IBS
Spectrum of diseases
Not a single entity

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DDRC/TUMS
IAGH July 2013
Tir 1392
IBS Disability

• It is the most common reason for which people seek gastroenterologist’s opinion and, although not life-threatening, people miss work for IBS more than for anything else, expect colds.

• Presenteeism (reduced efficiency and impairment at work due to sickness) also represents a common denominator in IBS, with deriving loss of productivity and additional costs to society.
The Rome III Criteria

Recurrent abdominal pain or discomfort at least 3 days/month in the last 3 months associated with 2 or more of the following:

- Improvement with defecation
- Onset associated with a change in form of stool
- Onset associated with a change in frequency of stool

*Criteria fulfilled for the last 3 months with symptom onset at least 6 months prior to diagnosis*
IBS Can be Classified into Multiple Subtypes Based on Stool Form

Subtype drives treatment modalities and recommendations

- **IBS-C**: Hard or lumpy stools
- **IBS-M**: Hard and loose stools over periods of weeks and months
- **IBS-U**: Unsubtyped IBS
- **IBS-D**: Loose or watery stools
Extra intestinal functional (EIFD) disease

• Functional GI (FGID)
• Extraintestinal functional (EIFD)

  Migraine
  Dizziness
  Urinary frequency
  ?Low blood pressure
  Weakness
  Anxiety depression
Biopsychosocial Model for IBS Integrates Psychosocial and Physiologic Factors

- **Early Life**
  - Genetics
  - Environment

- **Psychosocial Factors**
  - Life stress
  - Psychologic state
  - Coping
  - Social support

- **Physiology**
  - Motility
  - Sensation
  - Inflammation
  - Altered bacterial flora

- **FGID**
  - Symptoms
  - Behavior

- **Outcome**
  - Medications
  - MD visits
  - Daily function
  - Quality of life

- **Brain**
- **CNS**
- **Gut**
- **ENS**
Graded Treatment Response

- Psychological treatments
- Continuing care
- Improve functioning

+ 
- Follow-up visit
- Manage stress
- Pharmacotherapy

+ 
- Diet, lifestyle advice
- Positive diagnosis
- Explain, reassure

Severe
Moderate
Mild
The Phenomena of Hyperalgesia and Allodynia

- Pain
- Threshold
- Innocuous
- Noxious
- Stimulus Intensity
- Hyperalgesia
- Allodynia
- Normal state
- Insult
IBS is not a single disease
several disease entity discovered

• Bile salt Malabsorption/Deficiency
• Celiac/ None celiac Gluten sensitivity Entherapathy
• Immune reactivity
• Gut Microbiota abnormality.
• Increase Gut permeability
• Food Allergy/Intolerance
• Pelvic floor dysfunction
• Genetic basis for hyperalgesia
• Genetic basis for Brain dysfunction
About 30% of IBS-D patients have bile acid (BA) malabsorption (BAM)

Wedlake et al Aliment Pharmacol Ther. 2009; 30: 707-17

- Mechanisms for BAM and its relationship to colonic transit and permeability are unclear.
- Prior reports of association of small bowel or colonic transit with genes controlling:
  - BA metabolism (KLB and FGFR4)
  - BA receptor, TGR5 (also called GPBAR1)
- Prior reports of association of IBS phenotype with:
  - Serotonin reuptake (5HTTLPR)
  - Immune activation (TNFSF15)
IBS phenotype and accelerated colonic transit (GC24h) are associated with gene variations in BA homeostasis: Klotho β (KLB) and fibroblast growth factor receptor 4 (FGFR4).
Conclusions

These data suggest

- Association of bowel function with 5-HTTLPR is possibly mediated through a change in fecal BA excretion, but not through altered colonic transit.

- TGR5 appears to play an important role in the fecal BA excretion and overall colonic transit.

- TNFSF15 is associated with stool frequency, but this does not appear to involve altered fecal BA or colonic transit, consistent with its association with inflammation or immune activation.

- Future studies will include tissue mRNA and protein expression.
Elixobat (Ileal Bile Acid Transporter Inhibitor, IBAT)

- Decreased bile acid synthesis & bile acid concentration may contribute to pathogenesis of slow transit constipation
- Increasing delivery of bile acids to colon induces secretion and motility

- Elixobat partially blocks luminal side IBAT
- IBAT inhibition by Elixobat leads to decreases in plasma LDL cholesterol

GLUTEN CAUSES SYMPTOMS IN IBS

Mean Change in Symptoms Over 6 Weeks

Overall symptoms

Bloating

Pain

Tiredness

*P-value for analyses at Week 1 and entire study period.
Celiac in IBS patients

Should we routinely test for celiac disease in patients with IBS-D symptoms?
Non Celiac Gluten Sensitivity (GS)
"the land of no man"

- Adverse reaction to gluten
- Histology/serology –ve or inconclusive for a diagnosis of CD
- GS overlaps with IBS
- RC data indicating that GS improves with a gluten free diet

GS, gluten sensitivity; CD, celiac disease

Sapone et al., BMC Medicine 2012;10;13
Evolving Evidence of Immune Reactivity in IBS

- Increased inflammatory cells found in rectal biopsies of patients with PI-IBS
- Mast cells are increased and closer to nerve fibers in colonic mucosa in IBS
- Mast-cell mediators excite visceral sensory neurons in IBS
- Cytokine studies in IBS patients demonstrate mixed results

Alterations in the Gut Microbiome May Play a Role in IBS

- Changes in gut microbiome lead to acute and persistent functional changes \(^1,2\)
  - Insult (e.g., acute infectious gastroenteritis) may damage intestinal permeability
  - Upregulation of mast cells through Th2 pathway
  - Mast cells release histamine, proteases, and serotonin
  - Chemical signaling results in neural excitation and smooth muscle contraction

CFU = colony-forming units
Association of microbiota with IBS phenotype

- 37 IBS patients (Rome II, 15 D-IBS, 10 C-IBS, 12 A-IBS)
- 20 matched healthy controls
- Pyrosequencing of fecal microbiota

Jeffery et al., Gut 2012;61:997-1006
TJ abnormalities in the jejunum of IBS-D

- Healthy subjects
- IBS-D patients

Proportion of dilated junctions
- Healthy subjects: 40%
- IBS-D patients: 80%
  \[ p = 0.003 \]

Intercellular distance
- Healthy subjects: 25 nm
- IBS-D patients: 35 nm
  \[ p = 0.0001 \]

Cytoskeleton condensation
- Healthy subjects: 20%
- IBS-D patients: 50%
  \[ p = 0.0002 \]

Correlation with pain intensity \( r = 0.74; P = 0.002 \)

Martinez et al., Gut 2012 e-pub
Paracellular permeability in mucosal biopsies of IBS

Correlation with pain intensity (P=0.006)

Piche et al. Gut 2009;58:196-201
Dietary Considerations in IBS

Lactose intolerance

Food intolerances

Soluble fiber intake

FODMAPs

Excess Fructose
- Honey, apples, pears, peaches, mangos, fruit juice, dried fruit

Fructans
- Wheat (large amounts), rye (large amounts), onions, leeks, zucchini

Sorbitol
- Apricots, peaches, artificial sweeteners, gums

Raffinose
- Lentils, cabbage, brussels sprouts, asparagus, green beans, legumes
The FODMAP Diet
Fermentable Oligosaccharides, Disaccharides, Monosaccharides, and Polyols

Eliminate foods containing FODMAPs

<table>
<thead>
<tr>
<th>Excess Fructose</th>
<th>Lactose</th>
<th>Fructans</th>
<th>Galactans</th>
<th>Polyols</th>
</tr>
</thead>
<tbody>
<tr>
<td>fruit</td>
<td>milk</td>
<td>vegetables</td>
<td>legumes</td>
<td>fruit</td>
</tr>
<tr>
<td>apple, mango, pear, watermelon sweeteners, fructose, high fructose corn syrup other dried fruit, fruit juice, honey</td>
<td>milk from cows, goats, or sheep; custard, ice cream, yogurt cheeses soft unripened cheeses (eg, cottage cheese, ricotta)</td>
<td>asparagus, broccoli, brussel sprouts, cabbage, eggplant, garlic, onion cereals wheat and rye</td>
<td>baked beans, chickpeas, kidney beans, lentils</td>
<td>apple, apricot, avocado, blackberry, cherry, peach, pear, plum, prune, watermelon vegetables cauliflower, green pepper, mushroom, sweet corn sweeteners sorbitol, mannitol, xylitol</td>
</tr>
</tbody>
</table>

Food Elimination Reduces IBS Symptoms

12-week randomized, controlled trial with elimination diet based on IgG antibodies to food

- Sham Diet (n=66)
- True Diet (n=65)

P < .001
Don’t Miss Pelvic Floor Dysfunction

**REST**
- pubis
- puborectalis
- coccyx
- external anal sphincter

- Contraction of puborectalis
- Maintenance of anorectal angle
- Normal rectal sensation
- Contraction of sphincter

**STRAINING**
- pubis
- puborectalis
- coccyx
- external anal sphincter

- Relaxation of puborectalis
- Straightening of anorectal angle
- Relaxation of sphincter
Biofeedback Improves Dyssynergic Defecation: Results From a Controlled Trial

Satisfactory Ratings at 6 Months

- Laxatives
- Biofeedback

Patients (%)

- Worse
- No Change
- Fair
- Major

Graph showing the percentage of patients in different categories of satisfaction after 6 months.
Altered Brain Structure in IBS

Cortical Thinning in Anterior MCC

Effects of Amitryptyline on Reducing Global Brain Activation with Rectal Pain and Psychological Stress

Mertz H, Gut 2005; 54:601
Pain is a Modifiable Experience

Psychosocial Context
- Pain beliefs
- Cultural schema
- Expectation
- Conditioning

Cognitions
- Hypervigilance
- Attention
- Distraction
- Catastrophizing

Chemical / Structural
- Neurodegeneration
- Metabolic (opioidergic, dopaminergic)
- Maladaptive plasticity

Mood
- Depression
- Anxiety

Genetics

Injury
Peripheral and central sensitization

Nociceptive Modulation
Aδ or C nociceptive input
Amplified input
Sensory Signals Are Processed in Spinal Cord, Brain Stem, and Brain

- Gracilis and cuneatus nuclei
- Brain Stem
  - Dorsal column nociceptive pathway
  - Lat. spinothalamic tract
  - Spinoreticular tract
- Spinal Cord
- Dorsal Root
- Abdominal Viscus
IBS GWAS
Large-scale, whole-genome analyses from different populations

Reza malekzadeh
KEY POINTS

What is already known

The aetiopathogenesis of IBS is poorly understood.

A heritable component has emerged from epidemiological studies, but IBS risk genes have not yet been identified.

Most recent findings

• We have shown that NPSR1 and TNFSF15 gene polymorphisms influence IBS susceptibility, further supporting the existence of genetic predisposition.
To identify major IBS risk genes, through GWAS follow-up analyses in thousands of patients and controls from several independent cohorts.
Genetics

- A heritable component of IBS has been demonstrated in epidemiological studies, which have reported familial aggregation and higher incidence in monozygotic vs dizygotic twins.
  
- Despite this, only few studies have attempted the identification of IBS susceptibility genes, and no compelling evidence has been obtained for any of the markers of susceptibility thus far proposed.
Promising results

• Some promising results have been obtained through the analysis of intermediate phenotypes of disease, and we have recently shown that genetic variation in the Neuropeptide S Receptor Gene (NPSR1) Polymorphism can influence colonic transit rate.
Underpowered Study

• Genetic studies in IBS have so far been underpowered and generated contradictory results, because of:
  □ The small numbers of patients and gene variants (polymorphisms) analyzed, with repeated failures to replicate findings in independent populations.
Large-scale, whole-genome analyses from different populations.

• Given the extreme complexity of the phenotype, and the very high prevalence in the general population, it has become clear that definitive conclusions about IBS genetics may only be obtained if large-scale, whole-genome analyses are carried out in thousands of patients and controls, possibly from different populations.
GWAS of IBS, preliminary data

• The tumor necrosis factor (ligand) superfamily, member 15 (TNFSF15) study provided the first compelling evidence of specific IBS genetic risk factors, and hence prompted us to consider more demanding, large-scale genome-wide association studies.
Swedish Twin Registry

• Swedish Twin Registry and several research groups at KI, > 10000 twins from the Screening Across the Lifespan Twin Study (SALT) have been characterized (genotyped) for 1 million single nucleotide polymorphisms (SNPs) on the Illumina OmniExpress platform.

• For all SALT participants, extensive epidemiological information is available, including data on bowel symptoms that can be used to extrapolate a diagnosis of IBS.
GWAS on Monozygotic twin with IBS

- 700 IBS cases and 5000 controls in the SALT population was identified approximately and Swedish scientists currently running the first ever GWAS of IBS on this material.
Results of Preliminary analyses

• Approximately 80 regions (loci) and SNPs have already been identified, which are suggestive of true association signals ($p \sim 10^{-7} - 10^{-5}$),

• Need to be tested for confirmatory, replication analyses in additional cohorts.

• These results represent the scientific ground for the continuation of our studies, and the foundation of the current research application.
Much larger numbers of individuals need to be screened

• Starting from the series of SNP markers already identified in our index GWAS of the SALT twins.

• For this purpose, Swedish scientists actively sought study partners in Sweden and abroad, and committed substantial resources to the establishment of National and International collaborative Networks.
Translational research for potential biomarkers of disease and/or identify novel therapeutic targets

- Evaluate whether the expression profile of IBS risk genes is altered in the blood and/or intestinal mucosa of IBS patients compared to controls, in order to understand their contributions to pathogenesis, establish potential biomarkers of disease and/or identify novel therapeutic targets
SIGNIFICANCE

• Although generally disregarded as non life-threatening, IBS poses a dramatic burden on the healthcare and socio-economic system, and considerably affects quality of life in 15% of the general population.

• A better understanding of its underlying pathomechanisms not only will lead to improved diagnostics, but also facilitate the identification of novel therapeutic targets that may be exploited to increase patients’ quality of life. Indirectly, this will benefit the entire society at large.
• The genetic subtyping of IBS phenotypes ultimately could facilitate the implementation of symptomand pattern-specific treatment trials
Excess catecholamine signalling.

- Catecholamines, the primary neurotransmitters of the SNS, are elevated in both FGID and EIFD and augment pain signalling in both the ANS and CNS.
- There is evidence supporting aberrant ANS activity and abnormal stress response in both FGID and EIFD, and some symptoms, particularly pain, could be mediated by excess catecholamine signalling.
Beta-2-adrenergic receptor (ADRB2)

- Is the main target of the catecholamine epinephrine, and a primary mediator of the stress response.
- Blocking ADRB2 decreases pain sensitivity in both humans and animals.
- ADRB2 is widely expressed both in the gastrointestinal tract and in the CNS.
• Single-nucleotide polymorphisms (SNPs) located in the coding region of the ADRB2 gene have been shown to be associated with increased altered receptor response to catecholamines as well as altered receptor expression, mediated by catecholamine-induced receptor internalisation.
ADRB2 minor alleles at rs1042714 predict FGID and EIFD

- Adrenergic receptor gene polymorphisms (e.g. rs1042713, rs 1383914) have been linked to fibromyalgia and temporomandibular joint disorder, two EIFDs that are frequently encountered in FGID patients.
- ADRB2 minor alleles at rs1042714 predict FGID and EIFD, and may influence bowel symptom severity and HRQOL.
- These findings provide indirect evidence of sympathetic nervous system role in FGID pathophysiology.
ADRB2 minor alleles at rs1042714 predict FGID and EIFD
Beta-2 adrenergic receptor (ADRB2) polymorphisms

• The ADRB2 extracellular domain contains two polymorphisms, Arg16Gly (rs1042713; B16) and Glu27Gln (rs1042714; B27). Both are missense polymorphisms (orange), which lead to alterations in amino acid sequence.

• In the case of rs1042714, this may lead to decreased receptor degradation and down-regulation, in turn enhancing adrenergic response.

• The silent polymorphisms (green) have no known effect on amino acid sequence.
Gastrointestinal symptom burden among functional GI disorder (FGID) subgroups by rs1042714 genotype.

*P < 0.025 for each
Extraintestinal functional disorders (EIFDs) and Beta-2 adrenergic receptor (ADRB2) rs1042714 polymorphisms. Minor G allele carriers were at an increased risk for EIFDs, with the number of EIFDs increased in parallel with the number of FGIDs in the individual
The sympathetic branch of the autonomic nervous system and its catecholaminergic neurotransmission increasingly is gaining appreciation as an important mechanistic factor in the development of functional pain disorders, and is an attractive putative target for future FGID therapeutic strategies.

• Increasingly is gaining appreciation as an important mechanistic factor in the development of functional pain disorders, and is an attractive putative target for future FGID therapeutic strategies.
G allele carrier status

• portends a more severe phenotype in subjects with IBS.
• Greater number of EIFD in minor allele carriers within the rs1042714 polymorphism.
• Associated with poorer HRQOL, an effect that appears to be at least partially mediated by the presence of a greater burden of EIFD and psychiatric comorbidity.
Minor (G) allele carriers are more sensitive to endogenous catecholamines

- Elevated basal levels of norepinephrine have been found in the plasma of IBS patients when compared with controls.
- Similar alterations in ANS activity, specifically an increased SNS activity, have been observed in individuals with EIFDs.
- Due to increases in ADRB2 receptor affinity for norepinephrine resulting from the SNP examined in this study, minor (G) allele carriers are more sensitive to endogenous catecholamines
Therapeutic implication

• Use of beta-antagonist pharmacotherapies could be useful in the management of IBS-associated abdominal pain
Pathogenesis of IBS

- Low-grade inflammation,
- intestinal dysbiosis.
- visceral hypersensitivity
- psychological factors,
- immune activation.
- altered intestinal permeability
- Brain–gut axis
- Genetic variation in autonomic response
A familial clustering of FGIDs.

• A familial clustering of FGIDs.
• Studies involving over 50 SNPs for links to FGIDs many of have focused on the serotonin neurotransmission or gut-related immune pathways.
• Individual studies have had variable results, however, and associations between these genetic loci and FGIDs have been inconsistent
• Increases in mast cell numbers and in intestinal permeability have been independently linked to the pathogenesis of irritable bowel syndrome (IBS).
• Emerging data show that tryptase released from mast cells may alter intestinal epithelial permeability
Tryptase from mast cell

• Tryptase alone, or released from degranulating mast cells, significantly reduced intestinal epithelial permeability and the expression of junctional proteins junctional adhesion (JAM-A), zonula occludens-1 (ZO-1) and claudin-1 (CLD-1) in vitro.

• Inhibition of tryptase mitigated the effect of mast cell degranulation on epithelial integrity and on JAM-A.

• JAM-A appears to be clinically relevant as expression in IBS-A patients associated with more severe abdominal pain and longstanding symptoms.
Serotonin Receptors in GI Motor Function

- Excitatory motor neuron
  - 5-HT₃ (ACh)
  - 5-HT₄

- Inhibitory motor neuron
  - 5-HT₁A
  - 5-HT₁D (NO, VIP)

Contraction

Relaxation
TCA’s and SNRI’s Reset Dysfunctional Pain Regulation at the Brainstem via Descending 5HT and NA Activation

Important target for drug development