RESSALVA

Atendendo solicitação do(a) autor(a), o texto completo desta tese será disponibilizado somente a partir de 09/08/2025.

UNIVERSIDADE ESTADUAL PAULISTA
"JÚLIO DE MESQUITA FILHO"
FACULDADE DE MEDICINA

Igor de Carvalho Deprá

Síndrome de Resistência ao Hormônio Tireoidiano: Mecanismos e Manifestações Clínicas

Tese apresentada à Faculdade de Medicina, Universidade Estadual Paulista "Júlio de Mesquita Filho", Câmpus de Botucatu, para obtenção do título de Doutor em Fisiopatologia em Clínica Médica.

Orientadora: Profa. Dra. Célia Regina Nogueira

Coorientadora: Dra. Maria Cristina Crês

Botucatu

2024

Igor de Carvalho Deprá

Síndrome de Resistência ao Hormônio Tireoidiano: Mecanismos e Manifestações Clínicas

Tese apresentada à Faculdade de Medicina, Universidade Estadual Paulista "Júlio de Mesquita Filho", Câmpus de Botucatu, para obtenção do título de Doutor em Fisiopatologia em Clínica Médica.

Orientadora: Profa. Dra. Célia Regina Nogueira

Coorientadora: Dra. Maria Cristina Crês

Botucatu

2024

FICHA CATALOGRÁFICA ELABORADA PELA SEÇÃO TÉC. AQUIS. TRATAMENTO DA INFORM.
DIVISÃO TÉCNICA DE BIBLIOTECA E DOCUMENTAÇÃO - CÂMPUS DE BOTUCATU - UNESP

BIBLIOTECÁRIA RESPONSÁVEL: ROSANGELA APARECIDA LOBO-CRB 8/7500

Deprá, Igor de Carvalho.
Síndrome de resistência ao hormônio tireoidiano : mecanismos, manifestações clínicas e implicações terapêuticas / Igor de Carvalho Deprá. - Botucatu, 2024

Tese (doutorado) - Universidade Estadual Paulista (UNESP), Faculdade de Medicina, Botucatu
Orientador: Célia Regina Nogueira
Coorientador: Maria Cristina Crês
Capes: 40101061

1. Glândula tireóide. 2. Hormônios tireóideos. 3. Receptores beta dos hormônios tireóideos. 4. Genética. 5. Genes.

Palavras-chave: Síndrome de resistência ao hormônio tireoidiano; THRB; Tireoide.

UNIVERSIDADE ESTADUAL PAULISTA

Câmpus de Botucatu

ATA DA DEFESA PÚBLICA DA TESE DE DOUTORADO DE IGOR DE CARVALHO DEPRÁ, DISCENTE DO PROGRAMA DE PÓS-GRADUAÇÃO EM FISIOPATOLOGIA EM CLÍNICA MÉDICA, DA FACULDADE DE MEDICINA.

Aos 09 dias do mês de agosto do ano de 2024, às 09:00 horas, por meio de Videoconferência, realizou-se a defesa de TESE DE DOUTORADO de IGOR DE CARVALHO DEPRÁ, intitulada **Síndrome de Resistência ao Hormônio Tireoidiano: Mecanismos, Manifestações Clínicas e Implicações Terapêuticas**. A Comissão Examinadora foi constituida pelos seguintes membros: Profa. Dra. CELIA REGINA NOGUEIRA DE CAMARGO (Orientador(a) - Participação Presencial) do(a) Depto. de Clínica Médica / FM/Botucatu - Unesp, Profa. Dra. MIRIANE DE OLIVEIRA (Participação Virtual) do(a) Onkos Diagnósticos Moleculares / Ribeirão Preto, Profa. Dra. ADRIANA LUCIA MENDES (Participação Presencial) do(a) Depto. de Clínica Médica / FM/Botucatu - Unesp, Profa. Dra. NANCY BUENO FIGUEIREDO (Participação Presencial) do(a) Universidade Nove de Julho - Bauru, Profa. Dra. SUSAN CHOW LINDSEY (Participação Virtual) do(a) Depto. de Medicina / EPM/São Paulo - Unifesp. Após a exposição pelo doutorando e arguição pelos membros da Comissão Examinadora que participaram do ato, de forma presencial e/ou virtual, o discente recebeu o conceito final: aprovado . Nada mais havendo, foi lavrada a presente ata, que após lida e aprovada, foi assinada pelo(a) Presidente(a) da Comissão Examinadora.

Profa. Dra. CELIA REGINA NOGUEIRA DE CAMARGO

DEDICATÓRIA

À minha filha Amélie

AGRADECIMENTOS

À minha orientadora, a quem devo tantas oportunidades;

À Dra. Maria Cristina Crês, que gentilmente colaborou neste processo;

A Francisco, Mariella e Simone, a quem um dia retribuirei;

À Unidade de Pesquisa Experimental e ao Instituto de Biotecnologia, pelo apoio generoso à realização deste projeto;

Aos colegas de laboratório, por compartilhar os altos e baixos desta experiência;

Aos meus familiares, pela paciência;

À Dra. Gláucia M. F. S. Mazeto, pelo incentivo;

A todos os que me estimularam a seguir adiante.

“Não se devia permitir nos relógios de parede esses ponteiros
que marcam os segundos: eles nos envelhecem muito
mais que o ponteiro das horas.”

Mário Quintana

Resumo

A síndrome de resistência ao hormônio tireoidiano beta (RHTβ) é causada por mutações no gene codificante da isoforma beta do receptor de hormônio tireoidiano (*THRB*). Caracterizada bioquimicamente pela elevação sérica de tiroxina (T4) sem supressão do hormônio tireoestimulante (TSH), possui manifestação clínica variada, podendo afetar diferentes órgãos, e sua peculiaridade está na manifestação simultânea de sinais de hipo e hipertireoidismo. Recentemente, foi descrita uma mutação previamente desconhecida, substituindo a leucina do códon 341 por valina (L341V), que causa RHTβ, porém com pouca informação sobre a manifestação clínica. Neste estudo, foi acompanhada a evolução clínica da síndrome em uma família não relacionada, também portadora da mutação L341V, ao longo de 13 anos, encontrando características ausentes na literatura.

Abstract

Thyroid hormone resistance syndrome beta (THRβ) is caused by mutations in the gene coding the beta isoform of thyroid hormone receptor (*THRB*). Biochemically, it is characterized by elevation of serum thyroxine (T4) with unsuppressed thyrostimulating hormone (TSH), and has variable clinical manifestation, potentially affecting various organ systems. Its peculiarity resides in the simultaneous occurence of hipo- and hiperthyroidism hallmarks. It has been recently described a novel mutation, substituting leukine for valine in codon 341 of *THRB*, causing THRβ, though little information was reported on its clinical manifestation. This study reports the 13-year follow up of an unrelated family, also harboring the L341V mutation, finding characteristics previously absent in the literature.

Sumário

1. Introdução

1.1. Ação fisiológica dos hormônios tireoidianos (HT)

A capacidade de produzir ou metabolizar hormônios tireoidianos (HT) é encontrada amplamente no reino animal. Seus efeitos no desenvolvimento embrionário e larval são observados em diversos grupos de invertebrados, incluindo moluscos e equinodermos [1]. Em cordados, determinam o início da metamorfose de peixes [2] e anfíbios [3], e são indispensáveis para o desenvolvimento do sistema nervoso central [4,5] o que é demonstrado pelos efeitos deletérios do hipotireoidismo congênito no desenvolvimento cerebral em humanos [6]. No indivíduo adulto, alguns de seus efeitos mais notáveis incluem o controle da taxa metabólica basal e da produção de calor [7], além de funções fisiológicas concomitantes, como regulação do apetite [8], cujo efeito último é suprir os tecidos estimulados com os nutrientes necessários para sustentar o metabolismo. Há, ainda, efeitos tratados como pleiotrópicos por não terem relação óbvia com as alterações metabólicas, como a aceleração do *turnover* ósseo [9].

Em vertebrados, os HT são produzidos pela glândula tireoide, cujo parênquima consiste de estruturas globulares microscópicas denominadas folículos, preenchidas por uma substância coloidal e delimitadas por um epitélio simples de células foliculares. A partir dessa substância coloidal, as células foliculares sintetizam e secretam duas formas de HT, L-tiroxina (T4), sendo esta a forma majoritária, e 3,5,3´-triiodo-L-tironina (T3). Na circulação, cerca de 0,03% do T4 e 0,3% do T3 encontram-se livres, estando a maior fração ligada à globulina ligadora de tiroxina (TBG) e, em menor proporção, à transtirretina (TTR) e à albumina sérica, o que contribui para a estabilização dos níveis séricos de HT, cuja regulação será detalhada a seguir [10].

1.1.1. Regulação das concentrações de HT

Sistemicamente, as concentrações de HT circulantes são mantidas dentro de um intervalo estreito pelo sistema de *feedback* negativo conhecido como eixo hipotálamo-hipófise-tireoide. A produção e secreção de HT pela glândula tireoide depende de estímulo por hormônio tireoestimulante, ou tireotropina (TSH), produzido

2. Referências

1. Taylor, E.; Heyland, A. Evolution of thyroid hormone signaling in animals: Non-genomic and genomic modes of action. Molecular and Cellular Endocrinology 459:14-20, 2017. https://doi.org/10.1016/j.mce.2017.05.019
2. Campinho, M.A. Teleost metamorphosis: the role of thyroid hormone. Frontiers in Endocrinology 10:383, 2019. https://doi.org/10.3389/fendo.2019.00383
3. Tata, J.R. Amphibian metamorphosis as a model for the developmental actions of thyroid hormone. Molecular and Cellular Endocrinology 246 (1–2):10-20, 2006. https://doi.org/10.1016/j.mce.2005.11.024
4. McNabb, F.M.A. The hypothalamic-pituitary-thyroid (HPT) axis in birds and its role in bird development and reproduction. Critical Reviews in Toxicology 37:163-193, 2007. https://doi.org/10.1080/10408440601123552
5. Hu, C.; Wang; S.; Wu, D.; Yan, C.; Wu, M. Subclinical hypothyroidism in pregnancy rats impaired offspring's spatial learning and memory and the cerebellar development. Biochemical and Biophysical Research Communications 602:63-69, 2022. https://doi.org/10.1016/j.bbrc.2022.02.107
6. Grüters, A.; Krude, H. Detection and treatment of congenital hypothyroidism. Nature Reviews Endocrinology (8):104–113, 2012). https://doi.org/10.1038/nrendo.2011.160
7. Nicolaisen, T.S.; Klein, A.B.; Dmytriyeva, O.; Lund, J.; et al. Thyroid hormone receptor α in skeletal muscle is essential for T3-mediated increase in energy expenditure. The FASEB Journal 34(11):15480-15491, 2020. https://doi.org/10.1096/fj.202001258RR
8. Mitchell, C.S.; Savage, D.B.; Dufour, S.; Schoenmakers, N. Resistance to thyroid hormone is associated with raised energy expenditure, muscle mitochondrial uncoupling, and hyperphagia. The Journal of Clinical Investigation 120(4):1345-1354, 2010. https://doi.org/10.1172/JCI38793
9. Gogakos, A.I.; Bassett, J.H.D.; Williams; G.R. Thyroid and bone. Archives of Biochemistry and Biophysics 503(1):129-136, 2010. https://doi.org/10.1016/j.abb.2010.06.021

10. Mimoto;M.S.; Refetoff, S. Clinical recognition and evaluation of patients with inherited serum thyroid hormone-binding protein mutations. Journal of Endocrinological Investigation 43:31-41, 2020. https://doi.org/10.1007/s40618-019-01084-9
11. Ortiga-Carvalho, T.M.; Chiamolera, M.I.; Pazos-Moura, C.C.; Wondisford, F.E. Hypothalamus-pituitary-thyroid axis. Comprehensive Physiology 6(3), 2016. https://doi.org/10.1002/cphy.c150027
12. Sinkó, R.; Mohácsik, P.; Kővári, D.; Penksza, V. Different hypothalamic mechanisms control decreased circulating thyroid hormone levels in infection and fasting-induced non-thyroidal illness syndrome in male thyroid hormone action indicator mice. Thyroid 33(1), 2023. https://doi.org/10.1089/thy.2022.0404
13. Minakhina, S.; Oliveira, V.; Kim, S.Y.; Wondisford, F.E. Thyroid hormone receptor phosphorylation regulates acute fasting-induced suppression of the hypothalamic–pituitary–thyroid axis. Proceedings of the National Academy of Science 118 (39) e2107943118, 2021. https://doi.org/10.1073/pnas.2107943118
14. Ortiga-Carvalho, T.M.; Sidhaye, A.R.; Wondisford, F.E. Thyroid hormone receptors and resistance to thyroid hormone disorders. Nature Reviews Endocrinology 10(10):582–591, 2014. https://doi.org/10.1038/nrendo.2014.143
15. Groeneweg, S.; van Geest, F.S.; Peeters, R.P.; Heuer, H.; Visser, W.E. Thyroid hormone transporters. Endocrine Reviews 41(2):146–201, 2020. https://doi.org/10.1210/endrev/bnz008
16. Müller, J.; Heuer, H. Understanding the hypothalamus-pituitary-thyroid axis in Mct8 deficiency. European Thyroid Journal 1(2):72-79, 2012. https://doi.org/10.1159/000339474
17. Bianco, A.C.; Conceição, R.R. The deiodinase trio and thyroid hormone signaling. In: Plateroti, M.; Samarut, J. (orgs.). Thyroid homrone nuclear receptor - methods and protocols. 1 ed. Nova York: Humana New York, 2018, p. 67-83. https://doi.org/10.1007/978-1-4939-7902-8
18. Russo, S.; Salas-Lucia, F.; Bianco, A.C. Deiodinases and the Metabolic Code for Thyroid Hormone Action. Endocrinology 162(8):1-13, 2021. https://doi.org/10.1210/endocr/bqab059

19. Lum, S.M.; Nicoloff, J.T.; Spencer, C.A.; Kaptein, E.M. Peripheral tissue mechanism for maintenance of serum triiodothyronine values in a thyroxine-deficient state in man. The Journal of Clinical Investigation 73(2):570-575, 1984. https://doi.org/10.1172/JCI111245
20. McAninch, E.A.; Jo, S.; Preite, N.Z.; Farkas, E.; et al. Prevalent polymorphism in thyroid hormone-activating enzyme leaves a genetic fingerprint that underlies associated clinical syndromes. The Journal of Clinical Endocrinology & Metabolism 100(3):920–933, 2015. https://doi.org/10.1210/jc.2014-4092
21. Mayerl, S.; Schmict, M.; Doycheva, Darras, V.M. et al. Thyroid Hormone Transporters MCT8 and OATP1C1 Control Skeletal Muscle Regeneration. Stem Cell Reports 10(6):1959-1974, 2018. https://doi.org/10.1016/j.stemcr.2018.03.021
22. Dentice, M.; Marsili, A.; Zavacki, A.; Larsen, P.R.; Salvatore, D. The deiodinases and the control of intracellular thyroid hormone signaling during cellular differentiation. Biochimica et Biophysica Acta 1830(7):3937-3945, 2013. https://doi.org/10.1016/j.bbagen.2012.05.007
23. Patel, J.; Landers, K.; Li, H.; Mortimer, R.H.; Richard, K. Delivery of maternal thyroid hormones to the fetus. Trends in Endocrinology & Metabolism 22(5):164-170, 2011. https://doi.org/10.1016/j.tem.2011.02.002
24. Kester, M.H.A.; Mena, R.M.; Obregon, M.J.; Marinkovic, D. Iodothyronine levels in the human developing brain: major regulatory roles of Iodothyronine deiodinases in different areas. The Journal of Clinical Endocrinology & Metabolismv89(7):3117–3128, 2004. https://doi.org/10.1210/jc.2003-031832
25. Flamant, F.; Cheng, S.Y.; Hollenberg., A.N. Moeller, L.C. Thyroid hormone signaling pathways: time for a more precise nomenclature. Endocrinology 158(7):2052-2057, 2017. https://doi.org/10.1210/en.2017-00250
26. Morkin, E. Regulation of myosin heavy chain genes in the heart. Circulation 87(5):1451-1460, 1993. https://doi.org/10.1161/01.CIR.87.5.1451
27. Simonides, W.S.; Thelen, M.H.M.; Linden, C.G.; Muller, A.; Hardeveld, C. Mechanism of Thyroid-Hormone Regulated Expression of the SERCA Genes in Skeletal Muscle: Implications for Thermogenesis. Bioscience Reports 21:139-154, 2001. https://doi.org/10.1023/A:1013692023449

28. Alcalde, A.I.; Sarasa, M.; Raldúa, D.; Aramayona, J. Role of thyroid hormone in regulation of renal phosphate transport in young and aged rats. Endocrinology 140(4):1544-1551, 1999. https://doi.org/10.1210/endo.140.4.6658

29. Gong, D.W.; He, Y.; Karas, M.; Reitman, M. Uncoupling protein-3 is a mediator of thermogenesis regulated by thyroid hormone, b3-adrenergic agonists, and leptin. The Journal of Biological Chemistry 272(39):24129-24132, 1997. https://doi.org/10.1074/jbc.272.39.24129

30. Salgado, R.M.; Sheard, A.C.; Vaughan, R.A.; Parker, D.L.; et al. Mitochondrial efficiency and exercise economy following heat stress: a potential role of uncoupling protein 3. Physiological Reports 5(3):e13054, 2017. https://doi.org/10.14814/phy2.13054

31. Lopez, D.; Socarrás, J.F.A.; Bedi, M.; Ness, G.C. Activation of the hepatic LDL receptor promoter by thyroid hormone. Biochimica et Biophysica Acta - Molecular and Cell Biology of Lipids 1771(9):1216-1225, 2007. https://doi.org/10.1016/j.bbalip.2007.05.001

32. Mangelsdorf, D.; Thummel, C.; Beato, M.; Herrlich, P. The nuclear receptor superfamily: the second decade. Cell 83:835-839, 1995. https://doi.org/10.1016%2F0092-8674(95)90199-x

33. Weikum, E.R.; Liu, X.; Ortlund, E.A. The nuclear receptor superfamily: a structural perspective. Protein Science 27(11):1876-1892, 2018. https://doi.org/10.1002/pro.3496

34. Hönes, G.S.; Härting, N.; Mittag, J.; Kaiser, F.J. TRα2—An untuned second fiddle or fine-tuning thyroid hormone action? International Journal of Molecular Science 23(13):6998, 2022. https://doi.org/10.3390/ijms23136998

35. Umesono, K.; Murakami, K.K.; Thompson, C.C.; Evans, R.M. Direct repeats as selective response elements for the thyroid hormone, retinoic acid, and vitamin D3 receptors. Cell 65(7):1255-1266, 1991. https://doi.org/10.1016/0092-8674(91)90020-Y

36. Zhang, J.; Lazar, M.A. The mechanism of action of thyroid hormones. Annual Review of Physiology 62:439-466, 2000. https://doi.org/10.1146/annurev.physiol.62.1.439

37. Kassák, F.; Hána, V.; Saudek, V.; Kostrouchová, M. Novel mutation (T273R) in thyroid hormone receptor β gene provides further insight into cryptic negative regulation by thyroid hormone. Folia Biologica (Praha) 63:60-66, 2017. PMID: 28557707

38. Jansson, M.; Philipson, L.; Vennström, B. Isolation and characterization of multiple human genes homologous to the oncogenes of avian erythroblastosis virus. The EMBO Journal 2:561-565, 1983. https://doi.org/10.1002/j.1460-2075.1983.tb01463.x

39. Weinberger, C.; Thompson, C.C.; Ong, E.S.; Lebo, R.; Gruol, D.J.; Evans, R.M. The c-erb-A gene encodes a thyroid hormone receptor. Nature 324:641–646, 1986. https://doi.org/10.1038/324641a0

40. Kalyanaraman, H.; Schwappacher, R.; Joshua, J.; Zhuang, S.; et al. Nongenomic thyroid hormone signaling occurs through a plasma membrane–localized receptor. Science Signaling 7(326), 2014. https://doi.org/10.1126/scisignal.2004911

41. Zhao, R.L.; Sun, B.; Liu, Y.; Li, J.H; et al. Cloning and identification of a novel thyroid hormone receptor β isoform expressed in the pituitary gland. Molecular and Cellular Biochemistry 389:141-150, 2014. https://doi.org/10.1007/s11010-013-1935-9

42. Swanson, E.A.; Gloss, B.; Belke, D.D.; Kaneshige, M.; et al. Cardiac Expression and Function of Thyroid Hormone Receptor β and Its PV Mutant. Endocrinology 144(11):4820-4825, 2003. https://doi.org/10.1210/en.2003-0522

43. Williams, G.R. Cloning and Characterization of Two Novel Thyroid Hormone Receptor β Isoforms. Molecular and Cellular Biology 20(22):8329-8342, 2000. https://doi.org/10.1128/MCB.20.22.8329-8342.2000

44. Chatonnet, F.; Guyot, R.; Benoît, G.; Flamant, F. Genome-wide analysis of thyroid hormone receptors shared and specific functions in neural cells. 110(8):E766-E775, 2013. https://doi.org/10.1073/pnas.1210626110

45. Minahkina, S.; Bansal, S.; Zhang, A.; Brotherton, M.; et al. A direct comparison of thyroid hormone receptor protein levels in mice provides unexpected insights into thyroid hormone action. Thyroid 30(8):1193–1204, 2020. https://doi.org/10.1089/thy.2019.0763

46. Refetoff, S.; Bassett, J.H.D.; Beck-Peccoz, P.; Bernal, J.; et al. Classification and proposed nomenclature for inherited defects of thyroid hormone action, cell transport, and metabolism. Thyroid 24(3), 2014. https://doi.org/10.1089/thy.2013.3393.nomen

47. Refetoff, S.; DeWind, L.T.; DeGroot, L.J. Familial syndrome combining deaf-mutism, stippled epiphyses, goiter and abnormally high PBI: possible target organ refractoriness to thyroid hormone. *The Journal of Clinical Endocrinology & Metabolism* 27(2):279-294, 1967. https://doi.org/10.1210/jcem-27-2-279

48. Williams, G.R.; Bassett, J.H.D. Thyroid diseases and bone health. Journal of Endocrinological Investigation 41:99–109, 2018. https://doi.org/10.1007/s40618-017-0753-4

49. Ramos, L.S.; Kizys, M.M.L.; Kunii, I.S.; Spinola-Castro, A.M.; et al. Assessing the clinical and molecular diagnosis of inherited forms of impaired sensitivity to thyroid hormone from a single tertiary center. Endocrine 62:628-638, 2018. https://doi.org/10.1007/s12020-018-1673-6

50. Refetoff, S.; Weiss, R.E.; Usala, S.J. The syndromes of resistance to thyroid hormone. Endocrine Reviews 14(3):348-399, 1993. https://doi.org/10.1210/edrv-14-3-348

51. Moran, C.; McEniery, C.M.; Schoenmakers, N.; Mitchell, C.; et al. Dyslipidemia, insulin resistance, ectopic lipid accumulation, and vascular function in resistance to thyroid hormone β. The Journal of Clinical Endocrinology & Metabolism 106(5):e2005–e2014, 2021. https://doi.org/10.1210/clinem/dgab002

52. Dumitrescu, A.M.; Refetoff, S. The syndromes of reduced sensitivity to thyroid hormone. Biochimica et Biophysica Acta 1830:3987-4003, 2013. http://dx.doi.org/10.1016/j.bbagen.2012.08.005

53. Frank-Raue, K.; Lorenz, A.; Haag, C.; Höppner, W. Severe form of thyroid hormone resistance in a patient with homozygous/hemizygous mutation of T3 receptor gene. European Journal of Endocrinology 150 819–823, 2004. https://doi.org/10.1530/eje.0.1500819

54. Ferrara, A.M.; Onigata, K.; Ercan, O.; Woodhead, H.; Weiss, R.E.; Refetoff,S. Homozygous thyroid hormone receptor β-gene mutations in resistance to thyroid hormone: three new cases and review of the literature. The Journal of Clinical Endocrinology & Metabolism 97(4):1328–1336, 2012. https://doi.org/10.1210/jc.2011-2642

55. Feng, W.; Ribeiro, R.C.J.; Wagner, R.L.; Nguyen, H.; et al. Hormone-dependent coactivator binding to a hydrophobic cleft on nuclear receptors. Science 280:1747-1749, 1998. https://doi.org/10.1126/science.280.5370.1747

56. Suzuki, S.; Shigematsu, S.; Inaba, H.; Takei, M.; Takeda, T.; Komatsu, M. Pituitary resistance to thyroid hormones: pathophysiology and therapeutic options. Endocrine 40:366-371, 2011. https://doi.org/10.1007/s12020-011-9538-2

57. Wu, S.Y.; Cohen, R.N.; Simsek, E.; Senses, D.A.; Yar, N.E., Grasberger, H.; Noel, J.; Refetoff, S.; Weiss, R.E. A Novel Thyroid Hormone Receptor- Mutation That Fails to Bind Nuclear Receptor Corepressor in a Patient as an Apparent Cause of Severe, Predominantly Pituitary Resistance to Thyroid Hormone. *The Journal of Clinical Endocrinology & Metabolism* 91(5):1887–1895, 2006. https://doi.org/10.1210/jc.2005-2428

58. Flynn, T.R.; Hollenberg, A.N.; Cohen, O.; Menke, J.B.; Usala, S.J.; Tollin, S.; Hegarty, M.K.; Wondisford, F.E. A Novel C-terminal Domain in the Thyroid Hormone Receptor Selectively Mediates Thyroid Hormone Inhibition. The Journal of Biological Chemistry 269(52):32713-32716, 1994. https://doi.org/10.1016/S0021-9258(20)30048-X

59. Brucker-Davis, F.; Skarulis, M.C.; Grace, M.B., Benichou, J.; Hauser, P.; Wiggs, E.; Weintraub, B.D. Genetic and Clinical Features of 42 Kindreds with resistance to thyroid hormone: the National Institutes of Health prospective study. Annals of Internal Medicine 123(8), 1995. https://doi.org/10.7326/0003-4819-123-8-199510150-00002

60. Beck-Peccoz, P.; Chatterjee, V.K.K. The variable clinical phenotype in thyroid hormone resistance syndrome. Thyroid 4(2):225-232, 1994. https://doi.org/10.1089/thy.1994.4.225

61. Weiss, R.E.; Dumitrescu, A.; Refetoff, S. Approach to the patient with resistance to thyroid hormone and pregnancy. The Journal of Clinical Endocrinology and Metabolism 95(7):3094-3102, 2010. https://doi.org/10.1210/jc.2010-0409

62. Persani, L.; Asteria, C.; Tonacchera, M.; Vitti, P.; et al. Evidence for the secretion of thyrotropin with enhanced bioactivity in syndromes of thyroid hormone resistance. The Journal of Clinical Endocrinology & Metabolism 78(5):1034–1039, 1994. https://doi.org/10.1210/jcem.78.5.8175956

63. Pappa, T.; Refetoff, S. Resistance to thyroid hormone beta: a focused review. Frontiers in Endocrinology 12:656551, 2021. https://doi.org/10.3389/fendo.2021.656551

64. Brucker-Davis, F.; Skarulis, M.C.; Pikus, A.; Ishizawar, D.; Mastroiani, M.A.; Koby, M.; Weintraub, B.D. Prevalence and mechanisms of hearing loss in patients with resistance to thyroid hormone. The Journal of Clinical Endocrinology & Metabolism 81(8):2768-2772, 1996. https://doi.org/10.1210/jcem.81.8.8768826

65. Beebe, S.P. The relation of pathologic conditions in the nose and throat to the origin and treatment of hyperthyroidism. JAMA 63(9):769-773, 1914. https://doi.org/10.1001/jama.1914.02570090055016

66. Montesinos, M.D.M.; Pellizas, C.G. Thyroid hormone action on innate immunity. Frontiers in Endocrinology 10:350, 2019. DOI: 10.3389/fendo.2019.00350. Erratum in: Front Endocrinol (Lausanne) 10:486, 2019. https://doi.org/10.3389/fendo.2019.00486

67. Barish, G.D.; Downes, M.; Alaynick, W.A.; Yu, R.T.; et al. A nuclear receptor atlas: macrophage activation. Molecular Endocrinology 19(10):2466-2477, 2005. https://doi.org/10.1210/me.2004-0529

68. Skounti, M.; Philalithis, A.; Galanakis, E. Variations in prevalence of attention deficit hyperactivity disorder worldwide. European Journal of Pediatrics 166:117,123, 2007. https://doi.org/10.1007/s00431-006-0299-5

69. Song, P.; Zha, M.; Yang, Q.; Zhang, Y.; et al. The prevalence of adult attention-deficit hyperactivity disorder: A global systematic review and meta-analysis. Journal of Global Health 11:04009, 2021. https://doi.org/10.7189/jogh.11.04009

70. Hauser, P.; Zametkin, A.J.; Martinez, P.; Vitiello, B.; et al. Attention deficit-hyperactivity disorder in people with generalized resistance to thyroid hormone. New England Journal of Medicine 328(14):997-1001, 1993. https://doi.org/10.1056/NEJM199304083281403

71. Weiss, R.E.; Stein, M.A.; Refetoff, S. Behavioral effects of liothyronine (L-T3) in children with attention deficit hyperactivity disorder in the presence and absence of resistance to thyroid hormone. Thyroid (3):389-393, 1997. https://doi.org/10.1089/thy.1997.7.389

72. Anzai, R.; Adachi, M.; Sho, N.; Muroya, K.; Asakura, Y.; Onigata, K. Long-term 3,5,3'-triiodothyroacetic acid therapy in a child with hyperthyroidism caused by thyroid hormone resistance: pharmacological study and therapeutic recommendations. Thyroid 22(10):1069-1075, 2012. https://doi.org/10.1089/thy.2011.0450

73. Bongers-Schokking, J.J.; Keizer-Schrama, S.M.P.F.M. Influence of timing and dose of thyroid hormone replacement on mental, psychomotor, and behavioral development in children with congenital hypothyroidism. The Journal of Pediatrics 147(6)768-774, 2005. https://doi.org/10.1016/j.jpeds.2005.09.031

74. Villanger, G.D.; Ystrom, E.; Engel, S.M.; Longnecker, M.P.; et al. Neonatal thyroid-stimulating hormone and association with attention-deficit/hyperactivity disorder. Pediatric and Perinatal Epidemiology 34(5):590-596, 2020. https://doi.org/10.1111/ppe.12643

75. Siesser, W.B.; Zhao, J.; Miller, L.R.; Cheng, S.Y.; McDonald, M.P. Transgenic mice expressing a human mutant beta1 thyroid receptor are hyperactive, impulsive, and inattentive. Genes, Brain & Behaviour 5(3):282-297, 2006. https://doi.org/10.1111/j.1601-183X.2005.00161.x
76. Modesto, T.; Tiemeier, H.; Peeters, R.P.; et al. Maternal mild thyroid hormone insufficiency in early pregnancy and attention-deficit/hyperactivity disorder symptoms in children. JAMA Pediatrics 169(9):838–845, 2015. https://doi.org/10.1001/jamapediatrics.2015.0498
77. Korevaar, T.I.M.; Muetzel, R.; Medici, M.; Chaker, L.; et al. Association of maternal thyroid function during early pregnancy with offspring IQ and brain morphology in childhood: a population-based prospective cohort study. The Lancet Diabetes & Endocrinology 4(1)35:43, 2016. https://doi.org/10.1016/S2213-8587(15)00327-7
78. Levie, D.; Korevaar, T.I.M.; Bath, S.C.; Dalmau-Bueno, A.; et al. Thyroid function in early pregnancy, child IQ, and autistic traits: a meta-analysis of individual participant data. The Journal of Clinical Endocrinology & Metabolism 103 (8):2967–2979, 2018. https://doi.org/10.1210/jc.2018-00224
79. Weiss, R.E.; Stein, M.A.; Duck, S.C.; Chyna, B.; et al. Low intelligence but not attention deficit hyperactivity disorder is associated with resistance to thyroid hormone caused by mutation R316H in the thyroid hormone receptor beta gene. The Journal of Clinical Endocrinology & Metabolism 78(6):1525–1528, 1994. https://doi.org/10.1210/jcem.78.6.8200958
80. Anselmo, J.; Cao, D.; Karrison, T.; Weiss, R.E.; Refetoff, S. Fetal loss associated with excess thyroid hormone exposure. JAMA 292(6):691-695, 2004. https://doi.org/doi:10.1001/jama.292.6.691
81. Blair, J.C.; Mohan, U.; Larcher, V.F.; Rajanayagam, O.; et al. Neonatal thyrotoxicosis and maternal infertility in thyroid hormone resistance due to a mutation in the TRβ gene (M313T). Clinical Endocrinology 57(3):405-409, 2002. https://doi.org/10.1046/j.1365-2265.2002.01588.x
82. Heffernan, E.; Wallace, H.; Graham, U. Thyroid hormone resistance from misdiagnosis to successful pregnancy. Endocrine Abstracts 85:93, 2022. https://doi.org/10.1530/endoabs.85.P93

83. Pritchad, G.; Morris, S.; Wayte, A.; Chatterjee, V.K.K.; Halsall, D.; Wilton, A. Generalised resistance to thyroid hormone secondary to a novel heterozygous missense mutation with coincidental toxic nodular goitre. Endocrine Abstracts 19:351, 2009.
84. Allan, W.; Herndon, C.N.; Dudley, F. C. Some examples of the inheritance of mental deficiency: apparently sex-linked idiocy and microcephaly. American Journal of Mental Deficiency, 48(48), 325-34, 1944.
85. Stevenson, R.E.; Goodman, H.O.; Schwartz, C.E.; Simensen, R.J.; McLean Jr., W.T.; Herndon, C.N. Allan-Herndon syndrome. I. Clinical studies. American Journal of Human Genetics 47(3):446-453, 1990. PMID: 2393019
86. Dumitrescu, A.M.; Liao, X.H.; Best, T.B.; Brockmann, K.; Refetoff, S. A Novel syndrome combining thyroid and neurological abnormalities is aAssociated with mutations in a monocarboxylate transporter gene. American Journal of Human Genetics 74(1):168-175, 2004. https://doi.org/10.1086/380999
87. Friesema, E.C.H.; Grueters, A.; Biebermann, H.; Krude, H.; et al. Association between mutations in a thyroid hormone transporter and severe X-linked psychomotor retardation. The Lancet 364(9443):1435-1437, 2004. https://doi.org/10.1016/S0140-6736(04)17226-7
88. Lenzner, S.; Rosenkranz, M.D.; Grueters, A.; et al. Severe X-linked mental retardation caused by mutations in the gene for the thyroid hormone transporter MCT8 (abstract C32). European Human Genetics Conference, 2004.
89. Schwartz, C.E.; May, M.M.; Carpenter, N.J.; Rogers, R.C.; et al. Allan-Herndon-Dudley syndrome and the monocarboxylate transporter 8 (MCT8) gene. American Journal of Human Genetics 77(1):41-53, 2005. https://doi.org/10.1086/431313
90. Sundaram, S.M.; Pereira, A.A.; Müller-Fielitz, H.; Köpke, H.; et al. Gene therapy targeting the blood–brain barrier improves neurological symptoms in a model of genetic MCT8 deficiency. Brain 145(12):4264–4274, 2022. https://doi.org/10.1093/brain/awac243
91. Stromme, P.; Groeneweg, S.; Souza, E.C.L.; Zevenbergen, C. Mutated thyroid hormone transporter OATP1C1 associates with severe brain hypometabolism and juvenile neurodegeneration. Thyroid 28(11), 2018. https://doi.org/10.1089/thy.2018.0595

92. Dumitrescu, A.M.; Refetoff, S. Inherited defects of thyroid hormone metabolism. Annales d´Endocrinologie 72(2):95-98, 2011. https://doi.org/10.1016/j.ando.2011.03.011
93. Dumitrescu, A.M.; Liao, X.H.; Abdullah, M.S.Y.; Lado-Abeal, J. Mutations in SECISBP2 result in abnormal thyroid hormone metabolism. Nature Genetics 37:1247-1252, 2005. https://doi.org/10.1038/ng1654
94. Lee, K.W.; Shin, Y.; Lee, S.; Lee, S. Inherited disorders of thyroid hormone metabolism defect caused by the dysregulation of selenoprotein expression. Frontiers in Endocrinology 12:803024, 2021. https://doi.org/10.3389/fendo.2021.803024
95. Bochukova, E.; Schoenmakers, N.; Agostini, M.; Schoenmakers, E.; et al. A mutation in the thyroid hormone receptor alpha gene. New England Journal of Medicine 366:243-249, 2012. https://doi.org/10.1056/NEJMoa1110296
96. Furman, A.E.; Dumitrescu, A.M.; Refetoff, S.; Weiss, R.E. Early Diagnosis and Treatment of an Infant with a Novel Thyroid Hormone Receptor α Gene (pC380SfsX9) Mutation. Thyroid 31(6):1003-1005, 2020. https://doi.org/10.1089/thy.2020.0695
97. Zavacki, A.M.; Larsen, P.R. RTHα, a Newly Recognized Phenotype of the Resistance to Thyroid Hormone (RTH) Syndrome in Patients With THRA Gene Mutations. The Journal of Clinical Endocrinology & Metabolism 98(7): 2684–2686, 2013. https://doi.org/10.1210/jc.2013-2475
98. Barca-Mayo, O.; Liao, X.H.; Alonso, M.; Di Cosmo, C.; Hernandez, A.; Refetoff, S.; Weis, R.E. Thyroid hormone receptor α and regulation of type 3 deiodinase. Molecular Endocrinology 25(4):575-583, 2011. https://doi.org/10.1210/me.2010-0213
99. Paisdzior, S.; Knierim, E.; Kleinau, G.; Biebermann, H.; Krude, H.; Straussberg, R.; Schuelke, M. A new mechanism in THRA tesistance: The first disease-associated variant leading to an increased inhibitory function of THRA2. International Journal of Molecular Sciences 22:5338, 2021. https://doi.org/10.3390/ijms22105338

100. Persani, L.; Campi, I. Thyroid hormone resistance. In: Igaz, P. (org.) Practical clinical endocrinology. Springer, Cham., 2021. https://doi.org/10.1007/978-3-030-62011-0_20

101. Weiss, R.E.; Hayashi, Y.; Nagaya, T.; Petty, K.J.; et al. Dominant inheritance of resistance to thyroid hormone not linked to defects in the thyroid hormone receptor alpha or beta genes may be due to a defective cofactor. The Journal of Clinical Endocrinology & Metabolism 81(12):4196-4203, 1996. https://doi.org/10.1210/jcem.81.12.8954015

102. Hamon, B.; Hamon, P.; Bovier-Lapierre, M.; Pugeat, M.; et al. A child with resistance to thyroid hormone without thyroid hormone receptor gene mutation: A 20-year follow-up. Thyroid 18(1), 2008. https://doi.org/10.1089/thy.2007.0079

103. Weiss, R.E. “They have ears but do not hear” (Psalms 135:17): Non-thyroid hormone receptor β (non-TRβ) resistance to thyroid hormone. Thyroid 18(1), 2008. https://doi.org/10.1089/thy.2007.0373

104. Donnars, A.; Leplat, A.; Grosheny, C.; Briet, C.; et al. Clinically symptomatic resistance to thyroid hormone β syndrome because of *THRB* Gene mosaicism. The Journal of Clinical Endocrinology & Metabolism 107(9):e3548–e3552, 2022. https://doi.org/10.1210/clinem/dgac347

105. Schneider, M.J.; Fiering, S.N.; Pallud, S.E.; Parlow, A.F.; St. Germain, D.L.; Galton, V.A. Targeted disruption of the type 2 selenodeiodinase gene (DIO2) results in aphenotype ofpituitary resistance to T4. Molecular Endocrinology 15 (12):2137–2148, 2001. https://doi.org/10.1210/mend.15.12.0740

106. Reutrakul, S.; Sadow, P.M.; Pannain, S.; Pohlenz, J.; et al. Search for abnormalities of nuclear corepressors, coactivators, and a coregulator in families with resistance to thyroid hormone without mutations in thyroid hormone receptor β or α genes. The Journal of Clinical Endocrinology & Metabolism 85(10):3609–3617, 2000. https://doi.org/10.1210/jcem.85.10.6873

107. Rakheja, D.; Read, C.P.; Hull, D.; Boriack, R.L.; Timmons, C.F. A severely affected female infant with X-linked dominant chondrodysplasia punctata: A case

report and a brief review of the literature. Pediatric and Developmental Pathology 10(2), 2007. https://doi.org/10.2350/06-06-0111.1