Introduction

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SSC Genomics in Thrombosis and Hemostasis
Genomics in Thrombosis and Hemostasis Subcommittee

The aim of the subcommittee is to develop an approach to assist in reducing the time to diagnosis of rare inherited platelet, thrombotic and bleeding disorders (BTPD), by taking advantage of advances in high throughput sequencing (HTS) technologies. For this potential to be fully realized, it is essential to develop and maintain a publicly accessible database that provides an evidence-based catalogue of diagnostic-grade (TIER1) genes for all known BTPD. Next, an integrated reference database of gold-standard disorder-causing DNA variants should be developed, which are clearly pathogenic, likely pathogenic and of unknown significance. Integrating HTS for complex genetics in the field of BTPD and the development of polygenic risk scores.
Clinical management, ethics and informed consent related to multi-gene panel-based high throughput sequencing testing for platelet disorders: Communication from the SSC of the ISTH

Kate Downes, Pascal Borry, Katrin Ericson, Keith Gomez, Andreas Greinacher, Michele Lambert, Eva Leinoe, Patrizia Noris, Chris Van Geet, Kathleen Freson. Subcommittee on Genomics in Thrombosis, Hemostasis ... See fewer authors 

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Projects

- Ethical guidance document for high throughput sequencing of BTPD patients
  *project began: 2019, projected end: 2020*

- Standardizing Platelet Transcriptomics for Discovery, Diagnostics, and Therapeutics in the Thrombosis and Haemostasis Community: The STRIDE Study
  *project began: 2019, projected end 2022*

- Curation of gold-standard disorder-causing variants
  *project began: 2018, projected end: 2021*

- Diagnostic-grade TIER1 gene curation
  *project began: 2014, projected end: TBD*

If you are a member of the Society and would like to know how to participate in the work of this group, please join the group to receive updates on activity or submit an Expression of Interest Form to the Chairman or any of the Co-Chairmen. We would be pleased to learn of your interest.
## Program Workshop

<table>
<thead>
<tr>
<th>Time</th>
<th>Presenter</th>
<th>Topic</th>
</tr>
</thead>
</table>
| Kathleen 5 mins| Kathleen | Presentation SSC  
Intro gold variant project  
Introduce Kate & Karyn                                             |
| Kathleen 10 minutes | Kathleen | Tier1 & Tier2 genes                                                  |
|                 |           | Discussion                                                            |
| Kate 30 minutes | Kate     | Basics of genetics and variant interpretation  
Basics of variants (e.g. different types of variants)  
Variant interpretation (inc. ACMG)                          |
| Interactive introduction 5 minutes | Kate | Hands on variant interpretation  
Easy example                                               |
| (coffee break) 5 minutes |          | With harder example                                                 |
| Kate interactive discussion 5 minutes | Kate | Discussion                                                             |
| Karyn 20mn      | Karyn    | Why / how to share data (LOVD, LSDB, ClinVar)  
GoldVariant App                                                  |
|                 |           | Discussion                                                            |
Gene curation: TIER1 & TIER2 Genes


Heremans et al, IJLH, 2018
1st step is selection of Diagnostic-Grade (TIER1) genes for your NGS test.

Guidelines for diagnostic next-generation sequencing.
TIER 1
• Proven disease-associated gene (**DIAGNOSTIC-GRADE**)
• 3 unrelated pedigrees with co-segregation data
• Functional data (animal model and cell/protein studies)

TIER 2
• Evidence from 1 or 2 pedigrees with insufficient cosegregation data & without functional studies

TIER 3
• Evidence for role in platelet disorders (e.g. Functional studies or KO mice)
Gene curation to deliver diagnostic-grade genes (TIER1) for coagulation and platelet disorders and thrombosis

www.isth.org/page/GinTh_GeneLists

Yearly updates during the SSC session at ISTH congress
<table>
<thead>
<tr>
<th>Category</th>
<th>Gene symbol</th>
<th>Associated disorder(s)</th>
<th>Inheritance</th>
<th>Transcript</th>
<th>Location</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bleeding/coagulation</td>
<td>F10</td>
<td>Factor X deficiency</td>
<td>AR; AD</td>
<td>NM_000504.3</td>
<td>13q34</td>
</tr>
<tr>
<td>Bleeding/coagulation</td>
<td>F11</td>
<td>Factor XI deficiency</td>
<td>AR; AD</td>
<td>NM_000128.3</td>
<td>4q35.2</td>
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<tr>
<td>Coagulation</td>
<td>F12</td>
<td>Factor XII deficiency, Angioedema</td>
<td>AR (coagulation)</td>
<td>NM_000505.3</td>
<td>5q35.3</td>
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<tr>
<td>Bleeding/coagulation</td>
<td>F13A1</td>
<td>Factor XIII deficiency</td>
<td>AR</td>
<td>NM_000129.3</td>
<td>6p25.1</td>
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<tr>
<td>Bleeding/coagulation</td>
<td>F13B</td>
<td>Factor XIII deficiency</td>
<td>AR</td>
<td>NM_001994.2</td>
<td>1q31.3</td>
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<tr>
<td>Bleeding/coagulation</td>
<td>F2</td>
<td>Prothrombin deficiency, Thrombophilia due to thrombin defect</td>
<td>AR (bleeding/coagulation) AD (thrombosis)</td>
<td>NM_000506.4</td>
<td>11p11.2</td>
</tr>
<tr>
<td>Bleeding/coagulation</td>
<td>F5</td>
<td>Factor V deficiency, Thrombophilia due to activated protein C resistance</td>
<td>AR (bleeding/coagulation) AD (thrombosis)</td>
<td>NM_000130.4</td>
<td>1q24.2</td>
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<tr>
<td>Thrombosis</td>
<td>PROS1</td>
<td>Protein S deficiency</td>
<td>AR; AD</td>
<td>NM_000313.3</td>
<td>3q11.1</td>
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<tr>
<td>Thrombosis</td>
<td>SERPINC1</td>
<td>Antithrombin deficiency</td>
<td>AR; AD</td>
<td>NM_000488.3</td>
<td>1q25.1</td>
</tr>
<tr>
<td>Thrombosis</td>
<td>SERPIND1</td>
<td>Heparin cofactor 2 deficiency</td>
<td>AD</td>
<td>NM_000185.3</td>
<td>22q11.21</td>
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<tr>
<td>Thrombosis</td>
<td>THBD</td>
<td>Thrombomodulin deficiency, Bleeding due to high soluble thrombomodulin</td>
<td>AD</td>
<td>NM_000361.2</td>
<td>20p11.21</td>
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<tr>
<td>Platelet</td>
<td>ABCC4</td>
<td>Reduced ADP-induced platelet aggregation</td>
<td>AR</td>
<td>NM_005845.4</td>
<td>13q32.1</td>
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<tr>
<td>Platelet</td>
<td>ABCG5</td>
<td>Sitosterolemia with macrothrombocytopenia</td>
<td>AR</td>
<td>NM_022436.2</td>
<td>2p21</td>
</tr>
<tr>
<td>Platelet</td>
<td>ABCG8</td>
<td>Sitosterolemia with macrothrombocytopenia</td>
<td>AR</td>
<td>NM_022437.2</td>
<td>2p21</td>
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<tr>
<td>Mutational mechanism for the disease.</td>
<td>Level 1 evidence</td>
<td>Level 2 evidence</td>
<td>Level 3 evidence</td>
<td></td>
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<tr>
<td>Found in at least 3 independent families and if &lt;3 the number is indicated. Published reference or gene-specific variant database report the families. For large single families, linkage studies between gene locus and disease were taken into account.</td>
<td>Functional hemostasis, platelet or molecular assays supporting gene-disease association</td>
<td>Mouse model that matches the human bleeding, thrombotic or platelet disorder (MGI database accession number or PubMed reference)</td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

**Dominant activating missense variants (p.T309K/R)**

- **PMID: 16638441**
  - Normal FXII and C1 inhibitor levels in plasma

**Inactivating missense and LoF variants**

- **PMID: 23664564**
  - Prolonged PT and APTT and reduced factor X activity in plasma
- **PMID: 19652879**
  - Prolonged APTT and reduced factor XI levels in plasma
- **PMID: 18024408**
  - Normal PT and APTT and reduced FXII levels in plasma
- **PMID: 28520207**
  - Reduced levels of protein XIII activity and factor XIII A antigen levels in plasma
- **PMID: 20931752**
  - Reduced levels of protein XIII activity and factor XIII B antigen levels in plasma

**Inactivating missense and LoF variants**

- **PMID: 37713562, 7740448, 1421398**
  - Dysprothrombinemia (normal antigen levels but dysfunctional prothrombin) of hypoprothrombinemia (reduced antigen level)

**Inactivating missense and LoF variants**

- **PMID: 19486170**
  - Prolonged PT and APTT and reduced factor V activity and antigen in plasma
- **EAHAD F7 database: www.factorvii.org**
  - Prolonged PT and absent or reduced plasma factor VII activity and antigen in plasma
- **EAHAD F8 database: www.factorviii.org**
  - Prolonged APTT and reduced FVIII activity and antigen in plasma
- **EAHAD F9 database: www.factorix.org**
  - Prolonged APTT and reduced FX activity and antigen in plasma

**Inactivating missense and LoF variants**

- **PMID: 27019463**
  - Hypofibrinogenemia or afibrinogenemia, in which there are low or absent plasma fibrinogen antigen levels, respectively, and dysfibrinogenemia or hypodysfibrinogenemia, in which there are normal or reduced antigen levels associated with disproportionately low functional activity

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  - Model (MGI:99501) but no corresponding phenotype to human disease

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  - MGI:95526

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Report of Additional Patients in TIER2 Genes

Many recent BTPD gene discoveries were made for single small pedigrees. While those genes are relevant for BTPD diagnostics, they still require confirmation studies in independent pedigrees. Therefore, the SSC-GinTH encourages the publication of short reports describing additional pedigrees with causal variants in such novel genes to allow their upgrading to TIER1 status.

As of Sept. 2020, the TIER-2 genes are:

- **PRKACG**: linked to macrothrombocytopenia (PMID: 25061177, 2014)
- **TRPM7**: linked to macrothrombocytopenia (PMID: 27020697, 2016)
- **TPM4**: linked to macrothrombocytopenia (PMID: 28134622, 2017)
- **EPHB2**: linked to platelet function defect (PMID: 30213874, 2018)
- **PTPRJ**: linked to thrombocytopenia (PMID: 30591527, 2019)
- **NFE2**: linked to Thrombocytopenia (PMID: 31951293, 2019)
- **BLOC1S5**: linked to Hemansky-Pudlak (PMID: 32565547, 2020)
- **PTGES**: linked to aspirin effect in platelets (PMID: 32299908)

For any inquiries, or to suggest a new gene, please contact the Chair of the SSC Genomics in Thrombosis and Hemostasis Subcommittee, Kathleen Freson, at: kathleen.feson@kuleuven.be