BÖLÜM

3

KALSİYUM DUYARLI RESEPTÖR VE İLGİLİ BOZUKLUKLAR

Cevdet AYDIN[1]
Fatma Neslihan ÇUHACI SEYREK[2]

Giriş

Bir membran reseptörü olarak kalsiyum duyarlı reseptör (CaSR) ile ilgili araştırmalar, bilgiler, özellikler, bağlantılı farmakolojik ajanların keşfi ve klinik uygulamaya girmesi etkileyici bir biçimde artmaktadır. Reseptörün kendine has karakteri ve üzerindeki araştırıcı dikkatinin önemini vurgulamak için, sonuncusu 2017 yılında olmak üzere CaSR ile ilgili 3. uluslararası sempozyumun yapıldığını belirtmek sanırız yeterli olur.

Bu bölümde CaSR'nin keşfi, yapısı, ilgili gen, sinyal regülasyonu, doku dağılımı, paratiroid, kemik, tiroid ve renal dokulardaki fizyolojik davranışları tartışıldıktan sonra reseptörle ilgili bozukluklar ele alınacaktır.

CaSR Keşfi

19. yüzyılda Sydney Ringer'in, izole edilmiş kalbin kasılması için kalsiyumun önemli bir role sahip olduğunu keşfetmesinden beri bu iyonun fizyolojik önemi bilinmektedir (1).

Ca^{+2}, intrasellüler ve ekstrasellüler ortam için zorunlu bir iyondur. İntrasellüler Ca^{+2} (Ca^{+2}_i) düzeyi 100-180 nmol/L civarında tutulur. Hücre dışı iyonize kalsiyum 1.1-1.3 mmol/L konsantrasyonundadır. Hücresel uyarıları takiben hücre mebranındaki veya endoplazmik retikulumdaki kalsiyum kanallarının açılması ile hücre içi düzeyi nanomolar düzeylerden düşük mikromolar konsantrasyonlara ulaşır. Biyolojik süreçlerin dengeli seyretmesi için Ca^{+2} düzeyi sıkı bir şekilde düzenlenir. Sabit bir kalsiyum konsantrasyonu için karmaşık bir homeostatik sistem evrimleşmiştir. Kalsiyum ile ilgili bu dengenin organizmada nasıl gerçekleştiği ilgili çalışmalar CaSR'nin keşfi ile sonuçlanmıştır.

Bu keşif sürecini anlatmadan önce Parathormon (PTH)-kalsiyum dinamiğini kısaca hatırlamakta fayda vardır. Serum kalsiyum konsantrasyonundaki bir değişimi takiben saniyeler içinde dolaşımdaki PTH seviyesi değişir. PTH sekresyon hızı ile serum iyonize kalsiyum düzeyi arasındaki ilişki ters sigmoidal eğri oluşturacak şekildedir.

[1] Prof. Dr., Ankara Yıldırım Beyazıt Üniversitesi Tıp Fakültesi, İç Hastalıkları AD., Endokrinoloji ve Metabolizma Hastalıkları BD., cevdetaydin68@hotmail.com
[2] Doç. Dr., Ankara Yıldırım Beyazıt Üniversitesi Tıp Fakültesi, İç Hastalıkları AD., Endokrinoloji ve Metabolizma Hastalıkları BD., neslihan_cuhaci@yahoo.com

sini bozan ve renal medulla içinde CaSR ekspresyonunu azaltan ortak CaSR promoter-bölge SNP (rs6776158) (A>G))'nin kalsiyum içeren renal kalkülinin artmış riski ile ilişkili olduğu gösterilmiştir (151). rs6776158 CaSR promoter-bölge SNP'li hastalarda nefrolitiazis gelişiminin altta yatan mekanizmaları henüz belirlenmemiştir, çünkü çalışılan hastalarda idrar kalsiyum veya fosfat konsantrasyonlarında herhangi bir değişiklik bulunmamıştır (151).

Sonuç

CaSR, G proteinleri ve β-arrestin aracılığı ile sinyal oluşturan bir dimerik C GPCR ailesi üyesidir. PTH sekresyonunu, idrar kalsiyum atılımını, iskelet gelişimini, kemik hücresi fonksiyonunu ve laktasyonu etkileyerek kemik ve mineral metabolizmasında önemli bir rol oynar.

CaSR'nin veya hücre içi partner proteinlerinin germ-line fonksiyon kaybı veya fonksiyon artışına neden olan mutasyonları AHH1-3, ADH1, ADH2 gibi kalıtımsal kalsiotiropik bozukluklara yol açar. Paratiroidlerde CaSR ekspresyonunun kaybı ise PHPT ve SHPT'nin gelişimine katkıda bulunur.

CaSR, ayrıca, büyük oranda kalsiotiropik olmayan dokularda da eksprese edilir ve fizyolojik süreçleri etkiler; örneğin insülin ve enteroendokrin hormonların sekresyonu, nöral ve pulmoner gelişim, vasküler tonus ve yara iyileşmesi gibi. Ayrıca, CaSR ekspresyonu veya fonksiyonundaki patofizyolojik değişiklikler meme, prostat ve kolon kanserleri ve yanı sıra, iskemik beyin hasarı, kardiyovasküler hastalık ve astım ile ilişkilidir.

Kalsimimetikler, hiperparatiroid bozuklukların medikal tedavisinde değerlendirilen ilaçlardır ve semptomatik AHH ve NSHPT'nin bazı formlarında etkilidirler. Kalsilitik ilaçlar, ADH'nin tedavisi için potansiyel bir hedefdir ve diğer hipoparatiroid bozukluklarda da potansiyel etkisi olabilir. CaSR hedefli ilaçlar, ayrıca kalsiotiropik olmayan bozukluklarda da değerlendirilmektedir ve yeni stratejiler örneğin hedef dışı etkileri en aza indirmek için astım için inhale kalsilitiklerin kullanımı preklinik modellerde değerlendirilmektedir.

KAYNAKLAR

1. Ringer. A further contribution regarding the influence of the different constituents of the blood on the contraction of the heart.. Physiol. 1883;4(1):29–42.3.
2. LeBoff MS, Shoback D, Brown EM, et al. Regulation of parathyroid hormone release and cytosolic calcium by extracellular calcium in dispersed and cultured bovine and pathological human parathyroid cells.. Clin Invest. 1985;75:49–57.
3. Nemeth EF, Wallace J, Scarpa A. Stimulus-secretion coupling in bovine parathyroid cells. Dissociation between secretion and net changes in cytosolic Ca2+.. Biol Chem. 1986;261:2668–2674.
4. Brown EM, Enyedi P, Leboff M, et al. High extracellular Ca2+and Mg2+ stimulate accumulation of inositol phosphates in bovine parathyroid cells. FEBS Lett. 1987;218:113–118 .
5. Racke FK, Hammerland LG, Dubyak GR, et al. Functional expression of the parathyroid cell calcium receptor in Xenopus oocytes. FEBS Lett. 1993;333:132–136.
6. Brown EM, Gamba G, Riccardi D, et al. Cloning and characterization of an extracellular Ca2+-sensing receptor from bovine parathyroid. Nature. 1993;366:575–580.
7. Garrett JE, Capuano IV, Hammerland LG, et al. Molecular cloning and functional expression of human parathyroid calcium receptor cDNAs.. Biol Chem. 1995a;270:12919–12925.
8. Wellendorph P, Bräuner-Osborne H. Molecular basis for amino acid sensing by family. G protein-coupled receptors. Br. Pharmacol. 2009;156:869–884.
9. Hendy GN, Canaff L. Calcium-sensing receptor gene: Regulation of expression. Front Physiol. 2016; 7:394. doi: 10.3389/fphys.2016.00394.
10. Fajtova VT, Quinn SJ, Brown EM. Cytosolic calcium responses of single rMTC 44-2 cells to stimulation with external calcium and potassium. Am. Physiol. 1991;261:İE151–E158.
11. Meng K, Xu J, Zhang C, et al. Calcium sensing receptor modulates extracellular calcium entry and proliferation via TRPC3/6 channels in cultured human mesangial cells. PLoS One. 2014;9:e98777.
12. Katie L,Fadil MH, Tracy MJ, et al. Calcium-sensing receptor Nomenclature, Pharmacology, and Function, Pharmacol Rev. 2020;72(3):558–604.
13. Brown EM, Fuleihan GE, Chen CJ, et al.. comparison of the effects of divalent and trivalent cations on parathyroid hormone release, 3',5'-cyclic-adenosine monophosphate accumulation, and the levels of inositol phosphates in bovine parathyroid cells. Endocrinology. 1990;127:1064–1071.
14. Handlogten ME, Shiraishi N, Awata H, et al. Extracellular Ca(2+)- sensing receptor is. promiscuous divalent cation sensor that responds to lead. Am. Physiol

Renal Physiol. 2000; 279:F1083–1091.
15. Ruat M, Snowman AM, Hester LD, et al. Cloned and expressed rat Ca2+-sensing receptor.. Biol Chem. 1996;271:5972–5975.
16. Quinn SJ, Ye CP, Diaz R, et al. The Ca2+-sensing receptor:. target for polyamines. Am. Physiol. 1997;273:C1315–1323.
17. Gregory KJ, Kufareva I, Keller AN,et al. Dual action calcium-sensing receptor modülatör unmasks novel mode-switching mechanism. Pharm Trans Sci. 2018;1:96–109.
18. Brent GA, LeBoff MS, Seely EW, et al. 1988 Relationship between the concentration and rate of change of calcium and serum intact parathyroid hormone levels in normal humans.. Clin Endocrinol Metab. 1988;67:944-950.
19. Kifor O, Moore FD Jr., Wang P, et al. Reduced immunostaining for the extracellular Ca ² -sensing receptor in primary and uremic secondary hyperparathyroidism.. Clin Endocrinol Metab.1996;81:1598–1606.
20. Daniela Riccardi ,Edward M. Brown. Physiology and pathophysiology of the calcium-sensing receptor in the kidney. Am. Physiol Renal Physiol.2010;298:F485–F499.
21. Fudge NJ, Kovacs CS. Physiological studies in heterozygous calcium sensing receptor (CaSR) gene-ablated mice confirm that the CaSR regulates calcitonin release in vivo. BMC Physiol. 2004;4:5. doi: 10.1186/1472-6793-4-5.
22. Kantham L, Quinn S, Egbuna O, et al. The calcium-sensing receptor (CaSR) defends against hypercalcemia independently of its regulation of parathyroid hormone secretion. Am. Physiol Endocrinol Metab. 2009;297:E915–E923.
23. Santa Maria C, Cheng Z, Li A, et al. Interplay between CaSR and PTH1R signaling in skeletal development and osteoanabolism. Semin Cell Dev Biol. 2016;49:11–23.
24. Chang W, Tu C, Chen TH, et al. The extracellular calcium-sensing receptor (CaSR) is. critical modulator of skeletal development. Sci Signal. 2008;1(35):ra1.doi: 10.1126/scisignal.1159945.
25. Goltzman D, Hendy GN. The calcium-sensing receptor in bone--mechanistic and therapeutic insights. Nat Rev Endocrinol. 2015;11:298–307.
26. Hannan FM, Kallay E, Chang W, et al. The Calcium-sensing receptor in physiology and in calcitropic and ,non-calcitropic diseases. Nat Rev Endocrinol 2018;15(1):33–51. doi:10.1038/s41574-018-0115-0
27. Dvorak-Ewell MM, Chen TH, Liang N, et al. Osteoblast extracellular Ca2+-sensing receptor regulates bone development, mineralization, and turnover.. Bone Miner Res. 2011;26:2935–2947.
28. Engelstoft MS, Park WM, Sakata I, et al. Seven transmembrane. protein-coupled receptor repertoire of gastric ghrelin cells. Mol Metab. 2013;2(4):376–392.
29. Reimann F, Tolhurst G, Gribble FM. G-protein coupled receptors in intestinal chemosensation. Cell Metab. 2012;15(4):421–431.
30. Spreckley E, Murphy KG. The L-cell in nutritional sensing and the regulation of appetite. Front Nutr. 2015;2:23. doi: 10.3389/fnut.2015.00023.
31. Geibel J, Sritharan K, Geibel R, et al. Calcium-sensing receptor abrogates secretagogue- induced increases in intestinal net fluid secretion by enhancing cyclic nucleotide destruction. Proc Natl Acad Sci USA. 2006;103(25):9390–9397.
32. Beltinger J, McKaig BC, Makh S, et al. Human colonic subepithelial myofibroblasts modulate transepithelial resistance and secretory response. Am. Physiol. 1999;277(2):C271–C279.
33. Peiris D, Pacheco I, Spencer C, et al. The extracellular calcium-sensing receptor reciprocally regulates the secretion of BMP-2 and the BMP antagonist Noggin in colonic myofibroblasts. Am. Physiol Gastrointest Liver Physiol. 2007;292(3):G753–G766.
34. Cheng SX, Lightfoot YL, Yang T, et al. Epithelial CaSR deficiency alters intestinal integrity and promotes proinflammatory immune responses. FEBS Lett. 2014;588(22):4158–4166.
35. Bruce JI, Yang X, Ferguson CJ, et al. Molecular and functional identification of. Ca2+ (polyvalent cation)-sensing receptor in rat pancreas.. Biol Chem. 1999;274(29):20561–20568.
36. Babinsky VN, Hannan FM, Ramracheya RD, et al. Mutant mice with calcium-sensing receptor activation have hyperglycemia that is rectified by calcilytic therapy. Endocrinology. 2017; 158:2486–2502.
37. Thakker RV. The calcium-sensing receptor: and its involvement in parathyroid pathology. Ann Endocrinol (Paris). 2015;76(2):81–83.
38. Tennakoon S , Aggarwal A, Kállay E. The calcium-sensing receptor and the hallmarks of cancer. Biochim Biophys Acta. 2016;1863(6 Pt B):1398-407.
39. Hannan FM. Thakker RV. Calcium-sensing receptor (CaSR) mutations and disorders of calcium, electrolyte and water metabolism. Best Pract Res Clin Endocrinol Metab. 2013;27(3): 359–371.
40. Vahe C, Benomar K, Espiard S, et al. Diseases associated with calcium-sensing receptor. Orphanet. Rare Dis. 2017;12(1):19. doi: 10.1186/s13023-017-0570-z.
41. Hannan FM, Babinsky VN, Thakker RV. Disorders of the calcium-sensing receptor and partner proteins: insights into the molecular basis of calcium homeostasis.. Mol Endocrinol. 2016; 57(3):R127–R142.
42. Tőke J, Czirják G, Enyedi P, et al. Rare diseases caused by abnormal calcium sensing and signalling. Endocrine. 2021;71(3):611-617.
43. Hinnie J, Bell E, McKillop E, et al. The prevalence of familial hypocalciuric hypercalcemia. Calcif Tissue Int. 2001;68(4):216–218.
44. Gorvin CM, Metpally R, Stokes VJ, et al. Large-scale exome datasets reveal. new class of adaptor-related protein complex. sigma subunit (AP2sigma) mutations, located at the interface with the AP2 alpha subunit, that impair calcium-sensing receptor signalling. Hum Mol Genet. 2018;27(5):901–911.
45. Pollak MR, Brown EM, Chou YH,et al. Mutations in the human Ca(2+)-sensing receptor gene cause familial hypocalciuric hypercalcemia and neonatal severe hyperparathyroidism. Cell.

1993;75(7):1297–1303.
46. Nesbit MA, Hannan FM, Howles SA, et al. Mutations affecting G-protein subunit α11 in hypercalcemia and hypocalcemia.. Engl. Med. 2013;368(26):2476–86.
47. Nesbit MA, Hannan FM, Howles SA, et al. Mutations in AP2S1 cause familial hypocalciuric hypercalcemia type 3. Nat Genet. 2013;45(1):93–97.
48. Christensen SE, Nissen PH, Vestergaard P, et al. Discriminative power of three indices of renal calcium excretion for the distinction between familial hypocalciuric hypercalcaemia and primary hyperparathyroidism:. follow-up study on methods. Clin Endocrinol (Oxf). 2008;69(5):713–720.
49. Silverberg SJ, Clarke BL, Peacock M, et al. Current issues in the presentation of asymptomatic primary hyperparathyroidism: proceedings of the Fourth International Workshop.. Clin Endocrinol Metab. 2014;99(10):3580–3594.
50. Eastell R, Brandi ML, Costa AG, et al. Diagnosis of asymptomatic primary hyperparathyroidism: proceedings of the Fourth International Workshop.. Clin Endocrinol Metab. 2014;99(10):3570–3579.
51. Marx SJ. Letter to the editor: Distinguishing typical primary hyperparathyroidism from familial hypocalciuric hypercalcemia by using an index of urinary calcium.. Clin Endocrinol Metab. 2015;100(2):L29–L30.
52. Hannan FM, Nesbit MA, Zhang C, et al. Identification of 70 calcium-sensing receptor mutations in hyper- and hypo-calcaemic patients: evidence for clustering of extracellular domain mutations at calciumbinding sites. Hum Mol Genet. 2012;21(12):2768–78.
53. Chikatsu N, Fukumoto S, Suzawa M, et al. An adult patient with severe hypercalcaemia and hypocalciuria due to. novel homozygous inactivating mutation of calcium-sensing receptor. Clin Endocrinol (Oxf). 1999;50(4):537–543.
54. Lietman SA, Tenenbaum-Rakover Y, Jap TS, et al.. novel loss-of-function mutation, Gln459Arg, of the calcium-sensing receptor gene associated with apparent autosomal recessive inheritance of familial hypocalciuric hypercalcemia.. Clin Endocrinol Metab. 2009;94(11):4372–4379.
55. Dershem R, Gorvin CM, Metpally RPR, et al. Familial hypocalciuric hypercalcemia type. and autosomal-dominant hypocalcemia type 1: Prevalence in. large healthcare population. Am. Hum Genet. 2020;106(6):734–747.
56. Yeh MW, Ituarte PHG, Zhou HC, et al. Incidence and prevalence of primary hyperparathyroidism in. racially mixed population.. Clin Endocrinol Metab. 2013;98(3):1122–1129.
57. Geng Y, Mosyak L, Kurinov I, et al. Structural mechanism of ligand activation in human calcium-sensing receptor. Elife 2016;5:e13662. doi: 10.7554/eLife.13662.
58. Zhang C, Zhang T, Zou J, et al. Structural basis for regulation of human calcium-sensing receptor by magnesium ions and an unexpected tryptophan derivative co-agonist. Sci Adv. 2016; 2(5):e1600241. doi: 10.1126/sciadv.1600241.
59. Huang Y, Breitwieser GE. Rescue of calcium-sensing receptor mutants by allosteric modulators reveals. conformational checkpoint in receptor biogenesis.. Biol Chem. 2007; 282(13):9517–9525.
60. White E, McKenna J, Cavanaugh A, et al. Pharmacochaperone-mediated rescue of calcium-sensing receptor loss-of-function mutants. Mol Endocrinol. 2009;23(7):1115–1123.
61. Leach K, Wen A, Davey AE, et al. Identification of molecular phenotypes and biased signaling induced by naturally occurring mutations of the human calcium-sensing receptor. Endocrinology. 2012;153(9):4304–4316.
62. Firek AF, Kao PC. Heath. 3rd. Plasma intact parathyroid hormone (PTH) and PTH-related peptide in familial benign hypercalcemia: greater responsiveness to endogenous PTH than in primary hyperparathyroidism.. Clin Endocrinol Metab.1991;72(3):541–546.
63. Lee JY, Shoback DM. Familial hypocalciuric hypercalcemia and related disorders. Best Pract Res Clin Endocrinol Metab. 2018;32(5):609–619.
64. Alon US, VandeVoorde RG. Beneficial effect of cinacalcet in. child with familial hypocalciuric hypercalcemia. Pediatr Nephrol. 2010;25(9):1747–1750.
65. Timmers HJLM, Karperien M, Hamdy NAT, et al. Normalization of serum calcium by cinacalcet in. patient with hypercalcaemia due to. de novo inactivating mutation of the calcium-sensing receptor.. Intern Med. 2006;260(2):177–182.
66. Volpe A, Guerriero A, Marchetta A, et al. Familial hypocalciuric hypercalcemia revealed by chondrocalcinosis. Joint Bone Spine. 2009;76(6):708–710.
67. Pearce SH, Wooding C, Davies M, et al. Calcium-sensing receptor mutations in familial hypocalciuric hypercalcaemia with recurrent pancreatitis. Clin Endocrinol (Oxf). 1996;45(6):675–680.
68. Masson E, Chen JM, Férec C. Overrepresentation of Rare CASR Coding Variants in. Sample of Young French Patients With Idiopathic Chronic Pancreatitis. Pancreas. 2015;44(6):996–998.
69. Christensen SE, Nissen PH, Vestergaard P, et al. Familial hypocalciuric hypercalcaemia:. review. Curr Opin Endocrinol Diabetes Obes. 2011;18(6):359–370.
70. Forde HE, Hill AD, Smith D. Parathyroid adenoma in. patient with familial hypocalciuric hypercalcaemia. BMJ Case Rep. 2014;2014:bcr2014206473. doi: 10.1136/bcr-2014-206473.
71. Brachet C, Boros E, Tenoutasse S, et al. Association of parathyroid adenoma and familial hypocalciuric hypercalcaemia in. teenager. Eur. Endocrinol. 2009;161(1):207–210.
72. Egan AM, Ryan J, Aziz MA, et al. Primary hyperparathyroidism in. patient with familial hypocalciuric hypercalcaemia due to. novel mutation in the calcium-sensing receptor gene.. Bone Miner Metab. 2013;31(4):477–480.
73. Yabuta T, Miyauchi A, Inoue H, et al.. patient with primary hyperparathyroidism associated with familial hypocalciuric hypercalcemia induced by. novel germline CaSR gene mutation. Asian. Surg. 2009;32(2):118–122.
74. Eldeiry LS, Ruan DT, Brown EM,

et al. Primary hyperparathyroidism and familial hypocalciuric hypercalcemia: relationships and clinical implications. Endocr Pract. 2012; 18(3):412–417.
75. Burski K, Torjussen B, Paulsen AQ, et al. Parathyroid adenoma in. subject with familial hypocalciuric hypercalcemia:coincidence or causality?. Clin Endocrinol Metab. 2002; 87(3):1015–1016.
76. Carling T, Szabo E, Bai M, et al. Familial hypercalcemia and hypercalciuria caused by. novel mutation in the cytoplasmic tail of the calcium receptor.. Clin Endocrinol Metab. 2000; 85(5):2042–2047.
77. Wang XM, Wu YW, Li ZJ, et al. Polymorphisms of CASR gene increase the risk of primary hyperparathyroidism.. Endocrinol Invest. 2016;39(6):617–25.
78. Marx SJ. Hyperplasia in glands with hormone excess. Endocr Relat Cancer. 2016;23(1):R1–R14.
79. Vezzoli G, Scillitani A, Corbetta S, et al. Risk of nephrolithiasis in primary hyperparathyroidism is associated with two polymorphisms of the calcium-sensing receptor gene.. Nephrol. 2015;28(1):67–72.
80. Oddsson A, Sulem P, Helgason H, et al. Common and rare variants associated with kidney stones and biochemical traits. Nat Commun. 2015;6:7975. doi: 10.1038/ncomms8975.
81. Wettschureck N, Lee E, Libutti SK, et al. Parathyroid-specific double knockout of Gq and G11 alpha-subunits leads to. phenotype resembling germline knockout of the extracellular Ca2+ -sensing receptor. Mol Endocrinol. 2007;21(1):274–280.
82. Gorvin CM, Hannan FM, Cranston T, et al. Cinacalcet rectifies hypercalcemia in. patient with familial hypocalciuric hypercalcemia type. (FHH2) caused by. germline loss-of-function $G\alpha_{11}$ mutation.. Bone Miner Res. 2018;33(1):32–41.
83. Gorvin CM, Cranston T, Hannan FM, et al. G-Protein subunit-alpha11 loss-of-function mutation, Thr54Met, causing familial hypocalciuric hypercalcemia type. (FHH2).. Bone Miner Res. 2016;31(6):1200–1206.
84. Hannan FM, Howles SA, Rogers A, et al. Adaptor protein-2 sigma subunit mutations causing familial hypocalciuric hypercalcaemia type. (FHH3) demonstrate genotype-phenotype correlations, codon bias and dominant-negative effects. Hum Mol Genet. 2015;24(18):5079–5092.
85. Vargas-Poussou R, Mansour-Hendili L, Baron S, et al. Familial Hypocalciuric Hypercalcemia Types. and. and Primary Hyperparathyroidism: Similarities and Differences.. Clin Endocrinol Metab. 2016;101(5):2185–2195.
86. Gorvin CM, Rogers A, Hastoy B, et al. Ap2σ mutations impair calciumsensing receptor trafficking and signaling, and show an endosomal pathway to spatially direct g-protein selectivity. Cell Rep. 2018;22(4):1054–1066.
87. Howles SA, Hannan FM, Babinsky VN, et al. Cinacalcet for symptomatic hypercalcemia caused by AP2S1 mutations.. Engl. Med. 2016;374(14):1396–1398.
88. Fujisawa Y, Yamaguchi R, Satake E, et al. Identification of AP2S1 mutation and effects of low calcium formula in an infant with hypercalcemia and hypercalciuria.. Clin Endocrinol Metab. 2013;98(12):E2022–E2027.
89. Hendy GN, Canaff L, Newfield RS, et al. Codon Arg15 Mutations of the AP2S1 gene: common occurrence in familial hypocalciuric hypercalcemia cases negative for calcium-sensing receptor (CASR) mutations.. Clin Endocrinol Metab. 2014;99(7):E1311–E1315.
90. Hovden S, Rejnmark L, Ladefoged SA, et al. AP2S1 and GNA11 mutations. not. common cause of familial hypocalciuric hypercalcemia. Eur. Endocrinol. 2017;176(2):177–185.
91. Kelly BT, McCoy AJ, Spate K, et al.. structural explanation for the binding of endocytic dileucine motifs by the AP2 complex. Nature. 2008;456(7224):976–979.
92. McMurtry CT, Schranck FW, Walkenhorst DA, et al. Significant developmental elevation in serum parathyroid hormone levels in. large kindred with familial benign (hypocalciuric) hypercalcemia. Am. Med. 1992;93(3):247–258.
93. Nesbit MA, Hannan FM, Graham U, et al. Identification of. second kindred with familial hypocalciuric hypercalcemia type. (FHH3) narrows localization to. <3.5 megabase pair region on chromosome 19q13.3.. Clin Endocrinol Metabol. 2010;95(4):1947–1954.
94. Majid H, Khan AH, Moatter T. R990G polymorphism of calcium sensing receptor gene is associated with high parathyroid hormone levels in subjects with vitamin. deficiency:. cross-sectional study. Biomed Res Int. 2015; 2015:407159. doi:10.1155/2015/407159.
95. O'Seaghdha CM, Wu H, Yang Q, et al. Meta-analysis of genome-wide association studies identifies six new Loci for serum calcium concentrations. PLoS Genet. 2013;9(9):e1003796. doi: 10.1371/journal.pgen.1003796.
96. Díaz-Soto G, Romero E, Castrillón JL, et al. Clinical Expression of Calcium Sensing Receptor Polymorphism (A986S) in Normocalcemic and Asymptomatic Hyperparathyroidism. Horm Metab Res. 2016;48(3):163–168.
97. Guan B, Welch JM, Sapp JC, et al. GCM2-Activating Mutations in Familial Isolated Hyperparathyroidism. Am. Hum Genet. 2016;99(5):1034–1044.
98. Thakker RV. Genetics of parathyroid tumours.. Intern Med. 2016;280(6):574–583.
99. Duan K, Gomez Hernandez K, Mete O. Clinicopathological correlates of hyperparathyroidism.. Clin Pathol. 2015;68(10):771–787.
100. Molin A, Baudoin R, Kaufmann M, et al. CYP24A1 Mutations in. Cohort of Hypercalcemic Patients: Evidence for. Recessive Trait.. Clin Endocrinol Metab. 2015;100(10):E1343–1352.
101. Loyer C, Leroy C, Molin A, et al. Hyperparathyroidism complicating CYP 24A1 mutations. Ann Endocrinol (Paris). 2016;77(5):615–619.
102. Murphy H, Patrick J, Báez-Irizarry E, et al. Neonatal severe hyperparathyroidism caused by homozygous mutation in CASR:. rare cause of life-threatening hypercalcemia. Eur. Med Genet. 2016;59(4):227–231.
103. Hannan FM, Nesbit MA, Christie PT, et al.. homozygous inacti-

vating calcium-sensing receptor mutation, Pro339Thr, is associated with isolated primary hyperparathyroidism: correlation between location of mutations and severity of hypercalcaemia. Clin Endocrinol (Oxf). 2010;73(6):715–722.
104. Chattopadhyay. & Brown EM. Role of calcium-sensing receptor in mineral ion metabolism and inherited disorders of calcium-sensing. Mol Genet Metab. 2006;89(3):189–202.
105. Obermannova B, Banghova K, Sumník Z, et al. Unusually severe phenotype of neonatal primary hyperparathyroidism due to. heterozygous inactivating mutation in the CASR gene. Eur. Pediatr. 2009;168(5):569–573.
106. Glaudo M, Letz S, Quinkler M, et al. Heterozygous inactivating CaSR mutations causing neonatal hyperparathyroidism: function, inheritance and phenotype. Eur. Endocrinol. 2016; 175(5):421–431.
107. Egbuna OI, Brown EM. Hypercalcaemic and hypocalcaemic conditions due to calcium-sensing receptor mutations. Best Pract Res Clin Rheumatol. 2008;22(1):129–148.
108. Waller S, Kurzawinski T, Spitz L, et al. Neonatal severe hyperparathyroidism: genotype/phenotype correlation and the use of pamidronate as rescue therapy. Eur. Pediatr. 2004; 163(10):589–594.
109. Wilhelm-Bals A, Parvex P, Magdelaine C, et al. Successful use of bisphosphonate and calcimimetic in neonatal severe primary hyperparathyroidism. Pediatrics. 2012;129(3):e812–e816.
110. Kifor O, Moore FD Jr, Delaney M, et al.. syndrome of hypocalciuric hypercalcemia caused by autoantibodies directed at the calcium-sensing receptor.. Clin Endocrinol Metab. 2003; 88(1):60-72.
111. Pallais JC, Kifor O, Chen YB, et al. Acquired hypocalciuric hypercalcemia due to autoantibodies against the calcium-sensing receptor.. Engl. Med. 2004;351(4):362–369.
112. Song L, Liu L, Miller RT, et al. Glucocorticoid-responsive lymphocytic parathyroiditis and hypocalciuric hypercalcemia due to autoantibodies against the calcium-sensing receptor:. case report and literature review. Eur. Endocrinol. 2017;177(1):K1–K6.
113. Yamamoto M, Akatsu T, Nagase T, et al. Comparison of hypocalcemic hypercalciuria between patients with idiopathic hypoparathyroidism and those with gain-of-function mutations in the calcium-sensing receptor: is it possible to differentiate the two disorders?. Clin Endocrinol Metab. 2000;85(12):4583–4591.
114. Pearce SH, Williamson C, Kifor O, et al.. familial syndrome of hypocalcemia with hypercalciuria due to mutations in the calciumsensing receptor.. Engl. Med. 1996;335(15): 1115–1122.
115. Li D, Opas EE, Tuluc F, et al. Autosomal dominant hypoparathyroidism caused by germline mutation in GNA11: phenotypic and molecular characterization.. Clin Endocrinol Metab. 2014; 99(9):E1774–E1783.
116. Mannstadt M, Harris M, Bravenboer B, et al. Germline mutations affecting $G\alpha_{11}$ in hypoparathyroidism.. Engl. Med. 2013;368(26):2532–2534.
117. Piret SE, Gorvin CM, Pagnamenta AT, et al. Identification of. G-Protein subunit-α_{11} gain-of-function mutation, Val340Met, in. family with autosomal dominant hypocalcemia type. (ADH2).. Bone Miner Res. 2016;31(6):1207–1214.
118. Vargas-Poussou R, Huang C, Hulin P, et al. Functional characterization of. calcium-sensing receptor mutation in severe autosomal dominant hypocalcemia with. Bartter-like syndrome.. Am Soc Nephrol. 2002;13(9):2259–2266.
119. Kinoshita Y, Hori M, Taguchi M, et al. Functional activities of mutant calcium-sensing receptors determine clinical presentations in patients with autosomal dominant hypocalcemia.. Clin Endocrinol Metab. 2014;99(2):E363–368.
120. Roberts MS, Gafni RI, Brillante B, et al. Treatment of autosomal dominant hypocalcemia type. with the calcilytic npsp795 (shp635).. Bone Miner Res. 2019;34(9):1609–1618.
121. Rogers A, Nesbit MA, Hannan FM, et al. Mutational analysis of the adaptor protein. sigma subunit (AP2S1) gene: search for autosomal dominant hypocalcemia type. (ADH3).. Clin Endocrinol Metab. 2014;99(7):E1300–E1305.
122. Watanabe S, Fukumoto S, Chang H, et al. Association between activating mutations of calcium-sensing receptor and Bartter's syndrome. Lancet. 2002;360(9334):692–694.
123. Nemeth EF, Heaton WH, Miller M, et al. Pharmacodynamics of the type II calcimimetic compound cinacalcet HCl.. Pharmacol Exp Ther. 2004;308(2):627–635.
124. Hamano N, Komaba H, Fukagawa M. Etelcalcetide for the treatment of secondary hyperparathyroidism. Expert Opin Pharmacother. 2017;18(5):529–534.
125. Khan A, Bilezikian J, Bone H, et al. Cinacalcet normalizes serum calcium in. double-blind randomized, placebo-controlled study in patients with primary hyperparathyroidism with contraindications to surgery. Eur. Endocrinol. 2015;172(5):527–535.
126. Nemeth EF, Goodman WG. Calcimimetic and calcilytic drugs: feats, flops, and futures. Calcif Tissue Int. 2016;98(4):341–358.
127. Gannon AW, Monk HM, Levine MA. Cinacalcet monotherapy in neonatal severe hyperparathyroidism:. case study and review.. Clin Endocrinol Metab. 2014;99(1):7–11.
128. Rus R, Haag C, Bumke-Vogt C, et al. Novel inactivating mutations of the calcium-sensing receptor: the calcimimetic NPS R-568 improves signal transduction of mutant receptors.. Clin Endocrinol Metab. 2008;93(12):4797–4803.
129. Leach K, Wen A, Cook AE, et al. Impact of clinically relevant mutations on the pharmacoregulation and signaling bias of the calcium-sensing receptor by positive and negative allosteric modulators. Endocrinology. 2013;154(3):1105–1116.
130. Festen-Spanjer B, Haring CM, Koster JB, et al. Correction of hypercalcaemia by cinacalcet in familial hypocalciuric hypercalcaemia. Clin Endocrinol (Oxf). 2008;68(2):324–325.
131. Walter S, Baruch A, Dong J, et al. Pharmacology of AMG 416 (Velcalcetide),. novel peptide agonist

of the calcium-sensing receptor, for the treatment of secondary hyperparathyroidism in hemodialysis patients.. Pharmacol Exp Ther. 2013;346(2):229–240.
132. Block GA, Bushinsky DA, Cheng S, et al. Effect of etelcalcetide versus cinacalcet on serum parathyroid hormone in patients receiving hemodialysis with secondary hyperparathyroidism:. randomized clinical trial. JAMA. 2017;317(2):156–164.
133. Alexander ST, Hunter T, Walter S, et al. Critical cysteine residues in both the calcium-sensing receptor and the allosteric activator AMG 416 underlie the mechanism of action. Mol Pharmacol. 2015;88(5):853–865.
134. Hénaut L, Boudot C, Massy ZA, et al. Calcimimetics increase CaSR expression and reduce mineralization in vascular smooth muscle cells: mechanisms of action. Cardiovasc Res. 2014; 101(2):256–265.
135. Nemeth EF, Delmar EG, Heaton WL, et al. Calcilytic compounds: potent and selective Ca2+ receptor antagonists that stimulate secretion of parathyroid hormone.. Pharmacol Exp Ther. 2001; 299(1):323–331.
136. Gowen M, Stroup GB, Dodds RA, et al. Antagonizing the parathyroid calcium receptor stimulates parathyroid hormone secretion and bone formation in osteopenic rats.. Clin Invest. 2000;105(11):1595–1604.
137. Fitzpatrick LA, Dabrowski CE, Cicconetti G, et al. The effects of ronacaleret,. calcium-sensing receptor antagonist, on bone mineral density and biochemical markers of bone turnover in postmenopausal women with low bone mineral density.. Clin Endocrinol Metab. 2011;96(8): 2441–2449.
138. Halse J, Greenspan S, Cosman F, et al.. phase 2, randomized, placebocontrolled, dose-ranging study of the calcium-sensing receptor antagonist MK-5442 in the treatment of postmenopausal women with osteoporosis.. Clin Endocrinol Metab. 2014;99(11):E2207–E2215.
139. Dong B, Endo I, Ohnishi Y, et al. Calcilytic ameliorates abnormalities of mutant calcium-sensing receptor (CaSR) knock-in mice mimicking autosomal dominant hypocalcemia (ADH).. Bone Miner Res. 2015;30(11):1980–1993.
140. Babinsky VN, Hannan FM, Gorvin CM, et al. Allosteric modulation of the calcium-sensing receptor rectifies signaling abnormalities associated with G-protein alpha-11 mutations causing hypercalcemic and hypocalcemic disorders.. Biol Chem. 2016;291(20):10876–10885.
141. Rasmussen SG, DeVree BT, Zou Y, et al. Crystal structure of the β2 adrenergic receptor-Gs protein complex. Nature. 2011;477(7366):549–555.
142. Tenhola S, Hendy GN, Valta H, et al. Cinacalcet treatment in an adolescent with concurrent 22q11.2 deletion syndrome and FHH3 caused by AP2S1 mutation.. Clin Endocrinol Metab. 2015; 100(7):2515–2518.
143. Rodriguez M, Nemeth E, Martin D. The calcium-sensing receptor:. key factor in the pathogenesis of secondary hyperparathyroidism. Am. Physiol Renal Physiol. 2005;288(2):F253–F264.
144. Cunningham J, Locatelli F, Rodriguez M. Secondary hyperparathyroidism: pathogenesis, disease progression, and therapeutic options. Clin. Am Soc Nephrol. 2011;6(4):913–921.
145. Campion KL, McCormick WD, Warwicker J, et al. Pathophysiologic changes inextracellular pH modulate parathyroid calcium-sensing receptor activity and secretion via. histidineindependent mechanism.. Am Soc Nephrol. 2015;26 (9):2163–2171.
146. Brown AJ, Ritter CS, Finch JL, et al. Decreased calcium-sensing receptor expression in hyperplastic parathyroid glands of uremic rats: role of dietary phosphate. Kidney Int. 1999;55(4):1284–1292.
147. Mizobuchi M, Hatamura I, Ogata H, et al. Calcimimetic compound upregulates decreased calcium-sensing receptor expression level in parathyroid glands of rats with chronic renal insufficiency.. Am Soc Nephrol. 2004;15(10):2579–2587.
148. Coe FL, Parks JH, Moore ES. Familial idiopathic hypercalciuria.. Engl. Med. 1979; 300(7):337–340.
149. Lerolle N, Coulet F, Lantz B, et al. No evidence for point mutations of the calcium-sensing receptor in familial idiopathic hypercalciuria. Nephrol Dial Transplant. 2001;16(12):2317–2322.
150. Vezzoli G, Tanini A, Ferrucci L, et al. Influence of calcium-sensing receptor gene on urinary calcium excretion in stone-forming patients.. Am Soc Nephrol. 2002;13(10):2517–2523.
151. Vezzoli G, Teranegra A, Aloia A, et al. Decreased transcriptional activity of calcium-sensing receptor gene promoter. is associated with calcium nephrolithiasis.. Clin Endocrinol Metab. 2013; 98(9):3839–3847.