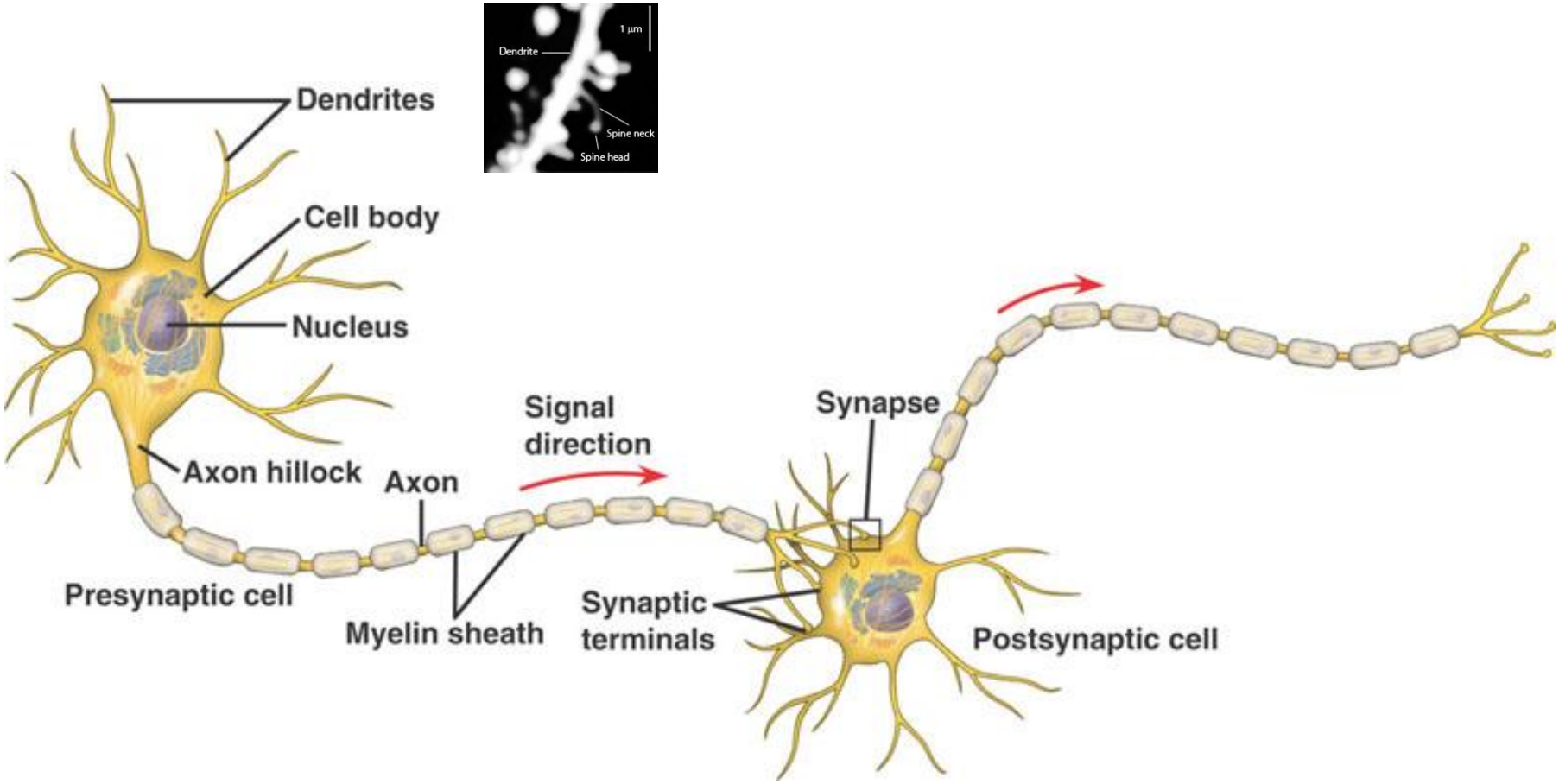
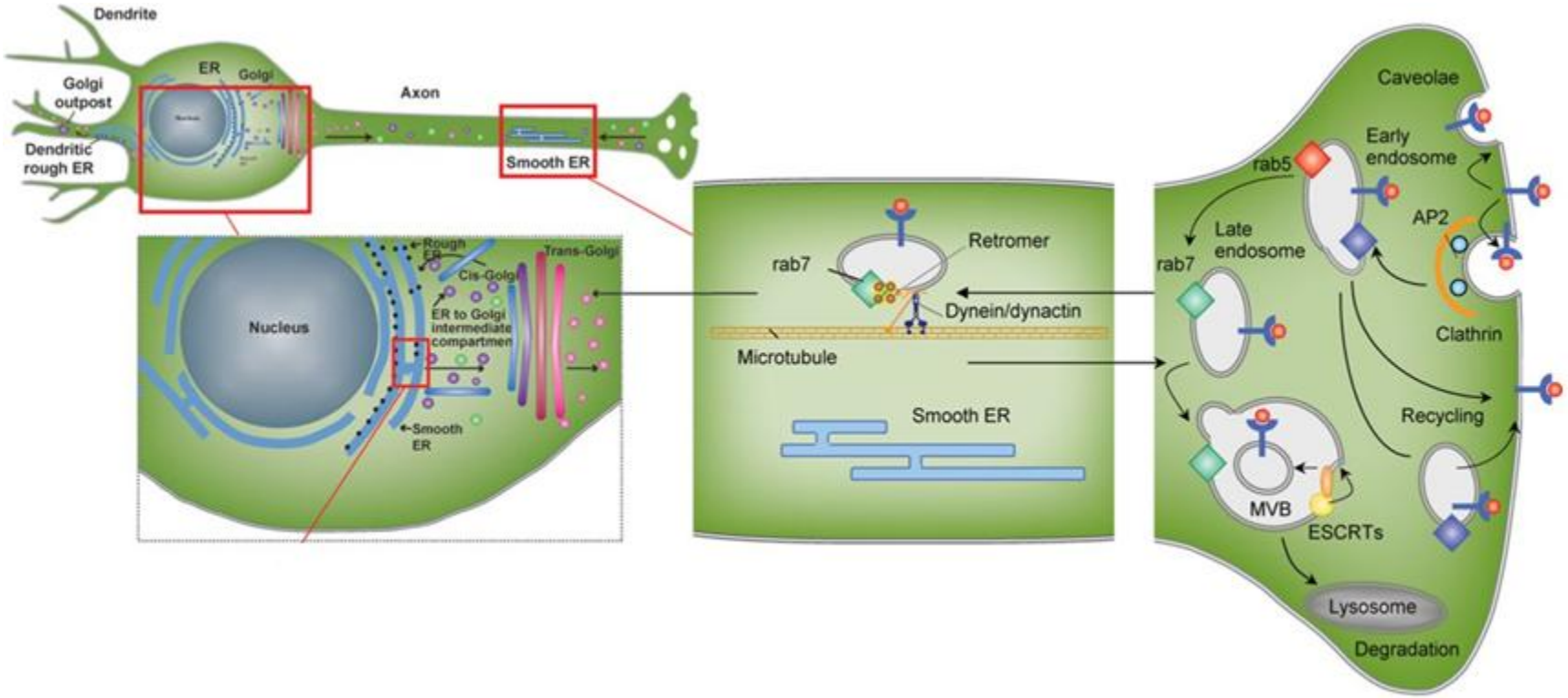
Nörogelişimsel Süreçte Endozomal Trafik

Sodyum/Hidrojen Değiştiricilerinin Önemi



Karmaşık, özelleşmiş, polarize, üst seviyede asimetri


Dendrite
Golgi outpost
Dendritic rough ER
ER
Golgi
Axon
Smooth ER
Nucleus
Rough ER
Cis-Golgi
Trans-Golgi
ER to Golgi intermediate compartmen
Smooth ER
rab7
Retromer
Dynein/dynactin
Microtubule
Smooth ER
Caveolae
Early endosome
rab5
AP2
Late endosome
rab7
Clathrin
Recycling
MVB
ESCRTs
Lysosome
Degradation

Endositozun işlevsel önemi

- Sinaptik membran dengesinin sağlanması
- Membran proteinlerinin hücre yüzeyinden uzaklaştırılması
- Nöronlarda hücre yüzeyindeki protein seviyesinin hızlı ve lokalize olarak düzenlenmesi

Rol oynayan Proteinler

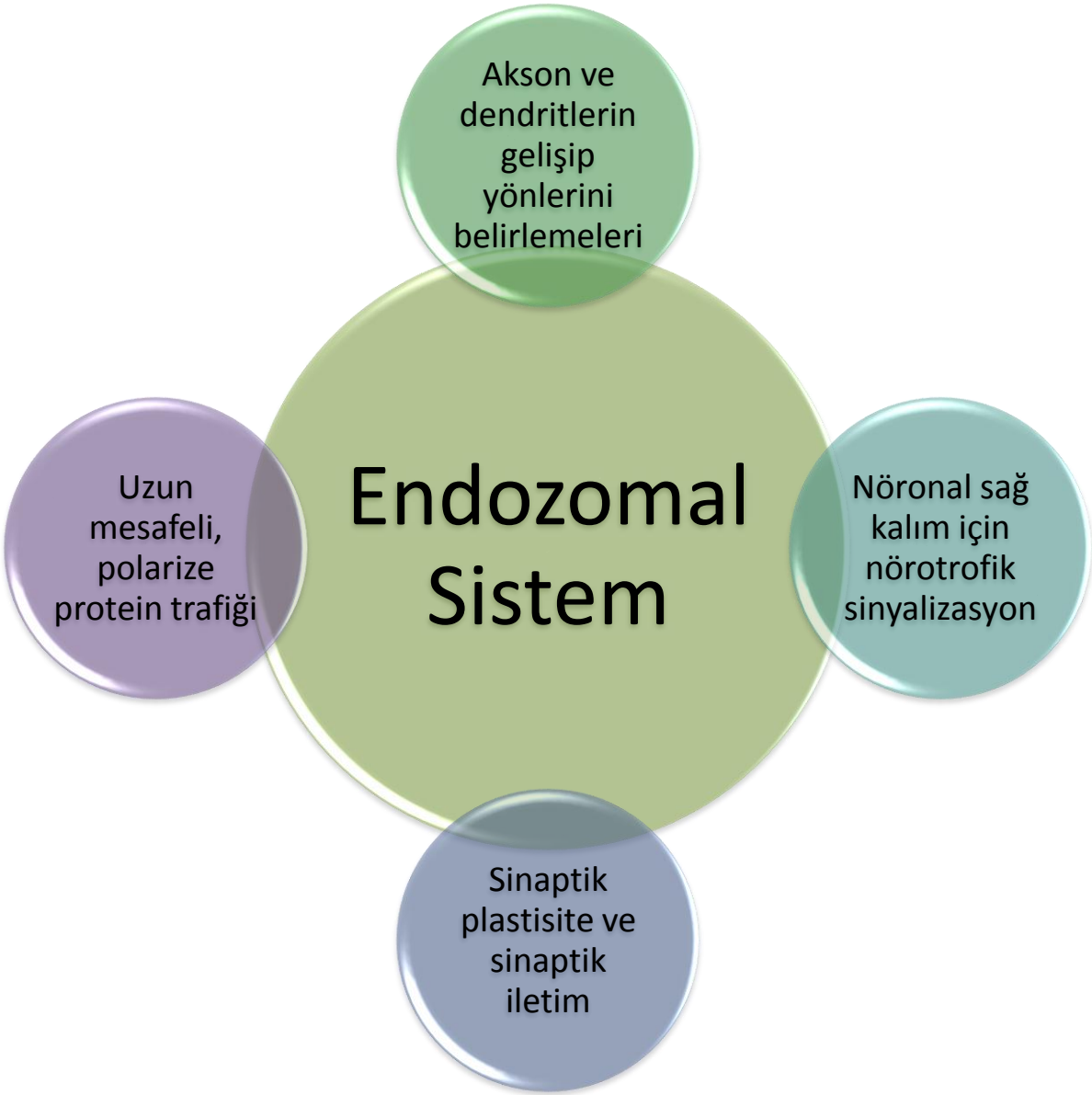
- Küçük GTPaz$_{lar}$ (Rab$_{lar}$)
- EEA1, APPL
- AP-1, -2, -3, -4
- SNARE proteinleri
- …

Sinapslarda ve Aksonal Büyüme Konilerinde Lokal Endozomal Sistemler

Hücre membranı reseptörleri ve adezyon moleküllerinin

- Sayı
- Erişilebilirlik

- Nöronlar büyük ve yapısal-fonksiyonel olarak özelleşmiş hücreler
- Uzak mesafelerde ve lokal olarak etki gösteren, büyüme faktörleri, nörotrofik faktörler ve elektriksel aktivite gibi hücre dışı uyaranlara duyarlı olan özelleşmiş endozomal sistemlere ihtiyaç duymaktadır


Akson ve dendritlerin gelişip yönlerini belirlemeleri
Endozomal Sistem
Uzun mesafeli, polarize protein trafiği
Nöronal sağ kalım için nörotrofik sinyalizasyon
Sinaptik plastisite ve sinaptik iletim

“Housekeeping” fonksiyon

- Çok sayıda reseptör sisteminin integrasyonu, nöral gelişme sırasında hücre davranışına yön verme açısından son derece kritik öneme sahip
- Hangi reseptör?
- Nerede?
- Ne zaman?
- Ne kadar?
- Sinyal iletimi üzerinde ne süre ile etkili?

Endositoz

- Membran reseptörlerinin zamansal ve mekansal dağılımlarını belirleme
- Başlangıç hücre kaderinin belirlenmesi
- Nöronal kutuplaşma
- Nöronal göç
- Sinaptogenez
- …

Endozomal Trafik ve Sinaps gelişimi

Drosophila larval Neuromuscular Junction

- GDE ve Liz'e yönlendirme mutant
- Sinyal iletimine devam
- Artmış sinaptik büyüme

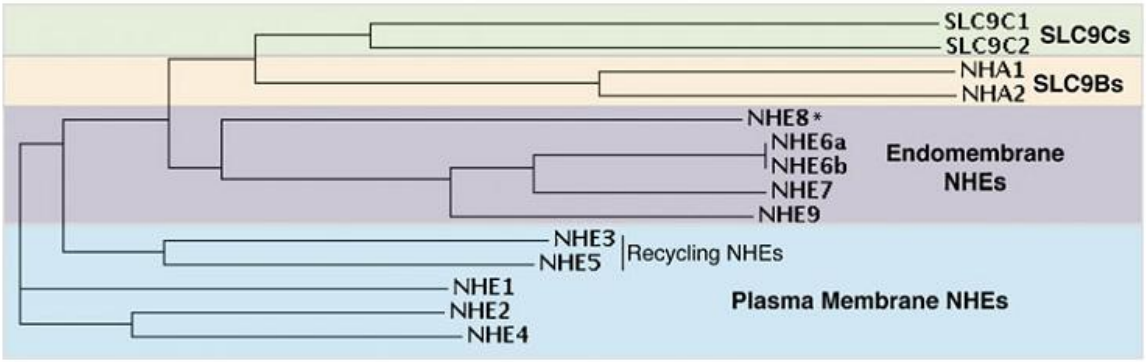
Neuron 2008 May 22;58(4):507-18

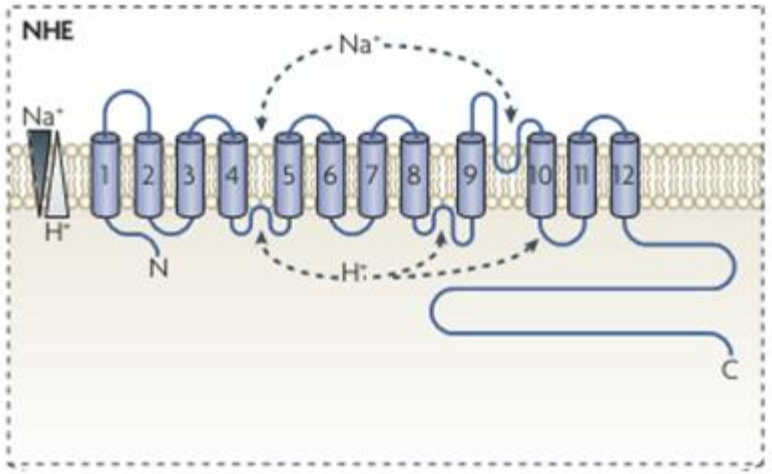
Endozomal Trafik ve Sinaps gelişimi

- Sinyal ileten endozom mutant
- Azalmış sinaptik büyüme

J Neurosci 2008; 28:8316-8325

Na+/H+ Değiştokuşçuları

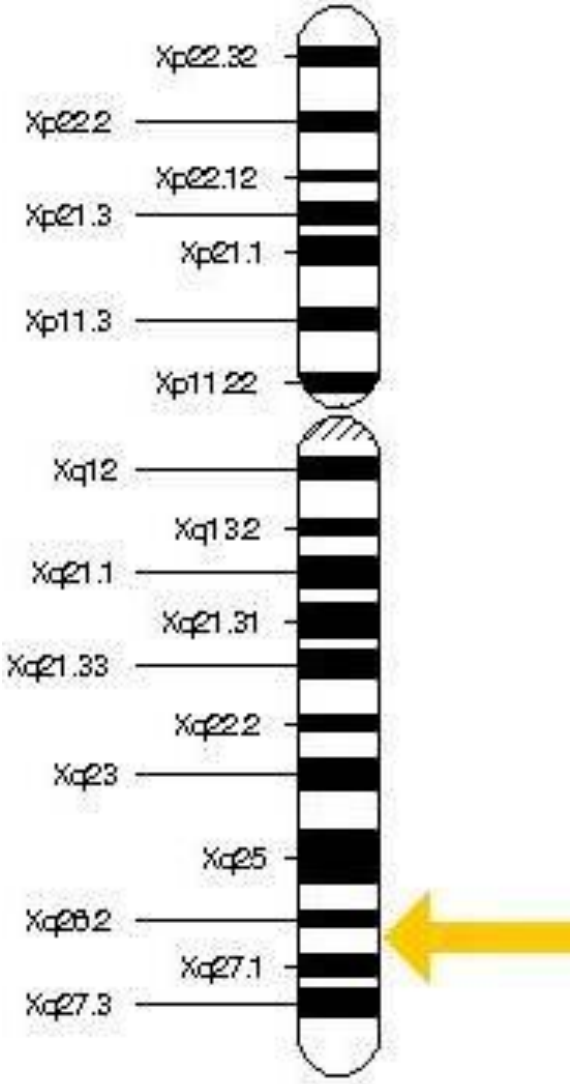




Protein *Gene* Name	Tissue distribution and subcellular expression	Human disease associations	KO mouse phenotype(s)
NHE1 *SLC9A1*	Ubiquitous (plasma membrane; basolateral surface of epithelia)	Cancer, ischemia-reperfusion damage, arterial hypertension (?)	Ataxia, growth retardation, seizures, slow-wave epilepsy, increased neuronal excitability, resistant to cardiac ischemia-reperfusion injury and pre-mature death.
NHE2 *SLC9A2*	Stomach, intestinal tract, skeletal muscle, kidney, brain, uterus, testis heart, lung; (plasma membrane; apical surface of epithelia)	?	Reduced viability of gastric parietal cells, hypochlorhydria. Increased renal renin content, impaired recovery of intestinal barrier function.
NHE3 *SLC9A3*	Intestinal tract, stomach, kidney, gall bladder, epididymis, brain; (apical surface and recycling endosomes of epithelia)	Congenital Na^+ diarrhea; Sudden infant death syndrome (?)	Mild-diarrhea, acidosis, impaired acid-base balance and Na-fluid volume homeostasis in kidney and intestine. Renal role confirmed in volume homeostasis confirmed by GI knock-in and renal specific KO. Hypercalciuria, reduced bone mineral density, reduced intestinal calcium absorption. Spontaneous distal colitis due to alteration of gut microbiome.
NHE4 *SLC9A4*	Stomach, kidney, brain; (plasma membrane; baso-lateral membrane of epithelia)	?	Stomach inflammation, hypochlorhydria, gastric necrosis. Defective in NH_4 absorption from renal thick ascending limb.
NHE5 *SLC9A5*	Brain (neurons); (plasma membrane and recycling endosomes/synaptic vesicles)	?	?
NHE6 *SLC9A6*	Ubiquitous (recycling endosomes)	X-linked mental retardation (Angel-man/Christianson syndrome).	Hyper-reactivity, increased susceptibility to pharmacologically induced seizures.
NHE7 *SLC9A7*	Ubiquitous (*trans*-Golgi network and endosomes)	Cancer (?)	?
NHE8 *SLC9A8*	Ubiquitous (mid- to trans-Golgi network) and apical plasma membrane in proximal tubule	?	Reduced mucus secretion, increased susceptibility to mucosal injury, increased bacterial adhesion in colon. NHE3/NHE8 double KO mice have lower blood pressure and lower proximal tubular NHE activity compared to NHE3 KO.
NHE9 *SLC9A9*	Ubiquitous (late recycling endosomes)	Familial autism; attention deficit hyperactivity disorder	?
NHA1 *SLC9B1*	Testis-specific	?	?
NHA2 *SLC9B2*	Ubiquitous (plasma membrane, endosomes)	Essential hypertension, diabetes mellitus (?)	Impaired insulin secretion by β-cells, impaired glucose tolerance
Sperm-NHE *SLC9C1*	Spermatozoa (sperm flagellum)	?	Male infertility, asthenozoospermia
NHE11 (?) *SLC9C2*	?	?	?

A Human, *B* v = variant, *?* means the data is not currently available, *(?)* means the data is not certain

NHE6 (*SLC9A6*)



- Xq26.3
- Nokta mutasyonları
- Delesyonlar
- “Truncation” mutasyonları

- Çoğunlukla otistik bulgular eşlik ediyor

J Med Genet 1999;**36**:759–766

X linked severe mental retardation, craniofacial dysmorphology, epilepsy, ophthalmoplegia, and cerebellar atrophy in a large South African kindred is localised to Xq24-q27

Arnold L Christianson, Roger E Stevenson, C H van der Meyden, Julie Pelser, Francois W Theron, Petro L van Rensburg, Michael Chandler, Charles E Schwartz

- Belirgin ID (100%)
- İşitme kaybı olmamasına rağmen konuşmama (100%)
- Epilepsi (87.5%)

SLC9A6 Mutations Cause X-Linked Mental Retardation, Microcephaly, Epilepsy, and Ataxia, a Phenotype Mimicking Angelman Syndrome

Gregor D. Gilfillan,[1,2,15] Kaja K. Selmer,[1,2,15] Ingrid Roxrud,[3] Raffaella Smith,[4] Mårten Kyllerman,[5] Kristin Eiklid,[1] Mette Kroken,[1] Morten Mattingsdal,[1] Thore Egeland,[1] Harald Stenmark,[3] Hans Sjøholm,[6] Andres Server,[7] Lena Samuelsson,[8] Arnold Christianson,[9] Patrick Tarpey,[4] Annabel Whibley,[10] Michael R. Stratton,[4] P. Andrew Futreal,[4] Jon Teague,[4] Sarah Edkins,[4] Jozef Gecz,[11] Gillian Turner,[12] F. Lucy Raymond,[10] Charles Schwartz,[13] Roger E. Stevenson,[13] Dag E. Undlien,[1,2] and Petter Strømme[2,14,*]

- Bağlantı analizi
- Xq24-q27.3
- Kodlayıcı ekzonlar ve ekzon-intron sınır bölgelerinin dizi analizi
- NHE6 geninde 6 bp delesyon
- p.E155_S256 del
- p.R468X
- p.H171fs
- p.V144_R169del

A systematic, large-scale resequencing screen of X-chromosome coding exons in mental retardation

Patrick S Tarpey[1], Raffaella Smith[1], Erin Pleasance[1], Annabel Whibley[2], Sarah Edkins[1], Claire Hardy[1], Sarah O'Meara[1], Calli Latimer[1], Ed Dicks[1], Andrew Menzies[1], Phil Stephens[1], Matt Blow[1], Chris Greenman[1], Yali Xue[1], Chris Tyler-Smith[1], Deborah Thompson[3], Kristian Gray[1], Jenny Andrews[1], Syd Barthorpe[1], Gemma Buck[1], Jennifer Cole[1], Rebecca Dunmore[1], David Jones[1], Mark Maddison[1], Tatiana Mironenko[1], Rachel Turner[1], Kelly Turrell[1], Jennifer Varian[1], Sofie West[1], Sara Widaa[1], Paul Wray[1], Jon Teague[1], Adam Butler[1], Andrew Jenkinson[1], Mingming Jia[1], David Richardson[1], Rebecca Shepherd[1], Richard Wooster[1], M Isabel Tejada[4], Francisco Martinez[5], Gemma Carvill[6], Rene Goliath[6], Arjan P M de Brouwer[7], Hans van Bokhoven[7], Hilde Van Esch[8], Jamel Chelly[9], Martine Raynaud[10], Hans-Hilger Ropers[11], Fatima E Abidi[12], Anand K Srivastava[12], James Cox[2], Ying Luo[2], Uma Mallya[2], Jenny Moon[2], Josef Parnau[2], Shehla Mohammed[13], John L Tolmie[14], Cheryl Shoubridge[15], Mark Corbett[15], Alison Gardner[15], Eric Haan[15], Sinitdhorn Rujirabanjerd[15], Marie Shaw[15], Lucianne Vandeleur[15], Tod Fullston[15], Douglas F Easton[3], Jackie Boyle[16], Michael Partington[16], Anna Hackett[16], Michael Field[16], Cindy Skinner[12], Roger E Stevenson[12], Martin Bobrow[2], Gillian Turner[16], Charles E Schwartz[12], Jozef Gecz[15,17], F Lucy Raymond[2], P Andrew Futreal[1] & Michael R Stratton[1,18]

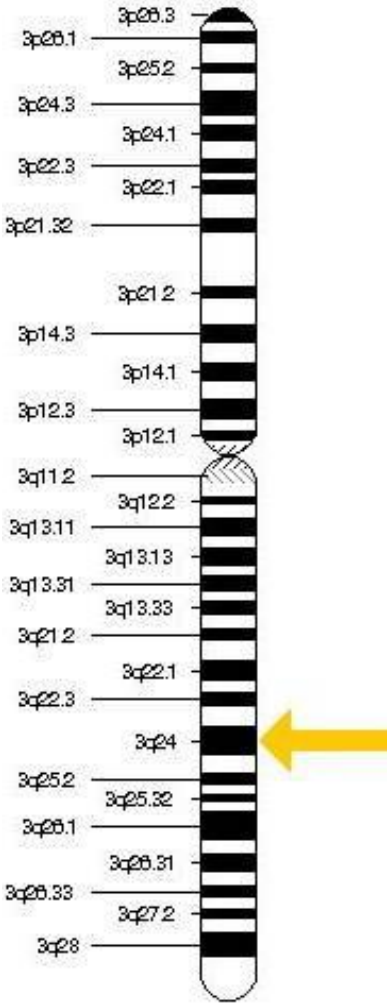
NATURE GENETICS VOLUME 41 | NUMBER 5 | MAY 2009

>200 pedigri

X kromozomunun kodlayıcı ekzonlarının dizi analizi

- ID, Otistik davranışlar, Ataksi
- ^{370}Trp-Ser-Thr^{372}
- Sentezde sorun yok
- Azalmış oligosakkarid maturasyonu ve yarı ömür
- Dendritik arborizasyon kaybı

NHE9 (*SLC9A9*)



- 3q24
- GWAS
- Nokta mutasyonları ve “Truncation” mutasyonları
- Otizm ve ADHD

Disruption of a novel member of a sodium/hydrogen exchanger family and *DOCK3* is associated with an attention deficit hyperactivity disorder-like phenotype

M G de Silva, K Elliott, H-H Dahl, E Fitzpatrick, S Wilcox, M Delatycki, R Williamson, D Efron, M Lynch, S Forrest

J Med Genet 2003;**40**:733–740

- ADHD + ID
- inv(3)(p14:q21)
- 10/21
- DOCK3 ve SLC9A9

American Journal of Medical Genetics Part B (Neuropsychiatric Genetics) 147B:1355–1358 (2008)

Rapid Publication

Genome-Wide Association Scan of the Time to Onset of Attention Deficit Hyperactivity Disorder

Jessica Lasky-Su,[1] Richard J.L. Anney,[2] Benjamin M. Neale,[3,4,5,6] Barbara Franke,[7,8] Kaixin Zhou,[1] Julian B. Maller,[9] Alejandro Arias Vasquez,[7,8] Wai Chen,[3] Philip Asherson,[3] Jan Buitelaar,[7] Tobias Banaschewski,[10] Richard Ebstein,[11] Michael Gill,[2] Ana Miranda,[12] Fernando Mulas,[13] Robert D. Oades,[14] Herbert Roeyers,[15] Aribert Rothenberger,[16] Joseph Sergeant,[17] Edmund Sonuga-Barke,[3,18,19,20] Hans Christoph Steinhausen,[21] Eric Taylor,[3] Mark Daly,[5,6] Nan Laird,[22] Christoph Lange,[1,22] and Stephen V. Faraone[4,23]*

- 930 paret-offspring trio
- SLC9A9 → 6 SNP

OPEN

Molecular Psychiatry (2013), 1–3

www.nature.com/mp

LETTER TO THE EDITOR

Genes for endosomal NHE6 and NHE9 are misregulated in autism brains

M Schwede[1], K Garbett[2], K Mirnics[2,3], DH Geschwind[4,5,6] and EM Morrow[1,7]

[1]*Department of Molecular Biology, Cell Biology and Biochemistry, Institute for Brain Science, Brown University, Laboratory for Molecular Medicine, Providence, RI, USA;*
[2]*Department of Psychiatry, Vanderbilt University, Nashville, TN, USA;*
[3]*Vanderbilt Kennedy Center for Research on Human Development, Vanderbilt University, Nashville, TN, USA;*
[4]*UCLA Center for Autism Research and Treatment, Semel Institute for Neuroscience and Behavior, Los Angeles, CA, USA;*
[5]*Program in Neurogenetics, Department of Neurology, David Geffen School of Medicine at UCLA, Los Angeles, CA, USA;*
[6]*Department of Human Genetics, David Geffen School of Medicine at UCLA, Los Angeles, CA, USA and*