Computed Tomography Colonography ("Virtual Colonoscopy") in Israel: Results of The National CT Colonography Survey of the Israeli Association of Abdominal Imaging and the Israeli Radiological Association

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Abstract

Background: Computed tomographic colonography, also known as virtual colonoscopy, is a rapid, non-invasive imaging technique to detect colorectal masses and polyps that is becoming increasingly popular.

Objectives: To evaluate the availability, technique, standards of performance and indications for CT colonography in Israel.

Methods: A questionnaire on CT colonography was sent to all radiology departments and private institutions that perform CTC in Israel. We evaluated multiple technical parameters regarding the performance and interpretation of CTC as well as radiologists’ training and experience.

Results: Fourteen institutions – 7 hospitals and 7 private clinics – participated in the study. Most of the small radiology departments and nearly all of the more peripheral radiology departments do not perform CTC studies. Since 2000 and until March 2007, a total of 15,165 CTC studies were performed but only 14% (2123 examinations) were performed at public hospitals and 86% (13,042 exams) at private clinics. CTC was performed after an incomplete colonoscopy or for various contraindications to endoscopic colonoscopy in up to a third of cases. In the various institutions patients were self-referred in 20–60% of cases, more commonly in private clinics. All CTC examinations were performed on 16–64 slice CT scanners and only a small minority was performed on 4-slice scanners in 2001. All but one center used low radiation protocols. Nearly all facilities used a 2 day bowel-cleansing protocol. All except one facility did not use stool tagging or computer-aided diagnosis. All facilities inflated the colon with room air manually. All institutions used state-of-the-art workstations, 3D and endoluminal navigation, and coronal multi-planar reconstructions routinely. There are 18 radiologists in the country who perform and interpret CTC studies; half of them trained abroad. Ten of the radiologists (56%) have read more than 500 CTC studies.

Conclusions: In Israel, CTC examinations are performed by well-trained and highly experienced radiologists using the latest CT scanners and workstations and adhering to acceptable CTC guidelines.

Computed tomographic colonography is the most recent technique for detecting colorectal neoplasms. This technique, also known as virtual colonoscopy [1], is a rapid, non-invasive imaging method to investigate the colon and rectum. It refers to a CT examination of a fully prepared and air-distended colon that acquires volumetric data of the entire colon within a few seconds of scanning, the total examination time is 10–20 minutes. The colon is then examined with specialized software at an offline workstation using regular axial CT sections, two-dimensional multi-planar reconstructions and three-dimensional endoluminal views.

Since the advent of CTC, it has been regarded as a potential alternative technique to conventional colonoscopy for the detection of colorectal polyps and cancers [1]. However, it is not covered by the four major health management organizations for use as a screening test for colorectal neoplasms.

CTC has been performed in Israel since 2000. Since its introduction it has gained popularity and thousands of examinations have been performed in numerous facilities. Recently, a national survey was conducted by the Israeli Radiological Association and the Israeli Association of Abdominal Imaging. The aim of the survey was to assess the availability of CTC in Israel, to evaluate the technical and professional standards of practice of the examination, and to compare it with acceptable guidelines. This manuscript summarizes the main findings of the survey.

Patients and Methods

In March 2007, after approval was obtained from the institutional review board of Tel Aviv Sourasky Medical Center, a questionnaire on CTC was sent to all radiology departments and to all private CT clinics in Israel. During the subsequent months until 31 August 2007, the questionnaires were returned and evaluated. The parameters evaluated were: number of institutions performing CTC studies, date of the first CTC study, total number of CTC examinations performed, CTC request parameters, CTC technical aspects, preparation for the CTC examination, CTC monitoring and examination practice, CTC workstation software, and post-processing technique (Table 1). We also assessed the number of radiologists performing the examination, the radiologists’ training and experience, and CTC interpretation policy (Table 2).
Table 1. Parameters in our questionnaire evaluating the CTC examination

<table>
<thead>
<tr>
<th>Type of data evaluated</th>
<th>Specific information asked</th>
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| Request Information    | • Percentage of patients referred by physician/self-referred  
                          • Clinical indication for the study: cancer screening, incomplete colonoscopy, contraindication for colonoscopy  
                          • Use of consent form  |
| Preparation technique  | • Medications used  
                          • Length of preparation  
                          • Use of stool tagging and oral liquid contrast material  |
| Technical aspects      | • Scanner type  
                          • Radiation exposure (mAs, kV)  
                          • Collimation, slice thickness and increment  
                          • IV contrast: indications, amount, rate of injection, scan delay  |
| Examination technique  | • Air insufflation technique (self, by a general physician, by a radiologist); room air versus carbon dioxide  
                          • Manual or automatic carbon dioxide pump insufflation  
                          • Type of catheter used for air insufflation  
                          • Use of dual positioning and order of positioning  |
| Monitoring of the exam | • Presence of a radiologist  
                          • Online evaluation of images by radiologist  |
| Post-processing software and technique | • Post-processing workstation and software type  
                          • Use of computer-aided diagnosis  
                          • Analysis of the exam: axial sections, coronal and sagittal reconstructions, 3D endoluminal views  |

Results

The survey was sent to 18 radiology departments of public hospitals around the country. Two departments of radiology did not respond to the survey (11%) and 9 departments (50%) stated that they do not perform CTC, the 7 radiology departments (39%) that perform the exam regularly were included in the survey. Four of the 7 departments (57%) are located in the central region of the country (the Dan area). Most of the small radiology departments and nearly all of the more peripheral departments do not perform CTC studies. The survey was also sent to four chains of private clinics with CT scans all over Israel that perform CTC (namely, Mor, Mar, Ramat Aviv Medical Center, and Asuta). Three of these four chains, including seven branches with CT scans that perform CTC examinations, responded to our survey. All of the private clinics perform CTC studies routinely and in large numbers and were thus included in the survey. The survey therefore comprised 14 facilities performing CTC studies routinely. All institutions started performing CTC examinations between the years 2001 and 2004 except for one that initiated a CTC program in 2006. Since 2001, a total of 15,165 CTC studies were performed in the institutions included in the survey [Table 3]. Self-referral was more common at private institutions and at least 6295 of the 15,165 examinations (42%) were performed on patients who were self-referred.

All institutions use a 2 day preparation protocol, except for one that uses only one day preparation and another that uses a 1–2 day preparation protocol. The preparation protocol used in nearly all institutions includes two 45 ml bottles of disodium hydrogen phosphate (Soffodex®, Dexxon Ltd, Israel). One institution recently stopped using Soffodex, replacing it with Pico-Salax® (magnesium citrate) because of the recently issued Food and Drug Administration warning about acute phosphate nephropathy, a type of acute renal failure that is a rare but serious adverse event associated with the use of oral sodium phosphate products for bowel cleansing. One institution always uses polyethylene glycol (Meroken®, Taro Pharmaceutical Industries Ltd., Israel). Meroken is employed as an alternative preparation in most other institutions in cases where Soffodex is contraindicated due to renal or heart failure. Only 6 of the 14 institutions (43%) use, in addition to Soffodex or Meroken, two to four bisacodyl tablets (Laxadin®, Teva Pharmaceutical Industries Ltd., Israel) routinely, and another institution uses it occasionally. One private chain started using liquid barium sulphate (E-Z-Cat, EZ-EM Inc., USA) for excess fluid and stool tagging. Only one institution routinely uses computer-aided diagnosis that labels polyps. Another institution occasionally uses the same software.

All the facilities are well equipped and use 16 or 64-slice CT scanners and state-of-the-art workstations, most commonly Philips, followed by Siemens, Viatronics and General Electric. All institutions use 3D and endoluminal navigation and coronal MPR routinely, and half of them also use sagittal MPR routinely.

Intravenous injection of iodinated contrast is used in 9 of the 14 institutions (64%) performing CTC examinations. Four institutions (29%) including 2 hospitals stated that they never use intravenous contrast, and one institution (7%) stated that contrast is used only when it is requested by the referring physician.

1MPR = multi-planar reconstruction
Intravenous contrast injection is used for suspected or known colonic tumors and when excess fluid is demonstrated. When IV contrast is used all institutions use 100 ml injection except for one where only 80 ml is injected. All centers employing IV contrast, except for one, use only non-ionic iodinated contrast material. Scan delay after IV contrast injection is 60–70 seconds in all centers except for one, which practices 100 sec delay, and when IV contrast is administered 200–280 mAs is used in all centers.

The examination is always performed by a radiologist in 6 of the 14 centers (43%) and by a general physician (who is in charge of patient preparation and IV contrast injection) in 4 private institutions (29%). In the other 4 facilities (28%), either a radiologist or a general physician performs the exam. All facilities inflate the colon with room air manually. None of the institutions use carbon dioxide pumps. All institutions except for one use barium enema catheters routinely. Some centers also use Foley catheters occasionally (size 14–20). When CTC studies are performed at public medical centers, radiologists are always present during the CTC examinations and inspect the images while the patient is undergoing the examination. A decision regarding the use of IV contrast material can therefore be made. The radiologist also conducts a short interview with the patient before the examination in six of the seven hospitals. In the private CT institutions CTC examinations are performed without the presence of a radiologist. Written informed consent is obtained in 11 of the 14 institutions, either by the radiologist or a general physician. The patient receives the result immediately after the exam is read in only three of the institutions (21%). In 2 institutions (14%) the result is received within 24 hours, in four institutions (29%) the result is given within 48 hours and in five institutions (36%) the result is given after more than 48 hours. A patient-radiologist interview to discuss the results of the CTC is conducted in only 3 institutions (21%). In the other institutions the interview is held only if a significant finding is diagnosed. When a tumor is diagnosed, the result is given to the patient by the radiologist in a personal interview, always in 8 of the institutions (57%) and sometimes in another 2 institutions (14%). The result is given to the referring physician in 9 institutions (64%). In only one institution is the diagnosis not given to either the referring physician or the patient. Only one institution (7%) follows the patient after the diagnosis is given in order to ensure treatment. Radiologists report every polyp in 7 (50%) of the institutions, while the others report only polyps larger than 5 mm. All institutions report abnormal findings in other abdominal or lower chest organs.

One public hospital has a combined CTC and endoscopic colonoscopy examination protocol. The patient undergoes a CTC examination that is interpreted while the patient is in the waiting room. If significant polyps are diagnosed or suspected, a consultation is held with a gastroenterologist and the patient then undergoes endoscopic colonoscopy.

Of the 450 radiologists in the country, 18 perform and interpret CTC studies (4%) [Table 4]. We did not get information from all institutions regarding the number of CTC studies read per session by one radiologist. In most of the institutions that provided this information radiologists usually read up to five CTC studies per session, but there were a few facilities where up to 30 CTC examinations are read by a single radiologist per session.

### Discussion

Colorectal cancer is the leading cause of cancer mortality in Israel and the second leading cause of cancer mortality in the United States, accounting for approximately 10% of all cancer mortalities.

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**Table 3. CTC examinations performed at public/private institutions, and CTC availability**

<table>
<thead>
<tr>
<th></th>
<th>Public hospitals</th>
<th>Private institutions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of CTC examinations</td>
<td>2152 (14%)</td>
<td>13013 (86%)</td>
</tr>
<tr>
<td>Average number per institution</td>
<td>307 (range 10–800)</td>
<td>2168 (range 998–7000)</td>
</tr>
<tr>
<td>Mean percentage of patients with physician referral</td>
<td>80% (range 18–100%)</td>
<td>42% (range 20–70%)</td>
</tr>
<tr>
<td>Type of CT</td>
<td>3: 64 slice (43%)</td>
<td>7: 64 slice (100%)</td>
</tr>
<tr>
<td>Slice thickness</td>
<td>0.5–3 mm</td>
<td>0.5–3 mm</td>
</tr>
<tr>
<td>mAs</td>
<td>30–100 mAs</td>
<td>100 mAs, 2 centers use 200 and 250</td>
</tr>
<tr>
<td>KV</td>
<td>120</td>
<td>120</td>
</tr>
<tr>
<td>Dual positioning</td>
<td>Always</td>
<td>Always</td>
</tr>
</tbody>
</table>
| Indications for CTC*    | Incomplete colonoscopy 45% (20–80%) 12% (5–20%) | Colonoscopy contraindicated 23% (20–30%), 8% (10–15%)
|                        |                   | Self-referral 40% (20–60%), 60% (50–60%) |
| Availability of CTC examinations |                  |                      |
| Northern Israel         | 2 institutions (886) | 2 institutions (1498) |
| Central Israel          | 5 institutions (1266) | 4 institutions (9372) |
| Southern Israel         | 0 institutions    | 1 institution (2143) |

* Partial information since some institutions did not provide these data. The data are given in ranges, thus the percentages do not add up to 100%.

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**Table 4. Assessment of the radiologists’ training and experience**

<table>
<thead>
<tr>
<th>Number of radiologists performing CTC studies in Israel</th>
<th>18</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radiologists performing CTC at more than one center</td>
<td>7/18 (39%)</td>
</tr>
<tr>
<td>Training</td>
<td>4/18 (22%)</td>
</tr>
<tr>
<td>Certified courses</td>
<td>5/18 (28%)</td>
</tr>
<tr>
<td>Training at various institutions performing CTC routinely in Israel</td>
<td>6/18 (34%)</td>
</tr>
<tr>
<td>Self-training (some with 15 CTC studies that were correlated with endoscopic colonoscopy)</td>
<td>3/18 (17%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Experience</th>
<th>4/18 (22%)</th>
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</thead>
<tbody>
<tr>
<td>Reading up to 100 CTC cases</td>
<td>4/18 (22%)</td>
</tr>
<tr>
<td>Reading up to 500 CTC cases</td>
<td>4/18 (22%)</td>
</tr>
<tr>
<td>Reading more than 500 CTC cases</td>
<td>10/18 (56%)</td>
</tr>
</tbody>
</table>
deaths in both men and women combined. Screening programs for colon cancer are based on the accepted opinion that most colorectal cancers arise from benign adenomatous polyps.

Until recent years only conventional colonoscopy and double-contrast barium enema were used for evaluation of the whole colon [1]. Conventional colonoscopy is considered to be highly sensitive and specific for the detection of colonic neoplasia, but it is not perfect and some lesions may be missed. In the study by Rex et al. [2] the miss rates were 6% for adenomas ≥ 10 mm in diameter, 13% for adenomas 6–9 mm in diameter, and 27% for adenomas < 5 mm in diameter. In addition, conventional colonoscopy may be associated with serious complications when used as a screening tool in an average-risk population [3]. The aim of colonoscopy is to completely evaluate the colon and to reach the cecum, but this is not always possible. Even experienced colonoscopists may be unable to complete the colonoscopy due to multiple reasons such as severe diverticulosis, stricture, obstructing mass, or fixation of colonic loops due to adhesions after surgery. In addition, performing colonoscopy requires that oral anticoagulation treatment be discontinued, which may not be advisable in some patients. Recent studies show that double-contrast barium enema has a poor sensitivity with detection rates as low as 48% for polyps and adenomas larger than 10 cm [4] and may be associated with considerable patient discomfort. Since this technique is used much less frequently, there is a significant decrease in the level of expertise of radiologists performing the examination, further lowering its accuracy. With acceptable screening techniques only 20–30% of all individuals at risk have undergone any form of colorectal screening. CT colonography, also known as virtual colonoscopy [5], is a relatively new, rapid and non-invasive imaging technique to investigate the colon and rectum and is becoming more popular.

Our survey shows that 15,165 CTC studies were performed in Israel during the 6 study years, mostly at private clinics. Private facilities have invested more in marketing and advertising this technique and were able to recruit a sufficient number of radiologists. Public hospitals on the other hand are mostly understaffed by radiologists who perform the examination. In addition, Israeli radiologists have a huge work load and, as a result, adequately trained radiologists do not have sufficient time to perform CTC studies, which are time consuming.

It is a matter of concern that the availability of CTC is not equal throughout the country. In the central, heavily populated Dan area, the examination is readily available at numerous public and private centers, while in the north and south of the country it is far less available, with only 4527 examinations performed in the period under study (Table 3).

As reported in the literature there are several accepted indications for CT colonography. CTC is performed following incomplete colonoscopy [6–9], which occurs in 5–15% of studies due to obstructing colorectal lesions or technical difficulties such as a long and tortuous colon, or due to the patient’s discomfort. In a large percentage of cases, CTC can complete the colonic evaluation as well as identify the cause for the endoscopic failure [6]. Synchronous carcinomas, which occur in about 5% of cases, may be detected when an occlusive carcinoma does not allow passage of the colonoscope to complete the colonic evaluation [6,7]. In a very recent article [7], CTC detected 88 endoscopically non-visualized lesions of ≥ 6 mm, including 12 masses > 20 mm in a cohort of 564 patients after incomplete colonoscopy. In our study up to a third of patients underwent CTC due to an incomplete colonoscopy. In fact, when only public hospitals are evaluated the percentage is even higher – up to 80% in some hospitals. This is because of the close cooperation between gastroenterologists and radiologists in some centers where CTC and colonoscopy complement each other.

Although CTC is a promising technique, it has not yet been approved for large-scale colorectal screening. However, our study shows that at least 42% of CTC studies performed in Israel were performed as a screening test for colorectal cancer. The use of CTC for screening was much more common in private institutions than in public hospitals. A recent study [10] compared primary CTC screening in 3120 consecutive adults with primary endoscopic colonoscopy screening in 3163 consecutive adults and concluded that primary CTC and endoscopic colonoscopy screening strategies resulted in similar detection rates for advanced neoplasia, although the numbers of polypectomies and complications were considerably smaller in the CTC group. These findings may support the use of CTC as a primary screening test before therapeutic conventional colonoscopy.

Some patients who require colonoscopy cannot undergo the procedure for various reasons, such as severe co-morbid disease, advanced age, bleeding disorders, extremely tortuous colon, or prior allergic reaction to sedation. In some cases colonoscopy is required but the patients refuse the procedure. CTC is also a good alternative in these cases. In our study, up to a third of patients had the CTC examination because of various contraindications to endoscopic colonoscopy.

We found that all institutions performing CTC in Israel are well equipped; more than 70% have 64-slice scanners while the rest use 16-slice scanners. The quality of the results of both scanners is similar. The technical parameters used for the CTC examination were also found to be in agreement with published international standards. Dual positioning is used in all institutions as required. Dual positioning has been shown to improve colonic distension, allowing confirmation of suspected findings, and to increase detection of colonic polyps ≥ 5 mm by approximately 15% compared with supine positioning alone [11,12].

Radiation exposure is one of the major drawbacks of CT colonography. In Israel nearly all institutions were found to use low radiation protocols, mostly 100 mAs in one position and 50 mAs in the second position compared to 280–300 mAs in routine CT of the abdomen and pelvis. The lifetime risk of developing fatal cancer as a result of ionizing radiation exposure is estimated by the International Commission on Radiological Protection, or ICRP, to be approximately 5% per Sievert [13]. Because of the long latency period, the age of radiation-induced cancer death becomes less probable the older the person being radiated. The
targeted population for CTC is 50 years of age and older. The ICRP data indicate that the probability of inducing fatal cancer in this age group is approximately 2.5% per Sievert, and at the age of 70 the risk is half. The effective dose of CTC is estimated at about 8.8 mSV (range 4–12 mSV) and carries a risk of 0.02% in a 50 year old individual and lower for older patients [14]. Low dose CTC was shown to have excellent sensitivity and specificity for detecting colorectal neoplasms ≥ 10 mm [15]. It was recently shown [16] that combined x, y and z-axis tube current modulation leads to significant reduction of radiation exposure without loss of image quality. We believe that with time, radiation exposure in CT colonography will continue to decrease.

CT colonography is performed without the routine use of intravenous contrast, although it has been shown to significantly improve readers’ confidence, colonic wall conspicuity, and depiction of sub-centimeter colorectal polyps [17]. Most institutions in Israel use intravenous contrast for problem solving. The amount of contrast used as well as the scanning delay and protocol are in agreement with published reports. However, 4 institutions (29%) including 2 hospitals stated that they never use IV contrast, and one institution (7%) uses intravenous contrast only when requested by the referring physician. We believe that this is not in the patients’ best interest and may result in some cases in additional CT scanning (for staging, when a tumor is detected) and in decreased accuracy in a minority of cases.

Preparation protocols in all institutions in Israel conform to acceptable standards. Stool tagging is not used routinely in most centers, with only two institutions using fluid tagging. Barium suspension is given to the patient before the CTC examination. The high attenuation contrast incorporates within the residual stool, facilitating differentiation from polyps. Hopefully, stool tagging will become more popular.

CT colonography is performed in Israel by a radiologist or a general physician who is employed for contrast injections to increase CT productivity. All facilities inflate the colon with room air manually, unfortunately, carbon dioxide pumps are not used. Carbon dioxide is considered to be more comfortable for the patient due to the more rapid absorption of CO2 through the colon wall and blood, causing less cramping after the procedure [18-20]. Because the price of CTC has dropped to $140 recently, investing in carbon dioxide pumps and using the required equipment is not economical in Israel.

In Israel all institutions have state-of-the-art workstations and the radiologists use axial images, 3D and endoluminal navigation and coronal multi-planar reconstructions routinely. Of the 450 radiologists in the country only 18 radiologists perform and interpret CTC studies (4%), a majority of them performing the examination at more than one center. The small number of radiologists who perform CTC studies is attributable to the low reimbursement for the examination and the time-consuming nature of both exam and interpretation. Most Israeli radiologists are well trained and very experienced. In most institutions radiologists usually read up to five CTC studies per session, but there are a few institutions where up to 30 CTC examinations are read by a single radiologist per session. This is again a result of both low pay and the insufficient number of radiologists doing CTC examinations.

There are a few limitations to our study. First, as mentioned, because of the retrospective nature of the study we were unable to evaluate the technical quality of the CTC examinations as well as the quality and accuracy of the interpretations. The time actually spent on CTC interpretation also could not be assessed.

In addition, we were unable to compare various technical issues such as the performance of the different cleansing protocols and CTC scanning protocols. We were also unable to evaluate patients’ attitudes and satisfaction with the examination. We believe that despite these limitations our study is important and provides valuable information on the performance of CTC examinations in Israel.

Conclusion

Our survey shows that in Israel, CTC examinations are performed by well-trained and highly experienced radiologists using the latest CT scanners and workstations, as well as acceptable CTC guidelines. Future improvements should focus on using carbon dioxide pumps to lower patient discomfort, more frequent use of stool and fluid tagging as well as electronic cleansing software, and the routine selective use of intravenous contrast administration. Our findings should be taken into consideration in future assessment of the possible inclusion of CTC as a reimbursed imaging study.

Acknowledgment: We thank all the institutions that participated in the survey: Assaf Haroof Medical Center (Zerifin), Carmel Medical Center (Haifa), Hadassah-Hebrew University Medical Center (Jerusalem), Rabin Medical Center (Pelah Tikva), Sheba Medical Center (Tel Hashomer), Tel Aviv Sourasky Medical Center (Tel Aviv), Western Galilee Medical Center (Nahariya), MAR Medical Imaging institutes (Beer Sheva, Jerusalem, Haifa), Mor Medical Institutes (Netanya, Bnei Brak), and Ramat Aviv Medical Center (Ramat Aviv).

We also thank the following institutions for their response: Hasharon Medical Center (Pelah Tikva), Hillel Yaffe Medical Center (Hadera), Kaplan Medical Center (Rehovot), Meir Medical Center (Kfar Saba), Padeh Medical Center (Poriyah), Ziv Medical Center (Safed), Rambam Medical Center (Haifa), Soroka Medical Center (Beer Sheva), Shaare Zedek Medical Center (Jerusalem), and Wolfson Medical Center (Holon).

References

Capsule

Small molecule inhibitor blocks signaling and prevents infection

Many bacterial pathogens sense that they are in a potential host because they can detect adrenergic molecules. These organisms share a sensor kinase that picks up the signal and relays it to virulence gene loci, thus kicking in the responses needed to ensure bacterial establishment. This pathway makes a good target for broad-spectrum antibiotic development because virulence inhibition should not present a strong selective pressure for resistance. Rasko and colleagues had some success with this approach using a non-toxic small molecule inhibitor of the sensor kinase QseC, which blocks signaling in a sensitive and specific manner. In animal models, the inhibitor was somewhat effective against gastrointestinal infections with enterohemorrhagic Escherichia coli and Salmonella typhimurium.

Encouragingly, the lead molecule was more effective against Francisella tularensis: a single oral dose protected 80% of infected mice from death.

Science 2008;321:1078

Eitan Israeli

Capsule

Genetic basis for Duane's retraction syndrome

About 1 in 1000 people are afflicted with Duane’s retraction syndrome (DRS, a complex congenital eye disorder characterized by a restricted ability to move the eye(s) outward or inward. The condition is thought to arise from faulty innervation of extraocular muscles by cranial motor neurons, which probably occurs early in embryogenesis. Miyake et al. provide genetic evidence that strongly supports this hypothesis. Studying families with a variant form of DRS, the authors discover that the mutations responsible for the disorder fall within a gene on chromosome 2 encoding 2-chimaerin, a RacGAP signaling protein previously implicated in axonal path finding of corticospinal nerves in mice. The human mutations cause 2-chimaerin to become overactive, and expression of the mutant protein in a chick embryo model did indeed disrupt oculomotor axon development.

Science 2008;321:839

Eitan Israeli