Introduction

We are delighted to welcome you to the first issue of the Marie Curie TS-EUROTRAIN initial training network (ITN) newsletter. Our ITN is focused on the study of Tourette Syndrome (TS), a common neuropsychiatric disorder with complex etiology and phenomenology, and no agreed upon pathophysiological mechanism. An international team of researchers, coordinated by Professor Peristera Paschou (Democritus University of Thrace), have secured funding in order to establish the Marie Curie Initial Training Network TS-EUROTRAIN, a pan-European research endeavor that aims to train future leaders in the field of TS. TS-EUROTRAIN aims to provide interdisciplinary training for the exploration of TS through the concerted efforts of experts at eight academic and three industrial partners. Our team is composed of researchers at the cutting edge of psychiatry, psychology, neurology, neuroscience, genetics, statistics and bioinformatics. The specific aims of our network are to (a) strive towards the elucidation of the complex etiology of the onset and clinical course of TS, (b) investigate the neurobiological underpinnings of TS and related disorders and (c) translate research findings into clinical applications, with a special emphasis on the glutamatergic pathway.

At this point, we are glad to announce that 11 motivated students have been successfully recruited as early stage researchers (ESRs). In this newsletter, we introduce you to these ESRs and the specifics of their respective projects. Last November, the ESRs met for the first time at the ITNs introductory workshops in Ulm, Germany. The students completed a series of lectures, shared their unique stories and developed both friendly and working relationships. Ahmad Kanaan (ESR12) was elected as the student representative of the ITN.

Mission Objective

Given the multifaceted nature and complexity of TS, our main aim is to form a dynamic and highly multidisciplinary team of researchers across Europe. In this newsletter series, we aim to offer updates on Tourette Syndrome research around the world, inform you about the progress of our own projects and we also wish to share with you stories of pioneering patients that were able to rise above the social stigma that is often associated with TS.
Meet the Early Stage Researchers!

Work Package 1: Susceptibility factors for TS. Genetics versus environment

**ESR 1: Muhammad Sulaman Nawaz**  
University of Iceland, Faculty of Medicine, deCODE genetics, Iceland  
**Project Title:** Genome-wide search for genes conferring risk of TS  
Hi, I am Sulaman from Pakistan and I am working in deCODE genetics Iceland to understand the heritable basis of TS. Here utilizing computational genomics and statistical power on a case-control group of hundreds of thousands of participants may help to discover causative genes (SNP’s) involved in TS. I am excited to work on this challenging goal and expect to have 3 wonderful years of research, commuting, exploring European lands and learning from fellow colleagues & ESRs. I extend my heartedly best wishes to every participant for their forthcoming achievements.

**ESR 2: Meharji Arumilli**  
Kennedy Center, Copenhagen University Hospital, Copenhagen, Denmark  
**Project Title:** Identification of susceptibility genes for TS and related disorders through investigation of structural CNVs  
My name is Meharji Arumilli. However, people call me Mehar and I am originally from India. I am working as an ESR in TS EUROTRAIN interdisciplinary network for Tourette syndrome at Kennedy centre, Copenhagen University Hospital, Denmark. My research focus is to identify susceptible genes and pathways for TS and related disorders through investigation of Copy Number Variations (CNVs) by applying Bioinformatic methods. I am looking forward to having a wonderful research experience during the next three years by contributing and sharing the findings with the research community.

**ESR3 : Padmanabhuni Shanmukha Sampath**  
Department of Molecular Biology and Genetics, Democritus University of Thrace  
**Project Title:** Gene-Environment interactions defining the onset and clinical course of tics and obsessive compulsive symptoms  
Hi, I am Padmanabhuni Shanmukha Sampath (in short Sam) from India. As a science enthusiast, I am stationed at Democritus University of Thrace, Greece pursuing my three year PhD study. My primary goal is to understand the complex interaction between genetics and environmental factors in TS. I am very delighted to work on this project to further enhance the scientific knowledge on TS.

**ESR4 : OPEN POSITION !!!**  
Institute of Medical Chemistry, Molecular Biology and Pathobiology, Semmelweis University, Budapest, Hungary  
**Project Title:** Epigenetic and functional characterization of proposed genetic variants and regions implicated in the pathogenesis of Tourette syndrome and related phenotypes  
Please refer to http://ts-eurotrain.eu/ for more information
Work Package 2: The neurobiological basis of TS and comorbidities through systems biology approaches.

ESR 5: Joanna Widomska  
*Radboud University Nijmegen Medical Centre, Department of Cognitive Neuroscience*  
*Project Title:* Integrated genetic networks underlying comorbid TS and OCD  
Hello, my name is Joanna and I joined TS-EUROTRAIN network just at the beginning of 2014, moving from Poland to charming Nijmegen, Netherlands. In my project I will investigate common genetic pathways and genetic networks underlying neurodevelopmental disorders, that are genetically related and clinically overlapping with TS, but still distinct (e.g. OCD, ADHD). Using bioinformatics and literature approaches I will try to identify common pleiotropic genetic risk variants as possible druggable targets.

ESR 6: Nuno Rodrigues Zilhão Nogueira  
*Department of Biological Psychology, Vrije Universiteit, Amsterdam*  
*Project Title:* The genetic epidemiology of TS and related phenotypes: a genetic epidemiology twin-family study.  
My name is Nuno Nogueira and I moved from Portugal to Amsterdam in August to enroll as a PhD student in the TS-EUROTRAIN project: ‘The Genetic Epidemiology of tics and comorbidities with OCD, hoarding and tic Symptoms.’ I come from a background in population genetics, and being employed by Utrecht University I will in this project be describing the relative contributions of genes and environment in the development of disease symptoms. My particular input in this work will be to better understanding the fundamental etiology of the onset and clinical course of these diseases.

ESR 7: John Alexander  
*Department of Molecular Biology and Genetics, Democritus University of Thrace*  
*Project Title:* Developing algorithmic prediction models for TS and related disorders  
Hi, I’m John Alexander from India. I am currently carrying out my PhD at Democritus University of Thrace, Greece. My primary research interest lies in utilizing bioinformatics to understand complex biological systems and find solutions to biological problems. With the help of a novel algorithmic prediction models and computational methods, my goal is to identify genetic signatures that would predict genetic risk in TS and related disorders.

ESR 8: Natalie Forde  
*University Medical Centre Groningen, the Netherlands*  
*Project Title:* Neural correlates of Tourette Syndrome and Attention deficit/hyperactivity disorder  
Hi, my name is Natalie Forde. I’m originally from Ireland and recently began my studies in UMCG. My research focus is on determining the neurobiological basis of TS and distinguishing it from attention deficit/hyperactivity disorder (ADHD) with the hope of better understanding and eventually treating these disorders. I’m delighted to be part of such a diverse and dynamic group and look forward to seeing how we can work together in the coming years.
Work Package 3: Basic investigations translating into new therapeutic approaches. The pathophysiological role of the glutamate metabolism in TS and OCD.

ESR 9: Ester Nespoli  
Boehringer Ingelheim Pharma GmbH & Co. KG, Biberach an der Riss, Germany  
**Project Title:** Development of a Tourette Syndrome model in juvenile rats  
Buongiorno a tuttii! My name is Ester, I come from Italy and I crossed the Alps and reached Biberach an der Riss, Germany, in order to join TS-eurotrain. My role in Tourette Syndrome research will be establishing an animal model of this disease. But is an animal model necessary to find a treatment for TS? Yes. Without a good animal model testing new therapeutic options would be impossible.

ESR 10: Francesca Rizzo  
University of Ulm, Germany  
**Project Title:** Investigation of the molecular effects of glutamatergic drugs in vitro and in vivo in TS rat and control animals  
Hi! I'm an Italian student re-located abroad and my name is Francesca. I first studied in Lecce and then I moved to Milano-Bicocca University where I got in touch with my passion for working with animals. My role in TS-EUROTRAIN group is to test drugs in a newly established animal model trying to underpin their mechanism and offer patient chances for novel therapeutic approaches development.

ESR 11: Sarah Fan  
Department of Biological Psychology, Vrije Universiteit, Amsterdam  
**Project Title:** Studying glutamatergic function in the frontal-striatal circuits in TS and OCD.  
My name is Sarah (Siyan) Fan. I am originally from China. I am now a PhD student from Utrecht University in Netherlands. However most of my research is conducted in the Vijre University Medical center in Amsterdam. My research focus is to investigate the glutamatergic concentration in frontal striatal circuitry in TS & OCD by using (functional) Magnetic Resonance Imaging (fMRI) as well as Magnetic Resonance Spectroscopy (MRS). I am very much looking forward to sharing and contributing my research work to the TS-Eurotrain in these coming three years.

ESR 12: Ahmad Seif Kanaan  
NMR unit, Max Planck Institute for Human Cognitive and Brain Science, Leipzig, Germany  
**Project Title:** Neurochemical and network based analysis of the pathophysiological mechanisms of TS.  
Hi, my name is Ahmad and I speak Canadian English! The overarching goal of my work is explore the pathophysiological mechanisms of common movement disorders in a bid to (i) explore the neural basis of fine motor and locomotor control and (ii) to translate this basic knowledge into therapeutic applications. As an ESR in this ITN, I will focus on (a) elucidating the role of the glutamatergic system, (b) iron deficiency and (b) cognitive control networks in pathophysiology of TS. My hope is that this work would introduce a role for glutamatergic modulatory therapy for tic suppression.
The 19th century was a remarkable period in the history of brain that saw the characterization of novel disorders of the brain and the clear documentation of previously recognized ones. Much of this is owed to the work of Jean-Martin Charcot (1825-1893) who spent 33 years studying the nervous system and teaching students at the Pitié-Salpêtrière Hospital in Paris. His reputation attracted many bright students who, themselves, later become pioneers in various fields. This list contains names that include Sigmund Freud, Joseph Babinski, Pierre Janet and George Gilles de la Tourette, among others. Under his mentorship, Gilles de la Tourette (1857–1904) began studying various neurological disorders before focusing on “obscure” movement disorders. At the age of 28, Gilles de la Tourette published a landmark article about a bizarre condition that exhibited stereotyped movements, phonic symptoms, premonitory sensations, echo- and copro- phenomena, which he referred to as that “maladie de tics”¹. Owing to Gilles de la Tourette’s pioneering work in which he documented this condition as a distinct neurological disorder, Charcot later renamed the disorder as the Gilles de la Tourette syndrome (GTS) in his honor. Interestingly, there is some discourse in the current academic arena of who should be the true bearer of the eponym. 12 years before 1885, descriptions of symptoms similar to that of Gilles de la Tourette’s were outlined in a monograph by Armand Trousseau (1801–1867)². The true nature of

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events and reason why Charcot bestowed the eponym upon Gilles de la Tourette is open for speculation. Notwithstanding this speculation, these symptoms were finally brought to the fore of medical discourse. For centuries, individuals exhibiting tics had been largely outcast, persecuted and victimized by organized groups within society. On the other hand, some individuals who exhibited these symptoms were incredibly successful and the most notable examples are Samuel Johnson, the author of the modern dictionary, and possibly Wolfgang Amadeus Mozart.

Following Gilles de la Tourette's landmark work, little progress was made in explicating the pathophysiological basis GTS or in developing new treatment strategies. In the early 20th century, GTS was primarily treated as a psychological disorder, where patients were usually told that their own psychological flaws were to blame for their symptoms. Nonetheless, the field took a positive turn in 1968 following Arthur and Elaine Shapiro's success in suppressing the tics of a 24-year-old patient with the drug haloperidol, a dopamine receptor blocker. The Shapiro's heavily criticized the psychoanalytic approach and paved the way for further progress in understanding the disorders' pathophysiology and treating it. However, it could be argued that their success in the treatment of tics is as significant as their work in establishing the first organized Tourette Syndrome Society in 1972. With the help of many patients and their families, the Shapiro's established the American Tourette Syndrome Association (TSA), which was instrumental in promoting information and increasing the public discourse about GTS in the following decades.

Nonetheless, funding the study of GTS remained scarce, as it was understood to be a rare disorder with very low prevalence rates. Owing in no small part to the significant public response towards several published articles highlighting GTS, the 1980s saw a marked increase in research funding and the inclusion of the disorder in the Diagnostic and Statistical Manual of Mental Disorders (DSM-III). Though there was an explosion of basic knowledge over the next three decades, the current scientific output concerning GTS is still overshadowed by other disorders such as Parkinson's and Autism. In the year 2000, a pan European Society for the study of GTS (ESSTS) was established by Marie Robertson and Anne Korsgaard in Copenhagen with the aims of increasing collaborative research and public awareness across Europe. In 2011, the society formulated the first set of European guidelines and published them in a series of four articles that focus on the assessment, pharmacological treatment, behavioral intervention, and deep brain stimulation of patients with GTS and other tic disorders. As a result of the endeavors of many scientists and physicians working within such societies, we now have a much better understanding of the pathophysiology of GTS and have much better ways of treating it. Along this line, several key points can be summarized as follows:

DEFINATION: GTS is a genetic, childhood-onset, neuropsychiatric and movement disorder with relatively high heritability and prevalence rates. The genetic basis of TS is still not well characterized though much research is currently being undertaken in this arena.

SYMPTOMS: The cardinal features of GTS are the presence of multiple motor and one or more phonic tics that last for at least one year with onset before the age of 18 (DSM-5, 2013). Tics are defined as sudden, rapid, recurrent, non-rhythmic motor movement or vocalization that are misplaced in context and time. Tics usually follow a waxing and waning course of intensity, frequency and severity, which usually improve or go into complete remission in adulthood. Most tics are understood to be preceded by unpleasant sensory sensations (premonitory urges) which are relieved by the tic.

COMORBIDITY: The majority of patients also present with psychiatric comorbidities that most commonly include attention deficit hyperactivity disorder (ADHD) (~50%) and obsessive compulsive disorder (OCD) (20-60%) thus complicating scientific inquiries and treatment strategies.

TREATMENT: Depending on the symptomatology and the clinical severity of the patient, different methods are currently being used to manage tics. Such strategies include (i) behavioral therapy, (ii) pharmacological therapy, (iii) deep brain stimulation, and (iv) alternative medicine.

PATHOPHYSIOLOGY: Various methods have been utilized in an attempt to uncover the pathological mechanism of GTS to affect a better treatment. Nonetheless, there is no currently accepted pathophysiological model of GTS; though the relevance of the dopaminergic system and cortico-striato-thalamo-cortical (CSTC) circuitry have been consistently highlighted.

References
ESST 2014 Annual Meeting and COST International Conference for Tourette Syndrome, Paris, France

The 2014 Annual meeting of the European Society for the Study of Tourette Syndrome and COST International Conference for Tourette Syndrome will take place on April 25-26, 2014, at the historic Pitié-Salpêtrière Hospital in Paris, home to Jean-Martin Charcot and one of his most famous students, Georges Gilles de la Tourette. The conference venue will be the newly built Brain and Spine Institute (Institut du Cerveau et de la Moelle Epinière – ICM) which also houses the Charcot Library.

Pre-registration (until March 25) and our call for abstracts (until March 1) are now open! Opportunities for travel awards also available! Junior Researchers may also apply for the Prof. Mary Robertson Award for Research Contribution.

The meeting will focus on advances in neuroimaging, genetics, neurobiology and therapy (deep brain stimulation) of Gilles de la Tourette syndrome. Also, a historical session has been specially scheduled to honour the memory of George Gilles de la Tourette and the Charcot school. Invited speakers will include experts from European countries and the US to make this the largest ESSTS meeting ever, bridging psychiatry and neurology, basic and clinical research. Also supported by COST Action BM0905 satellite events will include:

- **April 23-25th**: A three-day Clinical Training School for TS, focused on Behavioural Therapies for Tic Disorders.
- **April 23-24th**: The 1st European Workshop on Neuroimaging for Tourette Syndrome.
- **April 24th**: A TS-EUROTRAIN introductory training workshop on the Phenotype and Neurobiology of TS.
- **April 26th**: The 3rd COST International meeting of Tourette Syndrome Support and Advocacy Groups (April 26).

The list of confirmed speakers includes:

- **Bradley Peterson**, Columbia University, USA
- **Flora Vaccarino**, Yale University, USA
- **Frank Sharp**, University of California Davis, USA
- **Andrea Cavanna**, University of Birmingham, UK
- **Marie-Laure Welter**, Université Pierre et Marie Curie Paris, France
- **Thomas Foltynie**, University College London, UK
- **Kirsten Mueller-Vahl**, Medical School of Hannover, Germany
- **Danielle Cath**, Utrecht University, Netherlands
- **OA van den Heuvel**, VU University Amsterdam, The Netherlands
- **Yulia Worbe**, Pôle des Maladies du Système Nerveux, France
- **Jeremiah Scharf**, Harvard University, USA
- **Bahram Mohammadi**, International Neuroscience Institute Hannover

Looking forward to seeing you in Paris!
On behalf of the Organizing Committee:
Peristera Paschou, ESSTS Chair, Chair of COST Action BM0905
Andreas Hartmann, Local Host, Département e Neurologie, Pôle des Maladies du Système Nerveux

http://tourette-eu.org
Recent Developments in TS research

For over a century, basic and clinical research on Gilles de la Tourette syndrome (TS) remained stagnant. In the 1980's, a new era in TS research was ushered following the discovery of the effects of dopaminergic drugs on the suppression of tics. Although the field has exhibited marked advancements over the last three decades, the etiology of TS remain elusive. Today, various groups around the world are attempting to uncover the neurobiological basis of TS using methods from molecular biology, biochemistry, immunology, pharmacology, psychology, statistics, computer science and neuroimaging. In this section, we aim to review recently published articles on TS in such a way that this knowledge is accessible to both scientist working in the field and the general public.

Support of the histaminergic hypothesis in Tourette Syndrome
John Alexander

Based on: Support of the histaminergic hypothesis in Tourette Syndrome: association of the histamine decarboxylase gene in a large sample of families.
Authors: Karagiannidis et al.

This study aims to highlight the role of L-histidine decarboxylase gene (HDC) and the histaminergic system in Tourette syndrome (TS). Up to now, the histaminergic system has not received as much attention in TS aetiology studies as other monoaminergic systems of the brain. HDC gene is the protein-coding gene that produces histamine from L-Histidine. Histamine is found to play a central role in gastric acid secretion, innate and acquired immunity and immunomodulation, bronchoconstriction, vasodilation and neurotransmission. The neuronal histaminergic system is involved in a number of basic physiological functions, such as circadian rhythmicity, energy metabolism, neuroendocrine homeostasis, stress, sensory and motor functions, cognition, attention, learning and memory.

Initial linkage mapping study by Ercan-Sencicek et al. on a single family (one father and eight affected children with TS) indicated a linkage signal on chromosome 15. Further study on all the genes within the linked interval led to the discovery of a single rare coding nonsense mutation (p.W317X, c.951G>A) in the HDC gene, unidentified in 3000 controls of individuals of Western European origin. Rivière et al. also found association in genome wide scans of 95 French Canadian trios in the same region although, resequencing of the coding HDC region in 720 patients with TS and 360 controls revealed no additional nonsense variants, demonstrating the fact that the nonsense mutation identified in the index family is extremely rare. Lei et al. study on 100 Chinese Han patients with TS could only find three synonymous variants but no nonsense mutation.

Following up on the aforementioned studies on HDC, the authors within an international collaborative effort undertook a gene association study to analyse samples from 520 nuclear families originating from seven European populations (Greek, Hungarian, Italian, Polish, German, Albanian, Spanish) as well as a sample collected in Canada. The analysis involved the selection and genotyping of 12 tagging single nucleotide polymorphisms (SNPs) in order to interrogate genetic variation across a 40 kb region, including the HDC locus. By observing the over-transmission to under-transmission ratio using a Transmission Disequilibrium Test between parent and offspring, they were able to find significant over-transmission of alleles at two SNPs (rs854150 and rs1894236) in the complete sample, as well as a statistically significant associated haplotypes. Individual population specific analyses revealed positive signals of association in Italian, Canadian, and German samples, strengthening the histaminergic hypothesis for TS development. This study thus provides new insight and further support to the implication of HDC in TS aetiology. The authors indicate that a necessary next step would be the functional characterisation of RNA transcripts in samples that carry the associated HDC genetic variants, in order to help elucidate their role and possible involvement of histamine pathways not only in this disorder, but also in other neuron-developmental disorders.

References

Altered Intrahemispheric connectivity in Tourette Syndrome
Ahmad Kanaan

Based on: Altered intrahemispheric structural connectivity in Gilles de la Tourette syndrome.
Authors: Cheng et al.

Although there are a number of published articles that have interrogated cerebral structural and functional differences in Tourette Syndrome (GTS), studies that specifically investigate alterations of white matter pathways are scarce (Cheng, 2014). A few authors have previously demonstrated that GTS patients exhibit alterations in white matter tracts of somatosensory, fronto-striatal, and transcallosal circuits using diffusion tensor imaging (DTI). DTI is a powerful imaging modality that is used to reconstruct specific pathways of the brain using tractography methods. This method is based on the analysis of 4-Dimensional diffusion-weighted images (DWI) that are acquired using a standard MRI machine, with a scanning period of about 5 to 10 minutes. The intensity of each image element (voxel) reflects an estimate of the rate of diffusion of water molecules and this information can be used to reconstruct specific white matter pathways. In this article, the authors aimed on exploring structural connectivi-
ty patterns between regions involved in motor control. Utilizing DTI for the reconstruction of tracts between pre-defined specific regions of interest, the authors demonstrated that TS patients exhibit decreased structural connectivity in both cortico-cortical and cortico-subcortical networks involved in planning, controlling and executing movements. The authors also show that the structural connectivity between these regions is associated with tic severity, where decreased structural connectivity correlates with an increase in the severity of tics. These results led to the interpretation that decreased structural connectivity could reflect a primary disease marker or an adaptive plasticity during the course of the disorder. This conclusions lends support to the development model of TS, which suggests that response inhibition abnormalities result due the disruption of maturation processes of specific networks. In summary, this article supports the current cortico-striato-thalamo-cortical model of TS pathophysiology and extends further evidence on the presence of cortico-cortical abnormalities.

Neural adaptation in Tourette syndrome

Natalie Forde

Based on: Neural plasticity in functional and anatomical MRI studies of children with Tourette Syndrome

Authors: Heike Eichele and Kerstin J. Plessen

A recent review paper by Eichele and Plessen looked at the evidence that brains of children with TS adapt in response to their tics. I chose to review it here as it’s highly relevant for my research topic as I’m investigating neural correlates of TS and ADHD in children. Also it is a fascinating to see how the brain can alter and adjust to account for stimuli. The term neural plasticity refers to the adaptive nature of the brain, where neurons (nerve cells) can change and modulate, for example creating new connections. This is a vital mechanism in all of our brains allowing us to adapt to external as well as internal stimuli and do things like create memories.

In this study, from the literature the authors identified 13 studies that fit their criteria, excluding adults and including functional MRI and anatomical MRI studies from which evidence of plasticity could be inferred. Following a detailed review of these papers the authors discuss their findings and argue that many of the neurobiological differences seen in TS are due to compensatory processes in the TS brain. The functional data suggest a compensatory process which helps maintain performance despite impairments in motor function. Similarly anatomical data suggest a compensatory reorganisation that occurs in the brain facilitating the successful modulation and suppression of tics. Therefore the continuation of TS into adulthood may well be due to the brain not being as successful at adapting and thereby suppressing tics. There is also evidence to show that children with TS are superior to children without TS in cognitive control tasks, with enhanced self-regulatory control.

All studies included were cross-sectional, leading the authors to highlight the need for longitudinal studies to confirm the development of compensatory processes over time and disentangle these from causative factors. Furthermore large longitudinal studies are required to fully investigate the effect of medication, comorbidity, IQ and age on these neural changes.

Genome-wide association study of Tourette's syndrome

Nuno Nogueira

Based on: Genome-wide association study of Tourette's syndrome.
Authors: J.M Scharf et al.

A team composing an International Research Consortium, led by investigators at Massachusetts General Hospital (MGH) in Boston, has set up to address relevant questions on the genetics of Tourette Syndrome (TS), and they provided the first insight into a genome-wide analysis, in a large cohort of individuals. The report was published by the Nature Publishing Group in 2013, in the journal Molecular Psychiatry 1. This disorder has for some time been a topic of study for genetic, and twin and family studies. Among these, it has been shown that this disorder is highly heritable with a prevalence of up to 5-10 fold higher in families than in the general population.

But still, being a complex disorder, influenced by many genes variants, it has so far still remained uncharacterized the genes or the genetic variation responsible for the susceptibility to this disease. Between Linkage analysis provided so far inconsistent results, and candidate gene-studies have provided only a few findings in a few number of families, which suggests that a large proportion of causative genes is still missing. Also, most studies lacked sample size to detect the specific areas of the genome that contribute to disease risk. This is the motivation behind the study by Scharf et al., where the first Genome-Wide Association Study (GWAS) on Tourette Syndrome in the largest group of affected individuals and controls was performed.

The role of GWAS is to, agnostically (i.e. without any previous biologically relevant information) scan the entire genome for genetic variation (usually in the form of single nucleotide polymorphisms - SNPs), that, collectively, can explain, and shown be associated with, the trait/disease of interest. It is the analysis of choice to undertake in complex disorders, in which several small effect variants across the genome influence the disease [2].

For this study, twenty-two research groups across seven countries, were represented in the Tourette Syndrome Association International Consortium for Genetics and the TS GWAS Consortium, and 484,000 SNPs were analyzed across around 1500 cases and more than 5200 controls. A possible candidate SNP was found in the gene COL27A1, a fibrilar collagen expressed in the cerebellum during development, although none of this or other identified SNPs in this study did actually reach the desired genome-wide significance threshold. This was not unexpected given that studies for other also highly heritable neuropsychiatric diseases have required larger sample sizes to detect modest effect sizes for risk alleles, and considering that it is part of every good GWAS analysis to have replication studies in different groups of patients and controls to confirm some of the same variants, this report has laid important foundations for follow-up studies for the understanding of the underlying genetic architecture of TS. Finally this was also an important step in analyzing the proposed genetic relationship between this and other relevant neurodevelopmental conditions, such as OCD and ADHD 3.

This would definitely shed light in biological pathways shared by these comorbid conditions, and suggest new possible treatment targets.
Motor tics evoked by striatal disinhibition
Francesca Rizzo

Based on: Motor tics evoked by striatal disinhibition in the rat
Authors: Maya Bronfeld, Dorin Yael, Katya Belelovsky and Izhar Bar-Gad
Journal: Frontiers in Systems Neuroscience

Tourette Syndrome (TS) research can always improve. Since the beginning of the studies about TS, one of the most questioning point has been: how to best reproduce Tourette symptoms in a research animal model? Scientists have always needed a so-called in vivo animal model to exemplify the main features of any disorder. It makes it easier to study the etiology (the causes of the disease), the fisiopathology (conditions for disease onset and natural course) and, importantly, the response to drugs.

Why we need an animal and, for instance, a rat to investigate a human disease. As known, is mandatory by Law that any new-found therapeutic tool must be tested first in vitro (outside the living organism) and then in vivo (using living organisms). The clinical phase then starts bringing the drug to human patients enrolled in clinical trials and, hopefully, to the widest range of patients. It takes a lot of years, money and efforts, that’s why choosing a good animal model is fundamental to speed up scientific research. Also, since the last decade we know that rat, mouse and human genome encode a similar number of genes and that almost all human disease-related genes share the same sequence in the rat genome. So, in pre-clinical drug development, rats are routinely employed both to demonstrate therapeutic efficacy and to assess drugs toxicity.

A useful animal model should answer three questions: are the symptoms you induce in the animal the closest possible to the patient’s ones (face validity); how much the model and the patient’s response to the same treatment are similar (construct validity); how much the rationale behind the model and the model itself match (predictive validity). Maya Bronfeld and collagues recently published their results about a new animal model for TS. Through the injection of a compound in freely moving rat brain they were able to induce not only tics, but also some behavioural abnormalities typical of the most common TS comorbidities such as ADHD (Attention Deficit Hyperactivity Disorder) and OCD (Obsessive-compulsive Disorder).

Rats indeed, immediately after the injection, showed brief jerk-like movements as retraction or contraction of a body part, maintaining all their normal cognitive function such as exploration, rearing and grooming. Tics vary in frequency and area of the body involved, ranging from small twitches of one finger to strong deflections in an entire limb. Small tics initially occurred, rapidly became more pronounced and finally decrease reaching cessation, following the typical waxing and waning course. Occasionally rats also show increased locomotion and frequent switches between different behaviours such as rearing and sniffing.

Scientists first individuated that part of the rat brain involved in motor activity regulation that differs from the associative (memory, language and thought) and limbic (emotions, motivations and pleasure) ones. Motor activity, as well as all of the other brain functions, is regulated by the aminobutyric acid (GABA), the inhibitory neurotransmitter in the brain whose primary role is to “calm” it down. Then they used a drug able to block GABA activity and this resulted in a motor function on disinhibition leading to the onset of tics. Nowadays only some medications for TS have proven useful in mitigating tics, such as antipsychotics, but they often have side effects such as sedation, weight gain and cognitive dulling. Now, this model provide a new tool for researchers to study the involvement of this neurotransmitter in TS making it a new target for testing drugs efficacy.

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CNV Calling Algorithms
Mohammad Sulaman Nawaz

Based on: ParseCNV integrative copy number variation association software with quality tracking.
Authors: Glessner, Joseph T., Jin Li, and Hakon Hakonarson
Journal: Nucleic acids research

Copy number variations (CNVs) are variations (based on single nucleotide polymorphism; SNP) signalling genomic diversity extended on more than 1kb region. CNVs detection is significant because of their role in common and complex diseases. To identify true positive CNVs(3) number of CNVs calling algorithms are in development phase. Most of these are based on hidden Markov method HMM or Viterbi algorithms. In process of filtering false positive CNVs its important to get rid of poor sample (badly genotyped) and poor CNV calls (false positive detection). Poor sample(s) and bad CNV(s) calls can be filtered based on; (i) sample call rate/clustering quality; (ii) standard deviation of allelic intensity (SD LRR); (iii) G/C base content waviness factor (GCWF); (iv) count CNV; (v) majority ethnicity cluster using principle components analysis from Eigenstrat smartpc; (vi) multi-dimensional scaling (MDS). or population stratification correction by covariate; (vi) family information (1) and (vii) no duplicates. Using aforementioned filtering steps detection of true positive (TP) CNVs is still a demanding job, which attracts researchers to develop added methodologies for TP CNVs. I am happy to share that I am among those aspiring researcher and would be working at TS-Eurotrain platform to uncover this field of biomedical science.

References
5. Glessner, Joseph T., Jin Li, and Hakon Hakonarson. “ParseCNV integrative copy number variation association software with quality tracking.” Nucleic acids research 41.5 (2013): e64-e64.
By Michelle Dunlap

In 1993 this primary Patients Support Organization was founded to break the ice for Tourette patients and their families in Germany, Austria and Switzerland. The main goal is to provide TS patients with guidance, facilitate information to patients; patient support groups and general public alike and raise public awareness. In addition TGD e.V. supports scientific work.

In the meantime separate organizations in Austria and Switzerland have been established, also additional groups have been founded in country. TGD e.V. currently has 750 members and is supported by 15 independent regional patients support groups and a network of 20 service line contacts covering the entire country.

Our 3 member management board has a close rapport with the scientific advisory board whose members are located in the various scientific centers Aachen (Dr. Irene Neuner), Cologne (Dr. Katrin Woitecki), Dresden (Prof. Dr. Veit Rössner), Göttingen (Prof. Dr. Arbit Rothenberger), Hannover (Prof. Dr. Kirsten Müller-Vahl), Lübeck (Prof. Dr. Alexander Münchau), Munich (Prof. Dr. Norbert Müller) and Ulm (Prof. Dr. Andrea Ludoph). Prof. Rothenberger, head of the scientific advisory board, is also cofounder and honorary chairman of our organization.

Cooperation with various governmental social services departments (i.e. education authorities, youth welfare services etc.) is fundamental to our work in supporting our members in daily life. Also target group specific workshops are provided for hands-on support. Attendance at specific conventions and conferences is one pathway to improve public awareness and acceptance for TS in our society as well as seminars for members of the education system.

In March the regional patient support groups met for an annual meeting to brainstorm, discuss and decide on the activities to be organized for the upcoming 1st European Tourettes Day scheduled for June 7th, 2013. Participants from Hamburg, Osnabrück, Rostock, Soltau, Stuttgart and Würzburg joined together in Frankfurt for a busy afternoon of work.

Other activities to promote awareness included participation at Germany’s leading exhibition for Young People (YOU) offering teenagers initial guitar lessons by a pop artist from the serial ‘Germany’s next superstar’. Attending teenagers were given briefings on TS in general and TS in school. This was an extraordinary experience for the teenager as well as our staff.
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Our annual conference provides a casual and open atmosphere for members, health professionals, TS patients and their families as well as the general public to obtain up-to-date first hand information on research, diagnosis and therapies from our medical experts. Last year’s annual conference held October in Göttingen – marking our 20th anniversary – was chaired by Prof. Rothenberger. Our aim to create a close-knit dialog between medical experts and participants led to highly interactive and fruitful discussions. In addition 3 members gave extraordinary, emotional and exciting insights into their lives dealing with TS – this exceptional sharing was highly appreciated by a very attentive audience.

Looking back at 20 years as an organization we are on the verge of redefining our goals and activities to meet the challenges of today and continue to provide helpful and sustainable services to our community.

Please visit our website for more information: www.tourette-gesellschaft.de
Participating institutions