Publication

A low-frequency inactivating akt2 variant enriched in the finnish population is associated with fasting insulin levels and type 2 diabetes risk

JournalArticle (Originalarbeit in einer wissenschaftlichen Zeitschrift)

ID 3870852

Author(s) Manning, Alisa; Highland, Heather M.; Gasser, Jessica; Sim, Xueling; Tukiainen, Taru; Fontanillas, Pierre; Grarup, Niels; Rivas, Manuel A.; Mahajan, Anubha; Locke, Adam E.; Cingolani, Pablo; Pers, Tune H.; Viñuela, Ana; Brown, Andrew A.; Wu, Ying; Flannick, Jason; Fuchsberger, Christian; Gamazon, Eric R.; Gaulton, Kyle J.; Im, Hae Kyung; Teslovich, Tanya M.; Blackwell, Thomas W.; Bork-Jensen, Jette; Burtt, Noël P.; Chen, Yuhui; Green, Todd; Hartl, Christopher; Kang, Hyun Min; Kumar, Ashish; Ladenvall, Claes; Ma, Clement; Moutsianas, Loukas; Pearson, Richard D.; Perry, John R. B.; Rayner, N. William; Robertson, Neil R.; Scott, Laura J.; van de Bunt, Martijn; Eriksson, Johan G.; Jula, Antti; Koskinen, Seppo; Lehtimäki, Terho; Palotie, Aarno; Raitakari, Olli T.; Jacobs, Suzanne B. R.; Wessel, Jennifer; Chu, Audrey Y.; Scott, Robert A.; Goodarzi, Mark O.; Blancher, Christine; Buck, Gemma; Buck, David; Chines, Peter S.; Gabriel, Stacey; Gjesing, Anette P.; Groves, Christopher J.; Hollensted, Mette; Huyghe, Jeroen R.; Jackson, Anne U.; Jun, Goo; Justesen, Johanne Marie; Mangino, Massimo; Murphy, Jacquelyn; Neville, Matt; Onofrio, Robert; Small, Kerrin S.; Stringham, Heather M.; Trakalo, Joseph; Banks, Eric; Carey, Jason; Carneiro, Mauricio O.; DePristo, Mark; Farjoun, Yossi; Fennell, Timothy; Goldstein, Jacqueline I.; Grant, George; Hrabé de Angelis, Martin; Maguire, Jared; Neale, Benjamin M.; Poplin, Ryan; Purcell, Shaun; Schwarzmayr, Thomas; Shakir, Khalid; Smith, Joshua D.; Strom, Tim M.; Wieland, Thomas; Lindstrom, Jaana; Brandslund, Ivan; Christensen, Cramer; Surdulescu, Gabriela L.; Lakka, Timo A.; Doney, Alex S. F.; Nilsson, Peter; Wareham, Nicholas J.; Langenberg, Claudia; Varga, Tibor V.; Franks, Paul W.; Rolandsson, Olov; Rosengren, Anders H.; Farook, Vidya S.; Thameem, Farook; Puppala, Sobha; Kumar, Satish; Lehman, Donna M.; Jenkinson, Christopher P.; Curran, Joanne E.; Hale, Daniel Esten; Fowler, Sharon P.; Arya, Rector; DeFronzo, Ralph A.; Abboud, Hanna E.; Syvänen, Ann-Christine; Hicks, Pamela J.; Palmer, Nicholette D.; Ng, Maggie C. Y.; Bowden, Donald W.; Freedman, Barry I.; Esko, Tõnu; Mägi, Reedik; Milani, Lili; Mihailov, Evelin; Metspalu, Andres; Narisu, Narisu; Kinnunen, Leena; Bonnycastle, Lori L.; Swift, Amy; Pasko, Dorota; Wood, Andrew R.; Fadista, João; Pollin, Toni I.; Barzilai, Nir; Atzmon, Gil; Glaser, Benjamin; Thorand, Barbara; Strauch, Konstantin; Peters, Annette; Roden, Michael; Müller-Nurasyid, Martina; Liang, Liming; Kriebel, Jennifer; Illig, Thomas; Grallert, Harald; Gieger, Christian; Meisinger, Christa; Lannfelt, Lars; Musani, Solomon K.; Griswold, Michael; Taylor, Herman A.; Wilson, Gregory; Correa, Adolfo; Oksa, Heikki; Scott, William R.; Afzal, Uzma; Tan, Sian-Tsung; Loh, Marie; Chambers, John C.; Sehmi, Jobanpreet; Kooner, Jaspal Singh; Lehne, Benjamin; Cho, Yoon Shin; Lee, Jong-Young; Han, Bok-Ghee; Käräjämäki, Annemari; Qi, Qibin; Qi, Lu; Huang, Jinyan; Hu, Frank B.; Melander, Olle; Orho-Melander, Marju; Below, Jennifer E.; Aguilar, David; Wong, Tien Yin; Liu, Jianjun; Khor, Chiea-Chuen; Chia, Kee Seng; Lim, Wei Yen; Cheng, Ching-Yu; Chan, Edmund; Tai, E. Shyong; Aung, Tin; Linneberg, Allan; Isomaa, Bo; Meitinger, Thomas; Tuomi, Tiinamaija; Hakaste, Liisa; Kravic, Jasmina; Jørgensen, Marit E.; Lauritzen, Torsten; Deloukas, Panos; Stirrups, Kathleen E.; Owen, Katharine R.; Farmer, Andrew J.; Frayling, Timothy M.; O'Rahilly, Stephen P.; Walker, Mark; Levy, Jonathan C.; Hodgkiss, Dylan; Hattersley, Andrew T.; Kuulasmaa, Teemu; Stančáková, Alena; Barroso, Inês; Bharadwaj, Dwaipayan; Chan, Juliana; Chandak, Giriraj R.; Daly, Mark J.; Donnelly, Peter J.; Ebrahim, Shah B.; Elliott, Paul; Fingerlin, Tasha; Froguel, Philippe; Hu, Cheng; Jia, Weiping; Ma, Ronald C. W.; McVean, Gilean; Park, Taesung; Prabhakaran, Dorairaj; Sandhu, Manjinder; Scott, James; Sladek, Rob; Tandon, Nikhil; Teo, Yik Ying; Zeggini, Eleftheria; Watanabe, Richard M.; Koistinen, Heikki A.; Kesaniemi, Y. Antero; Uusitupa, Matti; Spector, Timo-

thy D.; Salomaa, Veikko; Rauramaa, Rainer; Palmer, Colin N. A.; Prokopenko, Inga; Morris, Andrew D.; Bergman, Richard N.; Collins, Francis S.; Lind, Lars; Ingelsson, Erik; Tuomilehto, Jaakko; Karpe, Fredrik; Groop, Leif; Jørgensen, Torben; Hansen, Torben; Pedersen, Oluf; Kuusisto, Johanna; Abecasis, Gonçalo; Bell, Graeme I.; Blangero, John; Cox, Nancy J.; Duggirala, Ravindranath; Seielstad, Mark; Wilson, James G.; Dupuis, Josee; Ripatti, Samuli; Hanis, Craig L.; Florez, Jose C.; Mohlke, Karen L.; Meigs, James B.; Laakso, Markku; Morris, Andrew P.; Boehnke, Michael; Altshuler, David; McCarthy, Mark I.; Gloyn, Anna L.; Lindgren, Cecilia M.
Author(s) at UniBasel Kumar, Ashish ;
Year 2017
Title A low-frequency inactivating akt2 variant enriched in the finnish population is associated with fasting insulin levels and type 2 diabetes risk
Journal Diabetes
Volume 66
Number 7
Pages / **Article-Number** 2019-2032
To identify novel coding association signals and facilitate characterization of mechanisms influencing glycemic traits and type 2 diabetes risk, we analyzed 109,215 variants derived from exome array genotyping together with an additional 390,225 variants from exome sequence in up to 39,339 normoglycemic individuals from five ancestry groups. We identified a novel association between the coding variant (p.Pro50Thr) in AKT2 and fasting plasma insulin (FI), a gene in which rare fully penetrant mutations are causal for monogenic glycemic disorders. The low-frequency allele is associated with a 12% increase in FI levels. This variant is present at 1.1% frequency in Finns but virtually absent in individuals from other ancestries. Carriers of the FI-increasing allele had increased 2-h insulin values, decreased insulin sensitivity, and increased risk of type 2 diabetes (odds ratio 1.05). In cellular studies, the AKT2-Thr50 protein exhibited a partial loss of function. We extend the allelic spectrum for coding variants in AKT2 associated with disorders of glucose homeostasis and demonstrate bidirectional effects of variants within the pleckstrin homology domain of AKT2.
Publisher American Diabetes Association
ISSN/ISBN 0012-1797
edoc-URL http://edoc.unibas.ch/55642/
Full Text on edoc No;
Digital Object Identifier DOI 10.2337/db16-1329
PubMed ID http://www.ncbi.nlm.nih.gov/pubmed/28341696