Late Breaking Chromosomes

From Single Locus Mendelian Syndromes to Multilocus Genetic-Epigenetic Networks in Human Genetics

For more than a century, Mendel's rules for transmission of traits have served as the paradigm of genetics in general and human genetics in particular. Thousands of Mendelian syndromes have been collected and made generally accessible via a web-based database (OMIM). Many of these syndromes have been linked to a single locus or gene, while a few turn out to be caused by mutations in several genes at distinct genomic loci (e.g. Xeroderma pigmentosum, Fanconi's anemia). In some apparently monogenic disorders, mutations in a single gene cannot completely predict the clinical phenotype. Therefore, complex mechanisms such as modifier genes, digenic and triallelic inheritance and imprinting have been proposed. Examples include cystic fibrosis, Huntington's disease, sensory neural deafness due to Connexin gene mutations, Beckwith-Wiedemann syndrome, severe myoclonic epilepsy of infancy, and autism with associated comorbidities [Gropman and Adams, 2007; Bolszak et al., 2009; van Daalen et al., 2011].

In 2001, a few families with an apparently Mendelian disorder that could not be subsumed under the paradigm of single locus inheritance have been resolved at the molecular level [Katsanis et al., 2001]. The authors analyzed Bardet-Biedl syndrome (BBS), a genetically heterogeneous disorder characterized by multiple clinical features that include pigmentary retinal dystrophy, polydactyly, obesity, developmental delay, and renal defects. BBS is considered an autosomal recessive disorder, yet in 4 out of 163 BBS families, the authors found a situation in which 3 mutations in 2 genes at 2 different BBS loci segregated with expression of the disease. They invoked a

novel model termed 'triallelic inheritance' to explain this particular constellation.

Investigation of copy number variations (CNVs) in patients with mental retardation or intellectual delay generated a second challenge to the single locus paradigm. These patients and their healthy siblings frequently carried CNVs, which are flanked by segmental duplications and unique CNVs [Hochstenbach et al., 2011]. While unique CNVs have frequently been linked to developmental disorders [Hochstenbach et al., 2011], single recurrent CNVs occurred both in healthy individuals and in patients [Poot et al., 2010]. By themselves, recurrent CNVs seemed to have a limited contribution to clinical phenotypes [Poot et al., 2011]. Combinations of 2 or even more recurrent CNVs, on the other hand, appear to be linked to complex developmental disorders [Girirajan et al., 2010]. Different combinations of recurrent CNVs were found among patients with different clinical phenotypes, which may aid in explaining the clinical variability among some of the developmental disorders [Girirajan et al., 2012]. Thus, a 2-site CNV model for developmental disorders had been proposed [Girirajan and Eichler, 2010]. This model, extended with de novo and inherited CNVs and single nucleotide variations at 2 or even more loci, has become the second challenge to the single locus paradigm [Poot, this issue].

Analyzing facioscapulohumeral dystrophy (FSHD), Lemmers et al. [2012] found a third pattern of polygenic inheritance. FSHD is characterized by weakness of facial and upper extremities that progresses to involve also the lower extremities. The disorder occurs in 2 forms. The autosomal dominant form, FSHD1, is due to a contracted array of D4Z4 repeats, a relaxed chromatin structure and expression of the *DUX4* gene. Overexpression of *DUX4* leads to derepression and overexpression of stem cell and

germline genes, eventually resulting in cell death by apoptosis. The cause of FSHD2, which is contraction-independent, was unclear. Performing linkage analysis on 14 individuals in 7 unrelated FSHD2 families, the authors found linkage to chromosomal region 18p11.32. By whole exome sequencing, they found mutations in the *SMCHD1* gene (encoding structural maintenance of chromosomes flexible hinge domain containing 1). These mutations resulted in reduced SMCHD1 protein levels and segregated with genome-wide D4Z4 CpG hypomethylation in the pedigree. FSHD2 occurs in individuals who inherited both a *SMCHD1* mutation and a normal-sized D4Z4 array on a chromosome 4 haplotype permissive for *DUX4* expression. Reducing SMCHD1 levels in skeletal muscle results in D4Z4 contraction-independent *DUX4* expression. This study identified *SMCHD1* as an epigenetic

modifier of the D4Z4 metastable epiallele and as a causal genetic determinant of FSHD2.

The genetic-epigenetic pattern described by Lemmers et al. [2012] may also apply to other human diseases subject to epigenetic regulation. These findings open a novel window of opportunity for the analysis of the complex genetic and epigenetic networks that may underlay expression of clinical phenotypes [Poot, this issue]. Eventually, single locus inheritance may represent a special form of inheritance, while multiple-locus networks of genetic and epigenetic interactions may become the general rule in human genetics. This does not diminish the ground breaking observations of Mendel, which have guided geneticists for more than a century and have provided a point-of-entry into the complex workings of our genome.

M. Poot

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