International Multiple Sclerosis Genetics Consortium (IMSGC)

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1. Principles.

- The principle on which the IMSGC was founded is that, through collaboration and synergy, collectively we will make more rapid progress towards fully understanding the inherited influences on etiology, pathogenesis, clinical course and response to treatment of multiple sclerosis (MS) than can be achieved individually.
- It follows that membership of IMSGC carries advantages for which some sacrifices of autonomy are considered to be a reasonable price – the corporate benefits outweighing any individual restrictions.
- Whereas this does not mean that all individual research efforts of those who elect for membership of IMSGC must be subsumed into a single Consortium effort, we do aspire to a community of ideas some of which will best be realized through collaboration.
- For any research that relies wholly or in significant part on access to IMSGC data, resources or intellectual property, Members are advised discuss their ideas within the Consortium, usually in advance of starting the work. This principle of 'no surprises' extends to all new programs and projects, and subsequent analyses of existing data before these are submitted for poster and oral presentations, or as manuscripts and other research outputs.
- Whilst summary data originating from IMSGC that are now in the public domain do not, by definition, have restrictions on their further use, in the interests of openness and collegiality, it is preferable that discussion also takes place with groups that contributed those data before submitting these for presentation or publication.
- In the same spirit of collaboration, Members are further encouraged, but not required, to share relevant ideas that do not require use of Consortium data or other resources.
- Amongst other advantages, the benefits of this cooperative approach are expected to include the strengthening and improving of preliminary ideas through discussion with colleagues, the possibility of attracting additional resources in support of proposed projects, access to larger sample and data sets, better analytical tools, and sharing of complementary skills.

2. Size and Shape of the Consortium.

Regular Members:

- Each individual associated with one of the constituent centers but not necessarily with any other rigidly defined criteria for inclusion.
- These individuals are added to the email listserv and receive notification of all IMSGC business.
- Each member is welcome to participate in the monthly teleconference calls.

Strategy Group

- Principal investigators who lead teams within which most work of the Consortium is coordinated.
- Individuals who propose and agree by consensus most medium-term research activities of the Consortium and communicate the work to Members for whom they have responsibility.
- Investigators who contribute a substantial number of multiple sclerosis DNAs and/or offer a key skill set or technical capacity of value to the Consortium.
- There are no fixed criteria for the scale of contribution but generally this would comprise more than 500 each typically providing 10-20µg for which appropriate consent has been obtained and with demographic and clinical descriptions made available to users.
- Individuals who participate in the monthly telephone conference calls and who usually attend face-to-face meetings.
- Membership is largely self-selected, but approved by other Members, determined by commitment to on-going projects and not necessarily time-limited.

Working Groups

- An *ad hoc* group of Members, usually relatively few in number and with inclusion agreed by consensus, who bring particular expertise to the management of specific projects.
- One member assumes leadership of each Working group by agreement within that group and with approval by the Governance Group.
- Working Groups communicate by additional *ad hoc* teleconference calls according to an agreed timetable.
- Working Groups routinely report progress and findings to all other Members at the monthly teleconferences.

Governance Group

- A small group of experienced individuals, including some founders of the IMSGC, who are able to set the long-term agenda and can be trusted to do what is best for the success and contributions to knowledge of the Consortium, including nurturing a culture of common purpose and collegiality across the many constituent groups and countries within the IMSGC.
- People who are non-partisan and whose style is conducive to maintaining a harmonious atmosphere and codes of behavior that underlie all work and interactions of the Consortium.
- Individuals who have responsibility for settling disputes and, where matters are contested, ultimately having the final word, and in whose opinions the Members have confidence.
- Individuals who routinely communicate amongst themselves and, when necessary, by additional telephone conference calls or face-to-face meetings.
- Members of the Consortium at least two of whom are always present (by prior agreement) on each monthly telephone conference and assist the convener by intervening or arbitrating if consensus on particular issues cannot be reached.
- Individuals able to commit to this role for three year terms, renewable by mutual consent.

- Potential new Governance Group members are identified and invited after detailed discussion and unanimous agreement within the existing Governance Group. Regard is given to gender and geographic balance.

Convener and Secretary

- One Member, likely to be from the Governance Group, who agrees to act as coordinator of the Consortium.
- The person who distributes material for each teleconference and ensures that records are kept.
- The individual through whom decisions are communicated to the Members, and documents that are being developed or finalized are distributed.
- The organizer of the face-to-face meetings.
- An individual for whom selfless dedication to the Consortium comes naturally and who is in a position to attract the necessary institutional, personal and infrastructure support to enable this highly responsible and demanding role to proceed efficiently.
- The duration of this role is not fixed but the Consortium should be sensitive to the work-load involved and make every effort to lighten the burden or rotate the post in advance of fatigue.

3. DNA Repositories.

- The technical work of the Consortium has changed over time as the cost and accuracy of genotyping have evolved: the trend has been for less domestic and more centralized laboratory work and distribution of results to the Working or Strategy groups in the first instance.
- Centralization has improved efficiency and the quality of data generated and published by the IMSGC.
- For ease of distribution to a central typing facility, and quality control, it is desirable to have a single repository; but for reasons of safety it is appropriate that DNAs are stored in more than one place.
- Therefore, in the past, most samples were submitted to the Consortium's main repository at the University of Miami, or held at the Sanger Centre in Cambridge, UK, but returned or destroyed after being held for 5 years.
- However, issues of consent and distribution have also influenced acceptance of DNA available to the Consortium that cannot be sent to a central repository.
- It follows that a variety of structures must be accommodated in order to ensure maximum availability of material for genotyping in individual projects especially as the numbers needed to achieve meaningful results increase.
- Where samples are submitted and stored in repositories, the use of such material remains under the direct control of the investigator who contributed these samples; that individual also has ethical and governance responsibilities as custodian.
- Any investigator who has submitted samples to a central repository may at any time, and for any reason, request the immediate repatriation of some or all these samples, and receive this material in a timely manner.
- Any project that calls for use of shared repository samples must be approved by the Strategy Group.

- Once a project has been approved, use of DNA samples for that project requires the stated written permission of the designated custodian using the prepared documents designed to grant or refuse authorization.
- Use of samples is an 'opt-in' process; the default position is 'no-use'; and investigators may withhold permission for any project without justification or explanation.
- Members may also request access to repository samples for local projects with the same rules of permission outlined above applying.
- Any member given approval to conduct a local project using repository samples must keep to an agreed timetable, or obtain agreement for delays, and promptly return unused DNA to the repository.
- No repository samples may be used for any primary or further purpose without the express permission of the contributing investigator(s).
- All results generated using samples contributed by a particular investigator must be shared promptly with that contributing individual.
- All data generated from any Consortium-sanctioned project (shared or local) must be submitted to the Consortium Data Repository.

4. Data Repository.

- The general principle of modern genomics is that material is put in the public domain in a timely manner.
- Members of the Consortium can reasonably expect to have early access to data generated in the name of the Consortium that has involved use of material that they contributed.
- The purpose of the IMSGC data repository is to meet these expectations by storing and managing all data derived by Members and generated in the name of the Consortium through IMSGC approved projects.
- Access to these data will be managed by the IMSGC Data Access Committee (IMSGC-DAC) which is one of the Working groups.
- These data include, but are not necessarily confined to:
    - Summary statistics data from completed studies
    - Genotypes generated for IMSGC projects and/or provided by Members using their own samples and genotypes
    - External genotypes from third parties working outside IMSGC held in the data repository for which agreement to share has been obtained
    - Independent genotypes from third parties working outside IMSGC held in the data repository for which agreement to share has not been obtained and for which additional approval from the local curator is still required
    - Phenotype data for individuals that have been included in IMSGC studies: these vary from simple demographic descriptions and diagnosis of MS, to more sophisticated information relating to severity and clinical course.
- All IMSGC Members seeking information held in the data repository must sign the *Internal Access Request* document.

In following these guidelines, it is important to recognize that:

- The IMSGC-DAC does not hold any participant identifying details (PID); these are only held by the respective custodians and are not shared within or outside the IMSGC.

- The summary statistics data from published studies are already in the public domain. Therefore Individual IMSGC members can share these without first obtaining permission from the IMSGC-DAC.
- However, it is expected that researchers using these summary statistics data routinely reference the original IMSGC papers and acknowledge IMSGC appropriately.
- The third party genotypes are not available via the IMSGC-DAC and have to be applied for separately. Whilst the list may change in the future, and Members notified by the IMSGC-DAC of any such alterations, at present these include:
  - The MIGEN data are available via dbGaP (phs000294.v1.p1)
  - The CHOP data are available via Center for Applied Genomics Children's Hospital of Philadelphia (https://caglab.org)
- The receipt of data from the IMSGC does not limit how individual groups use their own local genotypes even if these have also been submitted to the repository.
- Individual groups do not require permission from the IMSGC-DAC in order to share their own local genotypes with other collaborators.
- Members of IMSGC will notify the IMSGC-DAC as soon as any subject included in the IMSGC data repository withdraws consent, and this decision will be passed to all other IMSGC members who have received data from that subject.
- Each IMSGC member receiving data from the IMSGC-DAC commits to deleting, as rapidly as possible all genotypes and related phenotypes from subjects who withdraw consent.
- Any IMSGC member receiving data from the IMSGC-DAC must agree to ensure that all Members of the team with access to IMSGC data comply with these terms and conditions.

5. Project Decisions.

- Any new project (large or small) that intends to use samples obtained from a repository or using unpublished Consortium data, must be considered and agreed in principle by the Strategy Group.
- Each proposal should include:
  - A description of the samples or data sought
  - A description of the genotyping and analysis to be performed
  - A timetable
  - The name of the Strategy Group member responsible for the project and a list of others who will be involved
  - Confirmation of how data will be submitted to the Data Repository
  - A publishing/authorship plan
- These proposals will be distributed to other members of the Strategy and Governance groups for consideration before being approved (or declined) by consensus.
- Once a project is approved, no samples will be used until the express permission of the investigators who contributed those samples has been obtained.
- Despite careful planning, project details and direction may change: project leaders must involve the relevant Members with responsibility for specific samples and data-sets in approving any such changes.

6. Publishing/Authorship.

- All project proposals must include a specific publishing/authorship plan.
- IMSGC will follow the ICMJE recommendation for authorship (http://www.icmje.org/recommendations/browse/roles-and-responsibilities/defining-the-role-of-authors-and-contributors.html) which indicate that authorship requires:
  - Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work

  AND
  - Drafting the work or revising it critically for important intellectual content

  AND
  - Final approval of the version to be published

  AND
  - Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.
- Members of the Strategy group are responsible for nominating authors from their group according the guidance above recognizing that interpretation is somewhat subjective and agreeing that reasonable evenness of numbers across centers needs to be exercised. Where significant differences in the list of proposed authors are apparent, the Governance group will arbitrate.
- Typically the plan will be one of the following three options:
  - A full Consortium (Type 1) paper: The Consortium is listed as the author with a list of individual contributors made according to the journal's style; this option must include a suggestion for corresponding author(s). A typical example is *New Eng J Med* **357**, 851 (2007)
  - A partial Consortium (Type 2) paper: Individual authors are listed, and the Consortium name is included in the author list; this option must include a list of authors. A typical example is *Nat. Genet*. **41**, 776 (2009)
  - A local (Type 3) paper: This simply acknowledges the Consortium. A typical example is *Hum Mol Genet* **15**, 2813 (2006).
  - For all three options, it must be stated who will take responsibility for the paper.

7. Summary.

A Consortium works only if the constituent Members are motivated by the advance of knowledge on behalf of patients and the recognition that progress is faster, or only possible, through collaboration. It depends on selflessness and pride taken in collective discovery. It is not possible to anticipate every difficulty or awkwardness that a Consortium may encounter and the Charter is for general guidance rather than legislation. Membership of a Consortium does not limit individual effort. In general, simple questions requiring large amounts of information to yield an answer are the business of Consortia. More focused questions may be done better by small teams working in isolation. A fine line may exist but 'Do unto others as you would have them do unto you' and 'no surprises' are good binding principles of behavior to which all Members of the Consortium should subscribe.