

THE GILLBERG CENTRE FOR NEUROPSYCHIATRY AT THE SAHLGRENKA ACADEMY

• Background and aims

Classic autism is one of the most severely impairing conditions that affect human development. Other autism spectrum conditions (ASCs), including Asperger syndrome, are more common than autistic disorder and can lead to severe or moderate psychosocial dysfunction throughout childhood and into adult life. ASCs overlap with - and can be difficult to separate from - other early symptomatic syndromes eliciting neurodevelopmental clinical examinations (ESSENCE, a concept recently launched by Christopher Gillberg). ESSENCE comprise, among other syndromes, attention-deficit/hyperactivity disorder/ADHD, Tourette syndrome, and developmental coordination disorder (DCD). In the Gillberg Centre for Neuropsychiatry, ASCs and other ESSENCE (including anorexia nervosa) will be studied as regards epidemiology and cause, clinical presentation/early symptoms and comorbidity, heritability and genetics, neurobiology, neurophysiology, neuropsychology, and intervention.

During 2011-2015, the Gillberg Centre - under the supervision of Christopher Gillberg (CG) and the leader of the Birgit Olsson chair of Neuropsychiatry - will focus on

- I. **epidemiology and “comorbidity” of ASCs** – including autism and Asperger syndrome - and other ESSENCE (including anorexia nervosa and other early onset severe eating disorders), examining cultural, regional and gender variation, and time trends;
- II. **early (including infancy) symptoms** – early screening and diagnosis of ASCs;
- III. **genetic and epigenetic studies of ASCs and other ESSENCE** ranging from twin and extended family studies to DNA and gene function;
- IV. **the pathogenesis of ASCs and other ESSENCE**, including neurochemistry, imaging, and neurophysiology differences;
- V. **epilepsy in ESSENCE and ESSENCE in children with febrile seizures, and difficult-to-treat epilepsy;**
- VI. **ASCs in certain behavioural phenotype syndromes, including outcome studies;**
- VII. **the neuropsychology, including eye-tracking, of ASCs and other ESSENCE,;**
- VIII. **outcome and intervention, including quality of life and health economy in ASCs.**
- IX. **gender effects will be analysed in all of I-VIII and is the main focus of a particular “Girl” substudy.**

• Overview of the research field

ASC has become a prioritized area of research. The US NIH and the UK MRC have identified ASC as a research area in need of strong financial support from national funding bodies. Autistic disorder, once believed to be an extremely rare *disease* is now conceptualized as one clinical presentation of a wider spectrum/one of several syndromes with similar but not identical phenotypes. Much of this changed perspective on autism has been brought about by the pioneering ASCs studies of the Gothenburg group, and is reflected in the title of the applicant’s new major textbook for Oxford University Press, “The Autisms”. For more than 25 years, the Gothenburg group has been - and still is - at the forefront in the study of autism epidemiology, clinical presentation, genetics, epigenetics, neurobiology, and outcome. CG has supervised 30 successful PhD-students, 13 of whom within the Gillberg group, 6 of whom in the past 4 years, and he is currently supervising another 11 in the project. The Gothenburg group has generated 71 peer-reviewed publications since 2007. Most of the pioneering findings of the Gillberg-group have now been - or are in the process of being – replicated by other groups, including the higher prevalence, the high rate of associated medical disorders (12-35% of all cases of autistic disorder), the almost universal “comorbidity” with other diagnosable developmental or psychiatric disorders, the high rate of “autistic traits” in the general population of children, genes linked to autism (neuligins, neurexin, SHANK-3 and other early neurodevelopmental genes affecting synaptogenesis, as reported by Gillberg’s group in *Nature* and *Nature Genetics* in 2003, 2007, 2008, 2009 and 2010), frontotemporal brain dysfunction and brainstem damage (important parts of the default network system) often encountered in ASCs, high rate of ASCs in specific medical conditions (including a number of so called behavioural phenotype syndrome), and poor outcome in classic cases of autism, somewhat better in Asperger syndrome. In other instances, we have been first to replicate major findings of other groups, such as very high heritability indices (twin studies), and chromosomal regions of interest for fine-mapping and candidate gene analysis. Through research and development, CG has also contributed greatly to the

nationally and internationally changed perspective on childhood disruptive behaviour disorders, most notably ADHD. Gillberg, with fellow researcher and wife Carina Gillberg, and their colleague Maria Råstam and her PhD student Elisabet Wentz have also pioneered the field of longitudinal population studies of anorexia nervosa, demonstrating the close link between this severe eating disorder and ASC/ESSENCE.

• **Project description**

The overall design of the studies performed at the Gillberg Centre is as follows:

- 9 Identification of all possible cases within a geographically limited age cohort, followed by (a) careful clinical examination so as to identify all cases, and (b) longitudinal follow-up.
- 9 Recruitment of ASC and other ESSENCE (including anorexia nervosa) cases both at the Child Neuropsychiatry Clinic (CNC), which is the Gothenburg statewide ASCs diagnostic clinic, and through various population-based projects (in Gothenburg, Stockholm (where CG is a consultant), Glasgow and Bergen (CG visiting professor), and the Faroe Islands (CG consultant), and, when needed, adequate comparison groups for (a) cross-sectional case-control studies, (b) careful comparison with the population recruited samples in order to elucidate the representativeness (or not) of the clinically identified group, and (c) outcome studies in which ASC cases serve as their own controls.
- 9 All cases are diagnosed after comprehensive and detailed neuropsychiatric/ neuro-psychologic/neurobiologic evaluations and all meet strict operationalized phenomenological criteria for ASC. The screening and diagnostic instruments are internationally accepted, or, when methodology is lacking, are developed within the Gillberg Centre. In the latter case, these tools, in turn, often become the new international “standard” instruments in the field (e.g. CHAT, ASSQ, ASDI, ASDASQ, A-TAC, DISCO-11, see below).
- 9 Thus, the larger group of ASC/ESSENCE cases contains a representative proportion recruited after population screening. This representative group constitute unique samples in an international perspective. They are compared with clinically recruited samples on a wide variety of background variables. The analyses have shown that clinically recruited Gothenburg cases of autism are similar – on a group-basis – to those of the general population. New cases will be recruited during 2011-2015 both through the CNC, and several new population screening studies.
- 9 The population representative groups are followed in a prospective manner and contrasted with other groups both outwith and within the group of ESSENCE (epilepsy, mental retardation, ADHD, Down syndrome, 22q11 deletion syndrome, and “normals”) matched for various aspects (gender, age, social class etc), depending on questions asked in each particular study.
- 9 The population-recruited groups of cases with ASC/ESSENCE are of particular interest because one can justifiably assume that very few cases with the disorder have been missed (Steffenburg & Gillberg 1986, Gillberg et al 1991, Gillberg & Wing 1999). A register at the CNC serves as an “easy-access” database for all diagnosed cases in Gothenburg.

Definition of ASC and other ESSENCE sample populations

The Gothenburg, Stockholm, Bergen, Glasgow, and Faroe Islands cohorts of ASC are unique in an international perspective. No other group has access to similar large samples of population-representative cases (examined in accordance with an in-depth protocol shared across sites) that allow longitudinal follow-up. Large groups of individuals (n>1500) with ASC/ESSENCE who meet criteria for DSM-III-R/DSM-IV /proposed DSM-V autism spectrum disorder criteria, or Gillberg (1991) criteria for Asperger syndrome, have been identified by the Gothenburg autism research group, and are available for study. The new Gothenburg (n=120), Stockholm (n=200) and Glasgow cohorts (n=300), currently in the process of being screened and ascertained in collaboration with Carmela Miniscalco, Elisabeth Fernell and Helen Minnis, respectively, will be unique in that they are the largest-to-date pre-school and infancy populations of children with ASC/ESSENCE undergoing long-term longitudinal in-depth follow-up assessments.

International-interdisciplinary research

The Gillberg Centre for Neuropsychiatry is interdisciplinary and involves the collaboration of local, national, and international geneticists, neurophysiologists, pathologists, radiologists, epidemiologists, cognitive psychologists, education specialists, speech-language pathologists, pediatricians, GPs, neurologists and psychiatrists.

Work-plan

The project consists of several parts:

I. The epidemiology and “comorbidity” of ASC and other ESSENCE including cultural and regional variation, time trends and effects of gender and age at ascertainment

Eight population screening studies of ASC and other ESSENCE (including anorexia nervosa) have been performed or are in progress, three in Gothenburg (Wentz 2000, Gillberg et al 2006, Nygren et al 2009), two in the Faroe Islands (Ellefsen et al 2006, Biskupsto et al in progress), one in Bergen (Posserud et al 2006), one in Stockholm (Fernell & Gillberg 2010), and one in Glasgow (Thompson et al 2009, and in progress). The screening methods for the four cohorts of school children (one Gothenburg, two Faroese) have been or are similar to those used in Gillberg et al (1991), Ehlers & Gillberg (1993) and Posserud et al (2006, 2008). The ASSQ (Autism Spectrum Screening Questionnaire) and focused register searches have been used for detection, and either the DISCO (DIagnosis of Social and COmmunication disorders) or ADI-R, and, in some studies, the ADOS for refined diagnostic assessments. These diagnostic instruments have also been (or are currently) used in the three preschool cohorts (Gothenburg, Stockholm, Glasgow), but the screening methods instead include the M-CHAT and a language screen. There are also large ongoing studies of ADHD in collaboration with Bergen and Glasgow. All cases receive an appropriate IQ-test or the Vineland Social Maturity Scale. One of the catchment areas is Gothenburg (the target area in the previous studies of autism, ADHD, and anorexia nervosa), which allows analysis of possible prevalence changes over time within one geographical district. Special efforts are made to ensure that females with the disorders are not missed by the screening procedures, but, even so, we believe that, at least in the Faroese population, a number of girls with ASC have been missed in the first population study. The Faroese ASC cohorts and their families are currently taking part in a major family-genetic study (see below), and follow-up screening of the originally targeted general population sample using the ASSQ, and A-TAC (Hansson et al 2005), will focus on finding previously missed girl cases and on the factors that contributed to their being missed in the first instance. The access to these various cohorts allows analysis of possible regional, and age-at-ascertainment prevalence differences. The anorexia nervosa cohort and controls will be followed up with the same instruments 25 years or more after onset of their disorder. This will allow the further refinement of the phenotype in anorexia nervosa that has an outcome similar to that of ASC (whereas in the non-ASC anorexia subgroup, outcome appears to be generally very good).

A new screening questionnaire (Kopp and Gillberg submitted), tailored to “girl behaviours”, will be used alongside our well established ASSQ in the further follow-up of the cohorts. Two other newly developed parent screening questionnaire (the FTF (Kadesjö et al 2004) and A-TAC) will be used to cover the range of comorbid “ESSENCE” problems associated with autism. Epidemiological studies are cumbersome, time consuming and costly. However, good studies of this kind can still be performed with more rigour and better reliability in Scandinavia (and Scotland) than in most other regions of the world. The international research community is very interested in these studies. This is partly due to the exceptional opportunity to address the issue of whether or not autism prevalence is on the rise (in Gothenburg, the Faroe Islands, or both), and, if so, what the reasons might be. Our preliminary analyses suggest that, at least in Gothenburg, prevalence is stable, and that an increase in registered autism is due to better awareness rather than a real increase in number of “true” cases. The possibility to compare findings from our new studies with those of the previous Gothenburg and Faroe Islands population studies of autistic disorder is a unique asset that no other international group can boast. Eva Billstedt (psychologist) recently defended her thesis addressing these issues, and **Rannva Biskupsto** (psychologist), **Eva Kocovska** (psychologist), and **Martina Barnevik-Olsson** (child psychiatrist) are currently registering for PhD studies on the Faroe Islands and Stockholm cohorts (see further below).

II. Early symptoms/identification of ASC/ESSENCE, including possible differentiating effect of gender

An international collaborative study conjointly with leading autism researchers in the UK (Simon Baron-Cohen) and the US (Marian Sigman) has been completed but data have yet to be analysed. This project aims to identify early symptoms of autism by examination of infant siblings of individuals with a diagnosis of autistic disorder. The siblings are recruited prospectively and examined (including on video recordings) at 4, 8, 12, 18, 36 72, and 120 months. Siblings are chosen because they have about a 20-fold increased risk of having autism compared to children in the general population. As in other parts of the project, there is a specific focus on possible difference in phenotype across gender. The study also includes validation of the CHAT (Checklist for Autism in Toddlers), developed by us in the 1990s (Baron-Cohen et al 1992).

Another early symptoms study, that will form the basis for PhD students **Gudrun Nygren** (pediatrician) and **Gunilla Andersson** (special education teacher), has just been launched. All Gothenburg 30-month old children are screened for language problems and autistic symptoms (M-CHAT). Screen positive and a sample of screen negative children plus all children under age 30 months raising any suspicion of suffering from ASC at the Child Health Centre are referred to the CNC for in-depth assessment including the CNC-protocol referred to under *I*. The special education teacher visits the child in the pre-school setting and interviews staff, completely blind to all further work-up performed at the clinic with a specific view to assess the possibility that “live” pre-school assessment might be the best diagnostic instrument in young children with suspected ASC. All children diagnosed with ASC will be referred for immediate intensive multidimensional intervention and followed up according to structured protocols by blind raters over a period of several years. Intervention studies on these children will form the basis for PhD student **Birgitta Spjut** (psychologist). Subgroups of the children with and without ASC in this project will participate in genetic and neurophysiologic (EEG and eye-tracking) studies that will produce further PhD-projects.

The Glasgow and Stockholm studies (for which separate funding is available) will provide data on early symptoms (including prospective markers identified at birth) of ASC and provide the basis for suggesting improved infancy screening for the earliest possible identification of ASC (which has been shown to be important for early intervention and better outcome). The Stockholm cohort will be given the same and similar eye-tracking paradigms as those used in the new Gothenburg early symptoms study, and this will provide the opportunity to perform cross-regional comparison of results.

III. Genetic studies of ASC

Another international collaborative study is ongoing in the field of autism genetics. This study comprises a European sib-pair, triplet, and “affected individual” study launched and led by the applicant, in collaboration with Marion Leboyer, a leading French autism researcher, and Thomas Bourgeron, a world leading French molecular geneticist at the Pasteur institute. Candidate regions on chromosomes 1,2,6,7,15,16,17,18,22 and X – mostly identified in our first genome scan study of the sib pairs (Philippe et al 1999) – have been or are currently fine-mapped. The collaboration with the world leading French genetic laboratory is crucial. Together we have identified variant and mutated neuroligin genes (early developmental genes affecting synaptogenesis) in families multiply affected by autism (Jamain et al 2003) and have shown that neuroligin knock-out mice behave in a very autistic-type way, findings which have been or are in the process of being replicated by other groups. We have also found variant SHANK-3 genes (involved in glutamate metabolism) (Durand et al 2009). Together with the large international autism genetics consortium (AGP) we have found evidence implicating a neurexin gene (another early developmental gene affecting synaptogenesis) in autism. All of these findings have been published in Nature of Nature Genetics. We have recently also identified variations and mutations in the ASAT gene in autism and ADHD and shown these to be related to decreased melatonin activity (Melke et al 2008). We are currently involved in a major project with Thomas Bourgeron looking at the rate and type of CNVs in our large autism sample. We also collaborate with Niklas Dahl’s group in Uppsala, Britt-Marie Anderlid’s group in Stockholm, and Elias Eriksson at the Gothenburg Department of Pharmacology for various part-projects subsumed under the general heading of “Genetic studies”. Micro-array studies and studies of the possible association of ASC with androgen-related genes and function are ongoing (Henningson et al 2009). Our current “autism DNA bank” comprises full clinical data and DNA from about 760 individuals, including about 420 affected by ASC. This study will form part of the basis for at least two PhD-theses, including that of Gudrun Nygren.

We are also very actively involved in the new Young Swedish Twin Registry study of autism, for which funding is not included here. Several papers (e.g. Lichtenstein et al 2010) from this study have been published in very high impact journals.

IV. The pathogenesis of ASC including possible neurophysiology gender differences

GAP collaborates with several Swedish, Norwegian, Danish, UK, French, and US groups in the pursuit of underlying pathophysiology of ASC. All our studies in this area are partly guided by two complementary theories, the default network theory (Buckner et al 2008) and the synapse-clock-dysfunction theory (Bourgeron 2007).

We have published PET- and SPECT studies in AS and autistic disorder (Happé et al 1996, Gillberg et al 1993). The PET-study was a joint project with a leading autism group in London; the SPECT-study was performed in collaboration with colleagues from Gothenburg. We are planning further functional imaging studies with Martin Ingvar at the Karolinska Institute, including high-functioning adolescents with ASC undergoing cognitively challenging tasks.

An in-depth study of specific EEG-patterns, and EEG response to sensory stimuli in very young children with autistic disorder (without epilepsy) is ongoing in collaboration with Michael Elam and Elena Orekhova at the Gothenburg Department of Neurophysiology. This study, which will also analyse the influence of gender and genetic factors, will be part of the dissertation for PhD-student Gudrun Nygren.

Endocrine parameters/genetic markers are explored in a joint project with Elias Eriksson.

ASC brain pathology (particularly amygdala, brainstem and cerebellum) is examined in a joint autopsy project with the Albert Einstein School of Medicine in New York (Karen Weidenheim and Isabelle Rapin) (Weidenheim et al 2001).

We were first to demonstrate a strong connection between thalidomide embryopathy, first trimester brainstem damage, and autism (Strömland et al 1994). The finding led us to start a new study on three other early brain stem damage syndromes, viz. Moebius sequence, CHARGE-association, and oculo-auriculo-vertebral spectrum. Reports from this study have already been published (Johansson et al 2001, 2006), and several more formed the basis for a PhD-thesis by Maria Johansson 2007. ASC are strongly overrepresented in these syndromes. We are exploring the thalidomide-brainstem link further in an NIH-funded project with Pat Rodier, Rochester, USA.

V. Epilepsy in ESSENCE and ESSENCE in epilepsy

Epilepsy, which occurs in 25-35% of all individuals with autistic disorder (Danielsson et al 2005), is the focus of another PhD-thesis by pediatrician Susanna Danielsson (2009). The clinical type, EEG-correlates and neuroimaging results will be compared across representative groups of individuals with ASC. The longitudinal development of epilepsy in autism is monitored in the outcome study (*VIII. see below*). Follow-up of autism symptoms pre- and postoperatively in children undergoing epilepsy surgery is the subject of a special substudy. A cross-cultural autism-epilepsy study in collaboration with Brian Neville, Martin Bax, Jeremy Turk and Ph.D-student Nicola Barnes in London is in the process of completion. A new general population study of autism and other ESSENCE in febrile seizures which will form the basis for a PhD thesis for neuropsychiatrist **Gill Nilsson** is also under way

VI. ASCs and other ESSENCE in certain behavioural phenotype syndromes

As mentioned above, several “brainstem syndromes” are studied as regards prevalence and type of ASC. ASC behaviours and neuropsychology are also the subject of a major study of 100 individuals with 22q11deletion syndrome, which formed the basis for a PhD-thesis by psychologist Lena Niklasson. The follow-up after six-ten years of this group will provide the basis for a PhD-thesis by psychiatrist **Ylva Anckarcrona**. Studies of ASC behaviour/neuropsychology are also done in smaller groups of individuals with Down syndrome, Williams syndrome, Moebius syndrome, and tuberous sclerosis aiming to pinpoint brain mechanisms/risk factors that can account for the fact that only some cases with these chromosome/gene disorders have ASC.

VII. The neuropsychology of autistic disorder, AS, and anorexia nervosa, taking gender into account.

A neuropsychologist at the CNC who defended her MD thesis on neuropsychological and cognitive findings in autistic disorder in 2000 (Nydén 2000) has gone on to look at interhemispheric transfer in ASC. Based on a hypothesis of glutamatergic dysfunction in autism it was predicted that the autism group would do poorly on tests of callosal function. In the project – performed in collaboration with Arvid Carlsson – support for this hypothesis was gained (Nydén et al 2004). Nydén and PhD student **Bibbi Hagberg** will continue this neuropsychological work by measuring higher-order metarepresentations, central coherence, narrative skills, pragmatics, dichotic listening and other attentional tasks in families of sib-pairs identified in the genetic studies, and by measuring procedural learning and eye-tracking in the new epidemiological samples of ASC and in children with “specific” language impairment. In the 25-year-follow-up study of anorexia nervosa cases and controls from the general population, neuropsychology will be very much in focus.

VIII. Outcome and intervention in autistic disorder, Asperger syndrome, and anorexia nervosa including quality of life and health economy

A group of 120 individuals with autistic disorder/atypical autism identified after population screening by the Gothenburg research group in childhood (<10 years of age) have been followed-up at ages 17-40 years using in-depth clinical examination and the DISCO among other measures (Billstedt et al 2005). This is the longest ever prospective follow-up study of representative cases of autism. Some of the findings formed the basis for the PhD-thesis by psychologist Eva Billstedt (2007). The standardised mortality ratio in this group will be analysed in a new study.

A group of 100 males with Asperger syndrome identified after population screening and register searches by the Gothenburg research group in childhood (<15 years) have been followed-up 5-20 years later at ages 15-35 years. This is the first prospective long-term follow-up study of Asperger syndrome

ever performed (Gillberg & Cederlund 2005). Some of the results formed the basis for the PhD-thesis by child psychiatrist Mats Cederlund (2007). Neuropsychological findings from this study will be included in the PhD-thesis of psychologist Bibbi Hagberg. New follow-up of the cohort at age 20-40 years is in progress.

Another group of 60 clinic cases with Asperger syndrome are followed up in early adult age, using, among other measures, the DISCO. This group is contrasted with 60 age and gender matched schizophrenia cases in order to analyse overlap/boundaries across the two groups. Data collection is nearing completion. This study will form the basis for PhD-theses by PhD students psychiatrist **Tove Lugnegård** and child psychiatrist **Maria Hallerbäck**.

The one- and two-year outcomes after various types of intervention, including intensive multimodal training programmes, will be studied in a group of 208 Stockholm preschoolers. This work will form the basis for a PhD thesis for **Åsa Lundholm-Hedvall** (psychologist).

The adult outcome of ASC is also in focus in the PhD project by **Lena Nylander**, who is studying cohorts of adult psychiatric outpatients, with a view to identifying ASC and developing screening tools for ASC in adult psychiatric services.

The 25-year outcome of anorexia nervosa will be studied in the 51 cases and 51 gender and age matched comparison cases followed from their early teens.

In all these studies, family experiential, quality of life, and health economy aspects, will be analysed.

IX. Gender effects – the “Girl project”

ASC are much more common in the male, with childhood boy:girl ratios of about 4:1. We were among the first to draw attention to the possibility that girls/women when affected by the basic deficits typical of ASC might show a somewhat different behavioural phenotype as compared with boys /males (Kopp & Gillberg 1992, Gillberg 1992, Kopp 2010). For instance, girls may not present with a suspicion of ASC but with other disabling problems including depression and anorexia nervosa. As a consequence, a project in which girls were overselected has been going on since 1998. One hundred girls (aged 3-18 years) with social interaction problems were examined in great detail from the point of view of ASC and comorbidity. They have been contrasted with “non-clinic” community girls, and will be contrasted with clinic boys with social interaction problems with a view to identifying clinical/biological (including genetic/neurochemical) ASC gender specific markers. The 10-year outcome of these girls will be analysed in a new study, starting in 2011. The findings from the study of these girls will help inform the approach taken in several of the other substudies. The study forms the basis for PhD student **Svenny Kopp** (psychiatrist), who will be defending her thesis in September 2010.

• **Preliminary results**

The Gothenburg ASC/ESSENCE studies have been going on for 35 years and have been at the international frontline of research for more than 25 years. These prospective longitudinal population-based and clinical case-control studies address issues pertaining to prevalence (including temporal changes), diagnostic identification, genetics, pathogenesis, neuropsychology and outcome.

Our group was first to demonstrate a higher autism prevalence (than previously reported) (Gillberg et al 1991), a finding which has now been replicated by most other research groups (Fombonne 2005). The prevalence of autistic disorder is in the range of 1-3 in 1,000 individuals rather than 1-5 in 10,000, which was the cited rate in the literature up until the 1990s. There have recently been reports that the prevalence may be even higher (Gillberg & Söderström 2003, Baron-Cohen et al, personal communication) and a, highly controversial, claim that the increase could be due to changing vaccination patterns in the western world. Pioneering studies of Asperger syndrome by us found the prevalence of this disorder to be about 4 in 1,000 (Ehlers & Gillberg 1993, Kadesjö et al 1999). These findings are now replicated by others (e.g. see Fombonne 2005). We were first to report the high rate of ASC features in the general child population (Posserud et al 2006) and to suggest that empathy disorders, e.g. ASC (Gillberg 1992), might be on a continuum with normally distributed empathy skills in the population.

The Gothenburg group was among the first to document the importance of underlying specific brain disorder, damage and dysfunctions in autism in clinical, neuroanatomic and neuroimaging studies. We were early at the forefront of genetic research in the field, following in the footsteps of a landmark UK twin study (Folstein & Rutter 1977). Gillberg’s P.A.R.I.S. international consortium collaborates with Bayley’s group in the UK, and the large Autism Genome Project (AGP), and there are large separate (including EU and NIH) grants for these major autism genetics projects. Together, the British and the Gothenburg studies have produced strong evidence that classic autism has an extremely high heritability (e.g. Steffenburg et al 1989). New evidence from the large young Swedish twin study (in which Gillberg

and his group has collaborated from the start) provides even stronger evidence of this heritability in a population setting, including the shared heritability with some other disorder in the ESSENCE group (Lichtenstein et al 2010). Since the early 1990s, Gillberg has headed the P.A.R.I.S. autism genetic project which has identified chromosomal regions of interest and gene mutations in ASC (Philippe et al 1999). Several candidate genes are being explored, including neuroligins, neurexin, SHANK-3 (which have been found by us to be mutated/implicated in ASC, all these discoveries published in Nature or Nature Genetics), and other genes involved in glutamatergic, serotonergic, melatonergic, dopaminergic transmission (e.g. Jamain et al 2003, Durand et al 2007, 2007, Melke et al 2008, Pinto and AGP 2010). We have also been first to demonstrate the pathogenetic importance of the genetic findings in follow-up functional studies and knock-out mouse models. Most of our findings have now been corroborated by several other groups.

The Gothenburg group has also been leading the field in studies of phenomenological differences relating to gender, age, and type, degree and localisation of associated brain dysfunction in autism (Kopp & Gillberg 1992, Happé et al 1996, Gillberg 1999, Kopp 2010). The development of screening and diagnostic tools for autism and its spectrum disorder has been a most important and integral part of the research (Baron-Cohen et al 1992, Ehlers & Gillberg 1993, Leekam et al 2000, Nylander & Gillberg 2001, Gillberg et al 2001, Kadesjö et al 2004, Hansson et al 2005). Without this research the new epidemiological and clinical knowledge could not have been gained.

• Importance

The Gillberg Centre will be right up front at the cutting edge of international autism and other ESSENCE research. The epidemiological parts (new prevalence studies, early symptoms and comorbidity, methodological, genetic, and outcome/intervention studies) are unique and cannot be performed in other centres. Monitoring ASC/ESSENCE prevalence over time and region is particularly important and is being closely followed by the international research community. The genetic and pathophysiological studies are very important and will, together with results from other groups, greatly increase knowledge about the basic, including brain, mechanisms underlying the development of autistic and other neurodevelopmental symptoms, and, hence, the mechanisms responsible for normal social and communicative development. The intervention study is unique. Early identification of ASCs and other ESSENCE will lead to early intervention, which, in turn, will lead to better outcomes.

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