased thickness of the skull and of the cortices of the long bones. As already shown for the G171V mutation, they can present either with or without an enlarged mandible (Boyden et al. 2002; Little et al. 2002). In the former case, it might be difficult to differentiate from sclerosteosis and Van Buchem disease. However, these conditions present with an autosomal recessive mode of inheritance and are, in general, more severe, causing secondary features, such as facial nerve palsy and hearing loss. All the currently found missense mutations are located in the aminoterminal part of the *LRP5* gene, more exactly, in exons 2, 3, and 4 encoding the first of four propellers of the LRP5 protein. The evolutionary conservation of the altered residues is strong evidence of their functional importance (see fig. 8). Further, it has been shown that mutations in these YWTD motifs of the LDL receptor cause familial hypercholesterolemia, which indicates that these domains are of structural importance (Jeon et al. 2001). Experimental data have shown elsewhere that the normal inhibition of Wnt signaling was defective in the presence of the G171V mutation. The antagonistic protein Dickkopf-1 could not bind to mutated LRP5, resulting in a constitutive activity of the Wnt signaling pathway (Boyden et al. 2002). Further functional experiments on the other mutations will reveal whether the same pathogenic mechanism is underlying the other conditions and whether any form of genotype-phenotype correlation can be made.

Table 3

Novel Mutations in the LRP5 Gene

Mutation	Protein Change	Exon	Family
331G→T	D111Y	2	H
511G→C	G171R	3	F
640G→A	A214T	3	C
641C→T	A214V	3	E
724G→A	A242T	4	A B D G
758C→T	T253I	4	I J

Acknowledgments

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Electronic-Database Information

Accession numbers and URL for data presented herein are as follows:

Online Mendelian Inheritance in Man (OMIM), http://www.ncbi.nlm.nih.gov/Omim/ (for CMDD [MIM 123000], CED [MIM 131300], SOST [MIM 269500], VBCH [MIM 239100], OPPG [MIM 259770], HBM [MIM 601884], and endosteal hyperostosis [MIM 144750])

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