Comments by Dr. Henry Krous

This is a very interesting and provocative study, but the cases of siddt they report are not sids:

first,they describe a syndrome of dysgenetic testes (hence it occurs only in males, unlike sids, wherein 40% are girls) associated with sudden death in infancy, therefore, by definition, it is not SIDS, since in SIDS the death remain unexplained after complete postmortem evaluation;

an association with sleep is not reported in siddt, and as you know, sids is thought by nearly all researchers to have its onset during a sleep period;

sids cases do not have dysgenetic testes, I have examined the testes of many sids victims and have not seen dysgenesis in any of them;

in siddt, they report a very high incidence of sudden death recurring in individual families, recurrent sids is exceedingly uncommon in sids;

sids is not associated with close knit communities wherein one could expect a high level of inbreeding among close relatives, as is the case with siddt.

Their study raises many important questions, to ask a few:

What is the mechanism of death in siddt?

It is highly unlikely that it is directly related to testicular dysgenesis, is it associated with sleep?

Are there cardiac arrhythmias, such as long qt syndrome, ie, are there ekg abnormalities?

What were the studies that were done in these victims before their deaths?
Did they include polysomnography? What were the results?

Are there neuropathologic findings that parallel those found in sids?

Researchers Identify Gene for a Primary Form of Sudden Infant Death Syndrome
(SIDS)
Why some infants die suddenly is no longer a mystery

PHOENIX, July 19, 2004 — Scientists at the Translational Genomics Research Institute (TGen), Phoenix, Arizona, and the Clinic for Special Children, Strasburg, Pennsylvania, have found the genetic basis for one form of sudden infant death syndrome (SIDS). The researchers have named the newly described form as sudden infant death with dysgenesis of testes, or SIDDT. The finding, released this week on-line by the journal Proceeding of the National Academy of Sciences could provide new insight into the inexplicable, sudden deaths of some 3,000 infants a year in the US.

SIDS has long been a catchall term for infants that die unexpectedly of unknown causes before their first birthday. By discovering a gene linked to some of these deaths, a team of researchers led by Dr. Dietrich Stephan, director of neurogenomics at TGen, and the paper's senior author, has begun to expose the distinct genetic causes behind these deaths.

"This is one of the first genetic sub-classifications of SIDS," Stephan said.

"And it's going to be helpful in offering parents answers for sudden infant deaths, recognizing predisposition early, and hopefully saving a number of these babies."

The researchers first identified patients with SIDDT in a small Old Order Amish community in central Pennsylvania. Over two generations, nine families from this community had lost twenty-one infants to this sudden death syndrome.

This familial clustering suggested a genetic basis for the syndrome. All infants with SIDDT died before 12 months of age of abrupt cardiac and respiratory arrest. While many of these infants underwent testing at major medical centers, no abnormalities were found. Males with SIDDT may also have underdeveloped testes. Females appear to be normal and have normal female hormones in blood and urine. Despite these differences, male and female infants with SIDDT died suddenly at the same age.

The researchers analyzed the DNA from four of these infants, along with their parents, siblings, and extended family members. Using Affymetrix (Nasdaq:
AFFX) SNP arrays — which examine 11,555 single letter, or nucleotide, variations in the genome known as single nucleotide polymorphisms — the researchers narrowed the location of the disorder to a region on chromosome 6. By correlating the genes known to reside in the region with their clinical understanding of the syndrome, the researchers believed a gene called TSPYL, which is expressed both in the brainstem and in testes, might be responsible for the sudden deaths in these infants. DNA sequencing of this gene in all four patients revealed a severe alteration. All affected infants were found to have two abnormal copies of the TSPYL gene and all parents were carriers of the alteration. Although several other genes are known to be associated with SIDS, this is the first gene identified which causes a primary form of SIDS.

"This study provides new insight into how the nervous system is regulated and highlights the benefits of close collaborations between researchers, physicians, and the patients they care for," said Dr. Erik G. Puffenberger, Laboratory Director at the Clinic for Special Children, the paper's first author.

The discovery also demonstrates the rapidly increasing speed of modern medical research. The mapping and identification of the gene was performed in less than two months from start to finish.

According to the physicians at the Clinic for Special Children, SIDDT is a new disease that has never been described before. The alteration in TSPYL can affect the neurological system and cause sudden death, and in males can also affect the reproductive system. According to Stephan, the relationship of TSPYL mutations or polymorphisms to SIDS in the general population will be studied next. Future work will examine the effects of this gene on the normal control of breathing and heart rate in otherwise normal, premature infants. The gene may be used as a diagnostic marker and to develop treatments.

"This collaboration between the Clinic for Special Children, Translational Genome Research Institute (TGEN), and Affymetrix is an important example of how modern genetic knowledge can, and should be, used to help solve medical problems," said Dr. D. Holmes Morton, Director of the Clinic for Special Children