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The Compassionate Side of Neuroscience: Tony Sermone's Undiagnosed Genetic Journey—ADNP Mutation

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From the Editor Desk: the Compassionate Side of ADNP

Some science: searching for brain protective proteins and aiming to unravel genes shaping our brains, at the turn of the century, we have published our first paper describing the cloning and characterization of a novel complementary DNA encoding a protein, which we called activity-dependent neuroprotective protein (ADNP) (Bassan et al. 1999). We went on to clone the human ADNP (hADNP) from a fetal brain cDNA library. Comparative sequence analysis of mouse and man indicated 90 % identity with the mouse (Zamostiano et al. 2001). Our recent analysis revealed high conservation and appearance only in vertebrates, indicating an important function in higher organisms, with a complex brain structure (Gozes et al. 2015). We further showed that the hADNP gene structure spans ~40 kilobases and includes five exons and four introns with alternative splicing of an untranslated second exon (chromosome 20q12-13.2, a region associated with aggressive tumor growth). As we eluded to in 2001 (Zamostiano et al. 2001), and later described in detail, hADNP is also mutated in cancer (Gozes et al. 2015).

In an attempt to identify novel genes responsible for autism, a first de novo p.Lys408Valfs*31 mutation in the ADNP gene was identified in a large cohort of autistic patients (O'Roak et al. 2012b). Sequencing of the 209 families in this cohort did not reveal a second mutation in ADNP nor hardly in any other candidate gene; thus, a large-scale resequencing study was initiated (O'Roak et al. 2012a). In this study of 2446 probands, an additional p.Tyr719* de novo ADNP mutation was identified. By combining the data from WES and targeted resequencing studies initiated in multiple centers, Helsmoortel et al. (2014) identified a total of 10 patients with mutations in ADNP, including the two patients identified in both earlier studies. As all patients suffered from autism and shared characteristic facial features, it could be concluded that mutations in ADNP cause a syndromic form of autism. Remarkably, ADNP is one of a relatively small group of genes that appear to lead to autism in a substantial proportion of cases. Immediately following our initial report, two additional patients were identified that share many of the reported characteristics (Pescosolido et al. 2014; Vandeweyer et al. 2014). On top of that, Coe et al. (2014) reported five patients with a truncating ADNP mutation in a screening of 4716 patients with autism/ID. Most recently, De Rubeis et al. (2014) identified three more patients of a total of 3871 screened, and the DDD project reported four novel cases out of 1133 screened (Deciphering Developmental Disorders 2015).

Taking advantage of mouse genetics, we have shown that ADNP is crucial for brain formation (Pinhasov et al. 2003) and learning and memory (Vulih-Shultzman et al. 2007), in a sex-dependent manner (Malishkevich et al. 2015; Kleiman et al. 2015). Using biochemical and cell biology techniques,

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we showed multiple crucial interactions for ADNP, including the chromatin remodeling complex SWI/SNF (Mandel and Gozes 2007; Mandel et al. 2007), the RNA splicing machinery (Schirer et al. 2014), protein translation (Malishkevich et al. 2015), as well as the microtubule (Oz et al. 2014) and autophagy systems (Merenlender-Wagner et al. 2015). However, no good science can exist without listening and watching the society needs and hearing out the parents and wonderful caretakers of the ADNP children, which follows herein (Sandra Bedrosian Sermone, Our Undiagnosed Genetic Journey—ADNP mutation, 2015).

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Tony Sermone ADNP Story

Our Undiagnosed Genetic Journey—ADNP Mutation

We had a 1.5-year-old daughter when we found out that we were going to have another baby. A few months later, we found out that we were actually having twins. Somewhere around month 7, I started having concerns because one of the baby's heart rate would never go up during the routine stress test and that he was much less active than the other baby. This occurred many times, and I began to have a feeling that something was not right. My OB dismissed my concerns and said it was just the way they were "sitting" and assured me I was having a very healthy pregnancy and was right on track. After the boys were born by C-section, we were told that we had "2 healthy baby boys" (Tony and Rocco). But as soon as I was brought into the room with them and was able to see them, I had a horrible gut feeling something was not right with Tony. I did not know what it was, I was happy they were born but had a strange feeling that he looked different. Within hours, we were told that during his exam, they heard a heart murmur that they had not detected while I was pregnant. They put him into the NICU and that is when the "parent-panic" set in. They explained the heart defect and told us it was not an emergency because many kids have murmurs when they are born, and they referred us to Doernbecher Children's Hospital in 2 weeks. But I still had a horrible feeling something else was wrong. The more I would look at Tony, the more I felt like something was off. He just looked different, different than his twin brother, and different than his sister when she was born. I could not put my finger on it, but something looked off, and something looked strange to me. I did not think it was Down syndrome or anything specific at all, because I did not know what I thought. I had never had a friend or family member who had a child with a syndrome or any dramatic birth defect, so I was not even thinking "genetic;" it is not that he looked like a down baby, he did not. He looked normal to others, but to me, I just had a gut feeling "something" was off with my son. I questioned everyone, my OB, the pediatrician, and the NICU attending. They all dismissed my concerns and said he was just fine. Even my own twin sister who was my labor and delivery nurse told me there was nothing wrong and that I was just stressed out and "postpartum". Now in hindsight, my "Mommy Intuition" was spot on!

Two weeks went by, and we took Tony in to see the cardiologist. Once the echo report was read, we knew something was wrong. We were told that he not only had one hole but also had several holes and that one was very large but blocked a little at the moment. We were also told that his heart was arching the wrong way, a right aortic arch with a vascular ring. That is the first time we heard the words "genetic" and "syndrome". A full exam was performed, and he was hospitalized for testing where we were told about some of Tony's other "congenital abnormities" that are associated with genetic conditions. To us, it seemed like they started picking apart things like undescended testicles, small chest, large head, heart defects, etc. We were sent straight to the lab, and our doctor told us they suspected that Tony had something called Di George syndrome. Weeks went by of complete panic and worry. Let me tell you, nothing is as frightening as having a child with an "unknown medical/genetic condition." What does this mean? Will he be normal? Can they fix this? Will he die? Is his twin brother OK? Was this because of me? It was agonizing waiting to get the results of that first genetic test. But the call came, and it would be the first of many in this journey of an *undiagnosed child*. We heard the word—negative! Over the next 5 years, we would hear those words often. Chromosome 22 deletion—negative! Prader-Willi syndrome—negative! Opitz syndrome, Noonan syndrome, Sotos syndrome, and Angelman syndrome—all negative! Comparative genomic hybridization—negative; microarray chromosome genetic hybridization CGH, test after test after test.

During those years, we received what I refer to as a "laundry list" of diagnosis, sending us on an emotional rollercoaster. We were scared, shocked, and sad, and it felt almost like we were beginning to mourn the life we thought our child would have. Those are feelings that never go away. Another one of the byproducts of a child with a medical condition that is "unknown". Tony began being referred out to more specialists than I even knew existed. He began to have difficulty eating and

started aspirating fluids so he had to have a feeding tube surgically placed. As he grew older, we noticed he was having a hard time looking at us; he would stair off at the ceiling or lights all day, and he would not look or try to play with toys. He had very weak muscles and walked very late; he was not able to grasp on to objects and hold on to them. He began to blank out, and it was thought that he was having absent seizures, but EEGs would come back clear. We watched him develop further and further behind his twin, and we knew something was very wrong, but no one could give us any answers.

He was referred for every test under the sun, and he was sedated and hospitalized for most of them. It seemed like with each doctor appointment, they would discover our child had "another" condition. One after another, they came. Multiple heart defects, several brain abnormalities, pervasive development disorder, delayed milestones, severe cognitive delays, non-verbal, PDD, autism spectrum, cerebral palsy spectrum, mixed receptive-expressive language disorder, phonological disorder, motor skills disorder, hypotonia, gastroesophageal reflux disease, hyperactive gag reflux, frenulum linguae, oropharyngeal dysphagia with frank silent aspiration, dysphagia, feeding difficulties, undescended testicles, bilateral cryptorchidism, congenital hernia, cortical vision impairment (CVI), disorder of visual cortex, delayed visual maturation, irregular astigmatism, hyperopia, unspecified disorder of refraction and accommodation, strabismus, central nervous system disorder, hydrocephalus, and the list goes on and on. It was almost comical; every time he had a doctor appointment, we got a new diagnosis. "REALLY?" became my most common word used! ("really?" was in a sarcastic tone; I was not asking a question. I could not ask questions because the doctors had zero answers; just more diagnosis = "really?")

We quickly discovered what most parents with a "medically complicated undiagnosed genetic syndrome child" learn; just how much doctors and specialists do not know. They just kept "adding" to his list, but they could never tell us what was causing all of these things to our sweet baby.

During those first 5 years, our son had many surgeries. Two of his five were open heart surgeries, one at 2-months old and another at 3 ½years old. He suffered from strokes during his second surgery because he was on a bypass machine for so long. We were also taking him to the Children's Hospital 3–5 times a week to see specialists. He was being sedated and having procedures weekly. I lost count as to how many times I had to hold my tiny baby boy while they sedated him and felt his body go completely limp in my arms. I always panicked a little that he just died because that is what it feels like. Like the life just got sucked out of him. It is an awful feeling! The awesome sedation nurses who I got to know very well would hook him up to the monitors before going in just so I could see his heart beating on the screen and not panic. I had to hand him over to a nurse and watch him being taken away through those plain white double doors time and time again. I hate those double doors! And as the years went by, I lost count of how many ER visits we had and hospital stays. Sometimes we would be admitted into the hospital each week of the month. Our life became a constant flood of doctors, hospitals, evaluations, physical therapy, occupational therapy, feeding therapy, sensory integration therapy, vision therapy, and ABA therapy. We even tried out a neuroplasticity program and installed a full sensory gym in our home.

Then the "AH-HA" moment came. One that would change this "Undiagnosed" journey!

I finally realized something. If a child does not have something "inside" the "cookie cutter diagnosis box" that the doctors in our area seemed to stay inside, then those doctors were perfectly content to label these children, my child, as an "Undiagnosed Genetic Syndrome" child, and they had no desire to look "outside" of their box and search for answers. They would blame one diagnosis on another, like "vision impairment" as being "cognitive" or "Autism" as being "developmental delays." They were so confused that they chose to not diagnose him correctly, which led him to miss valuable and unreplaceable time doing therapy that he should have started years before. For us, being stuck in this "Kaiser" world of denials, denials, and denials, we became very frustrated. We became even more frustrated when we found out testing was available but not approved for our son because he had so much genetic testing already. So new cutting-edge genome sequencing testing was available for others, but not my son? The roll of the dice game was driving us just as crazy as the day to day drama of what had become our life.

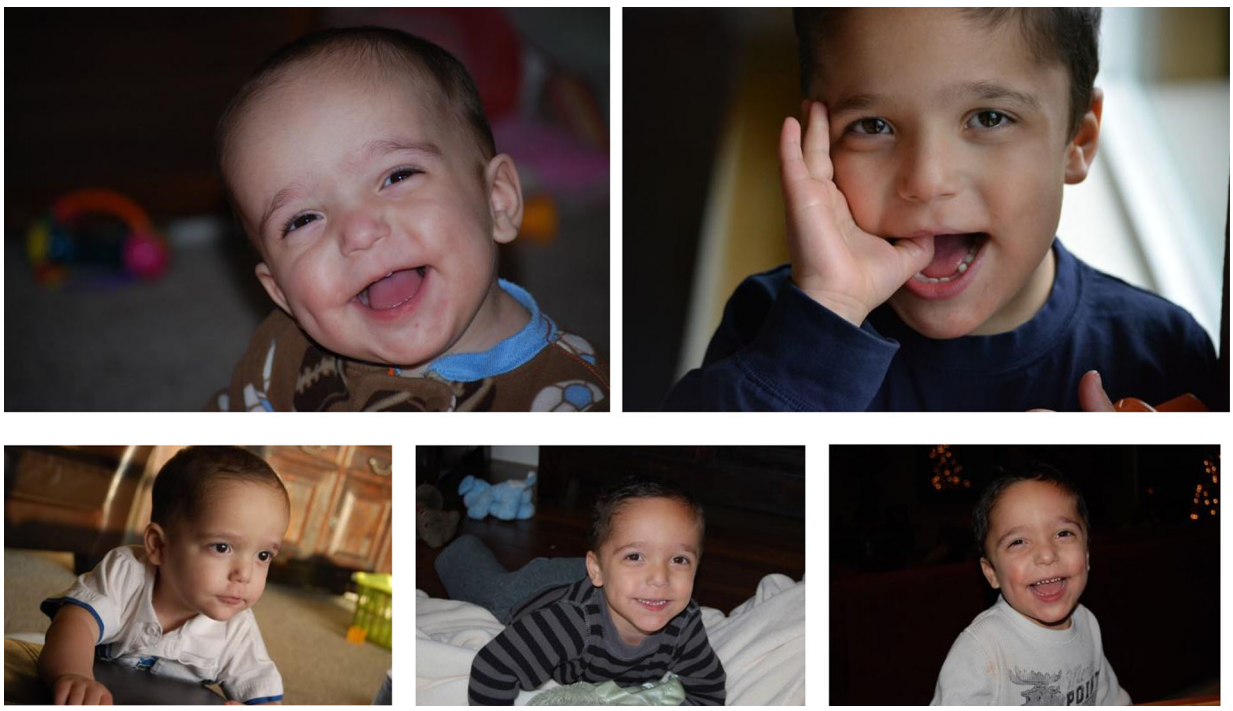
When Tony started experiencing significant developmental and cognitive regression, I decided this was *not good enough* for him, and I started looking outside for research studies and clinical trials. I became a very specialized medical researcher/detective and spent night after night stocking the internet and searching for help. After putting him in several neurological studies, I was referred to Duke University. They had a genetic research study for medically complicated children who were undiagnosed, and after several interviews, they accepted Tony into their study. They agreed to do full exome sequencing for Tony. Finally, someone was willing to find out what wrong with my undiagnosed child! After signing a mountain of paperwork and consent forms, we did the blood draws, and the waiting began. We were told this is a painstakingly long process that would take years and years, so I was quite surprised when only months later I got the call. "We found something." So off on a plane, I went and met with the team at Duke. "ADNP MUTATION" is what they told me they found. It was a "di novo" mutation which meant that it was a spontaneous mutation found only in Tony. It was not carried by me or my husband, and it was not in his twin brother or his sister. They explained to me that this is a newly discovered mutation seen in only ten other children in the world that causes an autism syndrome, developmental and cognitive delays, speech

and feeding difficulties, heart abnormities, and the list goes on. This is what a "syndrome" is, a list of symptoms caused by a hiccup in a gene.

Since discovering this ADNP syndrome, I went on a mission to find other families, and I set up a parent Facebook page to connect with others. After I talked to just a couple of moms, it was like a weight was lifted. It had been so isolating not having anyone to talk to who understood what we were going through. I began to meet other mothers, and it has been life changing! "Now we are not alone!" Our journeys have all been different in ways but identical in others. It did not take me much time to start to realize that there were much more similar features in our children, so I started to create a spreadsheet and started comparing symptoms and diagnosis. I realized these children were strikingly similar in so many other ways that was described so far. I have learned new information on our children that I never knew and also discovered the struggles that may lie ahead. I also have realized that there is so much more to learn about this ADNP syndrome.

But now, a new journey begins. Surprisingly, an even bigger struggle because our children are diagnosed with something that the "normal" medical world has no idea of. There are so many issues because this is a new and relatively unknown syndrome. The original name of the syndrome directs it as a mental retardation disease and has very limited details. There has been a family already denied neurology visits because "it isn't listed as a syndrome feature" even though the entire ADNP mutation is a brain disease/syndrome. I am frightened to tell my own insurance/doctors of this diagnosis since they denied the testing and will have no clue how to process something outside of "their system." It is insane that we have had to fight for years to find out "what" was wrong with our children; now, we have to fight because what they have is so "unknown."

My son is now 7 years old and currently functions cognitively as a 16-month-old. What I would give to hear him speak to me, to tell me he loves me, and to be able to communicate with me if he is hurt or needs something. He has an extremely difficult life in and out of hospitals; he has been in daily therapy practically his entire life; his doctors have failed him; his school has failed him, but still, he carries on and is the hardest working little guy around. He has this "laundry list" of disabilities, but he always has had a smile on his face. He is truly my hero! When he was a baby, we called him "Boo Boo" because he had a hole in his heart. Since then, he has earned the name "Superman" because he is the strongest, toughest, sweetest little man on the planet, and he is helping other children every day by being a part of this new genetic testing and syndrome research with the team and doctors who discovered it. He is a proof that mercury, led, MMR, and who knows what else did not cause his autism! He is proof that *autism is a real and genetic condition*. Because of this, we will continue to try as hard as we can to help him and all of the other children suffering from this rare genetic disease.



Tony's Laundry List

Cardiology Issues

Congenital heart disease
VSD type 2 perimembranous, paramenbranous, conoventricular (repaired in Sept 2011)
Postcardiac injury syndrome—pericarditis complications lasting 4 months
Right aortic arch
Vascular compression of esophagus by aberrant artery
Vascular ring (repaired in April 2008)
ASD (repaired in Sept 2011)

Neurology Issues

Delayed myelination pattern with poor arborization
Prominent left cerebral extra-axial space
Frontal extra-axial space
Extra-axial fluid noted for almost all brain scans
Mild widening of sagittal suture accompanied with fontanelle bulging
White matter delay and generous normal vents
Macrocephalus, relative (head circumference)
Central nervous system disorder (Casey)
Hydrocephalus
Monitored in 2008/2009 by neurosurgery for excessive fluid in the brain
Cerebral palsy noted by Dr. Morrison 4/25/08 and also cerebral palsy spectrum at CDRC neuro
Small strokes noted during last open heart surgery, degree of effect unknown
Cerebral atrophy noted 2014
Regression of skills—unknown cause
Sensory processing disorder

Developmental Issues

Pervasive development disorder otherwise unspecified—severe
Delayed milestones
Intellectual deficits—severe
Mixed receptive-expressive language disorder
Phonological disorder
Speech disorder—(non-verbal) presumed "Absent"
Developmental apraxia
Motor skills disorder
Hypotonia

Gastrology Issues

GERD gastroesophageal reflux disease
Hyperactive gag reflux
Frenulum linguae
Oropharyngeal dysphagia with frank silent aspiration
Barium swallow studies
Feeding difficulties
G-tube (Mickey) (surgically in Oct. 2008 and removed in July 2009)
Additional surgery for G-tube (surgery in Feb. 2009)
Incision and drainage of superficial abdominal wall abscess

Urology Issues

Undescended testicles (surgically repaired (both) in April 2009)
Bilateral cryptorchidism
Congenital hernia (left hernia surgically repaired in April 2009)
Penoplasty (surgery in April 2009)
Unspecified constipation

Vision Issues

Cortical vision impairment (CVI)
Unspecified visual delay
Disorder of visual cortex associated with cortical blindness
Delayed visual maturation
Irregular astigmatism
Hyperopia (farsightedness)
Unspecified disorder of refraction and accommodation
Strabismus (off and on)

Genetics Testing

Doernbecher CH, Seattle CH, Kaiser, and Duke University Syndrome, presumed undiagnosed
FISH chromosome 22 deletion—tested—negative
FISH Prader-Willi—tested—negative
Opitz syndrome—tested—negative (also scoped for a laryngeal cleft—none)
Noonan syndrome—tested—tier 1, 2, 3, 4, and 5—negative (2-year tier testing at 2 separate labs)
Sotos syndrome—reviewed—negative
Angelman syndrome—tested—negative
Comparative genomic hybridization—negative
Microarray chromosome genetic hybridization CGH—negative
****NEW (6/2014)****
ADNP mutation found by Duke University Results, heterozygous c.1016_1047delTG L349RfsX49

Diagnostic Testing (Most Done Sedated)

Brain MRIs (many)
Orbit MRIs
Chest MRIs (many)
Brain CTs (many)
Chest CTs (many)
Chest Xrays (many)
Electrocardiogram's (many)
EKGs (many)
Stomach ultrasounds
Electroretinogram
Barrium swallow study (many)
Electroencephalographys (EEG) both normal and sleep deprived (many)
Renal ultrasound (check for Noonan)
Laryngeal scope (Opitz)

Symptoms Noted for Genetic Testing

Heart defects (see above)
Brain abnormalities (see above)
Developmental delays (see above)
GI issues/GERD (see above)
Feeding issues (see above)
Multiple congenital anomalies
Hypotonia (low muscle tone) upper/lower as infant, upper body only as toddler
Unusual chest shape
"Dysmorphic" facial features including the following:

Eyes—wide spaced and down sloping	Ears—posteriorly rotated
Relative macrocephaly	Long flat philtrum
Thin upper lip	Narrow vermillion boarder to upper lip
Flat nasal bridge	Hypertoloric
Large head/prominent forehead	
Wide-spaced inner canthi with inner distance of 2.5 cm and outer 7.5 cm Chubby	

Small hands/small feet
Deep creases on hands and feet
Short stature
Small penis, scrotum underdeveloped
Failure to grow in length
Teeth (full set of teeth including molars by age 1)
AROM at time of delivery was clear fluid. Delivered via repeat C-Section. *Apgar scores were 8 at 1 and 9 a 5 min*. The infant was bulb suctioned on the perineum and cried spontaneously. *Twin brother cried much louder and was much more active*.

Sandra Bedrosian Sermone, co-organizer of the ADNP Association, USA

References

Bassan M, Zamostiano R, Davidson A, Pinhasov A, Giladi E, Perl O, Bassan H, Blat C, Gibney G, Glazner G, Brenneman DE, Gozes I (1999) Complete sequence of a novel protein containing a femtomolar-activity-dependent neuroprotective peptide. J Neurochem 72:1283–1293

Coe BP, Witherspoon K, Rosenfeld JA, van Bon BW, Vulto-van Silfhout AT, Bosco P, Friend KL, Baker C, Buono S, Vissers LE, Schuurs-Hoeijmakers JH, Hoischen A, Pfundt R, Krumm N, Carvill GL, Li D, Amaral D, Brown N, Lockhart PJ, Scheffer IE, Alberti A, Shaw M, Pettinato R, Tervo R, de Leeuw N, Reijnders MR, Torchia BS, Peeters H, Thompson E, O'Roak BJ, Fichera M, Hehir-Kwa JY, Shendure J, Mefford HC, Haan E, Gecz J, de Vries BB, Romano C, Eichler EE (2014) Refining analyses of copy number variation identifies specific genes associated with developmental delay. Nat Genet 46:1063–1071

De Rubeis S, He X, Goldberg AP, Poultney CS, Samocha K, Ercument Cicek A, Kou Y, Liu L, Fromer M, Walker S, Singh T, Klei L, Kosmicki J, Fu SC, Aleksic B, Biscaldi M, Bolton PF, Brownfeld JM, Cai J, Campbell NG, Carracedo A, Chahrour MH, Chiocchetti AG, Coon H, Crawford EL, Crooks L, Curran SR, Dawson G, Duketis E, Fernandez BA, Gallagher L, Geller E, Guter SJ, Sean Hill R, Ionita-Laza I, Jimenez Gonzalez P, Kilpinen H, Klauck SM, Kolevzon A, Lee I, Lei J, Lehtimaki T, Lin CF, Ma'ayan A, Marshall CR, McInnes AL, Neale B, Owen MJ, Ozaki N, Parellada M, Parr JR, Purcell S, Puura K, Rajagopalan D, Rehnstrom K, Reichenberg A, Sabo A, Sachse M, Sanders SJ, Schafer C, Schulte-Ruther M, Skuse D, Stevens C, Szatmari P, Tammimies K, Valladares O, Voran A, Wang LS, Weiss LA, Jeremy Willsey A, Yu TW, Yuen RK, Study DDD, Homozygosity Mapping Collaborative for A, Consortium UK, Autism Sequencing C, Cook EH, Freitag CM, Gill M, Hultman CM, Lehner T, Palotie A, Schellenberg GD, Sklar P, State MW, Sutcliffe JS, Walsh CA, Scherer SW, Zwick ME, Barrett JC, Cutler DJ, Roeder K, Devlin B, Daly MJ, Buxbaum JD (2014) Synaptic, transcriptional and chromatin genes disrupted in autism. Nature 515:209–215

Deciphering Developmental Disorders (2015) Large-scale discovery of novel genetic causes of developmental disorders. Nature 519:223–228

Gozes I, Yeheskel A, Pasmanik-Chor M (2015) Activity-dependent neuroprotective protein (ADNP): a case study for highly conserved chordata-specific genes shaping the brain and mutated in cancer. J Alzheimers Dis 45:57–73

Helsmoortel C, Vulto-van Silfhout AT, Coe BP, Vandeweyer G, Rooms L, van den Ende J, Schuurs-Hoeijmakers JH, Marcelis CL, Willemsen MH, Vissers LE, Yntema HG, Bakshi M, Wilson M, Witherspoon KT, Malmgren H, Nordgren A, Anneren G, Fichera M, Bosco P, Romano C, de Vries BB, Kleefstra T, Kooy RF, Eichler EE, Van der Aa N (2014) A SWI/SNF-related autism syndrome caused by de novo mutations in ADNP. Nat Genet 46:380–384

Kleiman GH, Barnea A, Gozes I (2015) ADNP: a major autism mutated gene is differentially distributed (age and gender) in the songbird brain. Peptides

Malishkevich A, Amram N, Hacohen-Kleiman G, Magen I, Giladi E, Gozes I (2015) Activity-dependent neuroprotective protein (ADNP) exhibits striking sexual dichotomy impacting on autistic and Alzheimer's pathologies. Transl Psychiatry 5, e501

Mandel S, Gozes I (2007) Activity-dependent neuroprotective protein constitutes a novel element in the SWI/SNF chromatin remodeling complex. J Biol Chem 282:34448–34456

Mandel S, Rechavi G, Gozes I (2007) Activity-dependent neuroprotective protein (ADNP) differentially interacts with chromatin to regulate genes essential for embryogenesis. Dev Biol 303:814–824

Merenlender-Wagner A, Malishkevich A, Shemer Z, Udawela M, Gibbons A, Scarr E, Dean B, Levine J, Agam G, Gozes I (2015) Autophagy has a key role in the pathophysiology of schizophrenia. Mol Psychiatry 20:126–132

O'Roak BJ, Vives L, Fu W, Egertson JD, Stanaway IB, Phelps IG, Carvill G, Kumar A, Lee C, Ankenman K, Munson J, Hiatt JB, Turner EH, Levy R, O'Day DR, Krumm N, Coe BP, Martin BK, Borenstein E, Nickerson DA, Mefford HC, Doherty D, Akey JM, Bernier R, Eichler EE, Shendure J (2012a) Multiplex targeted sequencing identifies recurrently mutated genes in autism spectrum disorders. Science 338:1619–1622

O'Roak BJ, Vives L, Girirajan S, Karakoc E, Krumm N, Coe BP, Levy R, Ko A, Lee C, Smith JD, Turner EH, Stanaway IB, Vernot B, Malig M, Baker C, Reilly B, Akey JM, Borenstein E, Rieder MJ, Nickerson DA, Bernier R, Shendure J, Eichler EE (2012b) Sporadic autism exomes reveal a highly interconnected protein network of de novo mutations. Nature 485:246–250

Oz S, Kapitansky O, Ivashco-Pachima Y, Malishkevich A, Giladi E, Skalka N, Rosin-Arbesfeld R, Mittelman L, Segev O, Hirsch JA, Gozes I (2014) The NAP motif of activity-dependent neuroprotective protein (ADNP) regulates dendritic spines through microtubule end binding proteins. Mol Psychiatry 19:1115–1124

Pescosolido MF, Schwede M, Johnson Harrison A, Schmidt M, Gamsiz ED, Chen WS, Donahue JP, Shur N, Jerskey BA, Phornphutkul C, Morrow EM (2014) Expansion of the clinical phenotype associated with mutations in activity-dependent neuroprotective protein. J Med Genet 51:587–589

Pinhasov A, Mandel S, Torchinsky A, Giladi E, Pittel Z, Goldsweig AM, Servoss SJ, Brenneman DE, Gozes I (2003) Activity-dependent neuroprotective protein: a novel gene essential for brain formation. Brain Res Dev Brain Res 144:83–90

Schirer Y, Malishkevich A, Ophir Y, Lewis J, Giladi E, Gozes I (2014) Novel marker for the onset of frontotemporal dementia: early increase in activity-dependent neuroprotective protein (ADNP) in the face of Tau mutation. PLoS One 9, e87383

Vandeweyer G, Helsmoortel C, Van Dijck A, Vulto-van Silfhout AT, Coe BP, Bernier R, Gerdts J, Rooms L, van den Ende J, Bakshi M, Wilson M, Nordgren A, Hendon LG, Abdulrahman OA, Romano C, de Vries BBA, Kleefstra T, Eichler EE, Van der Aa N, Kooy RF (2014) The transcriptional regulator ADNP links the BAF (SWI/SNF) complexes with autism. Am J Med Genet C: Semin Med Genet 166C:315–326

Vulih-Shultzman I, Pinhasov A, Mandel S, Grigoriadis N, Touloumi O, Pittel Z, Gozes I (2007) Activity-dependent neuroprotective protein snippet NAP reduces tau hyperphosphorylation and enhances learning in a novel transgenic mouse model. J Pharmacol Exp Ther 323:438–449

Zamostiano R, Pinhasov A, Gelber E, Steingart RA, Seroussi E, Giladi E, Bassan M, Wollman Y, Eyre HJ, Mulley JC, Brenneman DE, Gozes I (2001) Cloning and characterization of the human activity-dependent neuroprotective protein. J Biol Chem 276:708–714