American Journal of Medical Genetics Part A 143A:1021–1024 (2007)

Invited Comment
What to Call a Syndrome

Raoul C.M. Hennekam[1,2]*

[1]Clinical and Molecular Genetics Unit, Institute of Child Health, Great Ormond Street hospital for Children, UCL, London, UK
[2]Department of Pediatrics, Academic Medical Centre, Amsterdam, The Netherlands

Received 12 December 2006; Accepted 20 December 2006

How to cite this article: Hennekam RCM. 2007. What to call a syndrome. Am J Med Genet Part A 143A:1021–1024.

BACKGROUND

In the early days of Dysmorphology it was relatively simple to delineate a syndrome as a discrete entity [Aimes, 1950]. One encountered a patient or a family with an unusual combination of signs, was unable to find patients with similar features described in literature, concluded this was something "new," and published the observation. Colleagues around the world read the description, realized they had seen patients with a similar, but usually not identical, combination of signs, and published their patients too, comparing their clinical data to those of the earlier described patients. Syndrome delineation and dysmorphology flourished and the number of entities grew with the speed of bamboo [Gorlin and Pindborg, 1964; Smith, 1966; Wiedemann et al., 1976].

As the number of syndromes increased and were better delineated, we as clinicians began to realize that some syndromes that were initially thought to be distinct were not that different after all, and should be called variations within the spectrum of a single disorder (syndrome fusion). The reverse also occurred: a combination of signs that we initially thought formed a single syndrome was found to be comprised of two or more discrete syndromes, that could be separated based on the presence of one or more important features. In other cases, it was not clear where to draw a line between syndromes, and often we stated that time would be on our side, as molecular delineation of syndromes would finally resolve these issues [Allanson, 1989; Cohen, 1989; Hall, 1993; Donnai, 1994; Winter, 1996].

So the molecular area started. But instead of becoming clearer, the situation became more complicated. Our idea of a single gene causing a single syndrome was too simple [Biesecker, 2004]. We now know that almost invariably mutations within a single gene can cause various combinations of manifestations, which we had delineated as distinct syndromes before. We are faced with the problem whether these syndromes should be kept separate or merged. There are differences in opinions what should prevail: is it the clinical, or is it the cytogenetic, molecular, or metabolic basis?

ETIOLOGY CENTRAL

Deciding that etiology is the core issue in the definition of syndromes has a major advantage: one can test for the etiologic factor by cytogenetic, molecular or biochemical means, and the result provides an objective result. The importance of this cannot be overestimated: the ease this provides to physicians and the certainty this provides to patients and their relatives will be an unparalleled and extremely powerful tool in diagnostics and patient care alike. It will also have far reaching consequences on more distant areas such as insurance and employment ("If the test is negative, you do not have the disorder").

This will make life easier! Or not? We do know mutations in a single gene can cause different syndromes. A well-known example is the *RET* proto-oncogene: mutations in this gene can cause Hirschsprung disease, but also multiple endocrine neoplasia type II, central hypoventilation syndrome, or occasionally two of these syndromes simultaneously. A correlation of genotype and phenotype has been demonstrated, but only in a limited way and not for all presently known mutations. If a mutation in the *RET* gene is found, it is therefore not yet clear what this will mean for the patient, and how the physician in charge will use this result to provide the best care. In the patient with a

*Correspondence to: Dr. R.C.M. Hennekam, Clinical and Molecular Genetics Unit, Institute of Child Health, 30 Guilford Street, London WC1N 1EH, UK. E-mail: R.Hennekam@ICH.UCL.ac.uk
DOI 10.1002/ajmg.a.31674

RET mutation, will tumor surveillance be indispensable or early removal of the thyroid gland needed, or is this a complete overshoot and will it result in unneeded anxiety for the patient and the family? Should the insurance company be reassured that with cure of the Hirschsprung the patient will have a normal life expectancy, or consider allowance of only a limited life insurance for someone with such a risk to develop a tumor?

We also know that a single syndrome can be caused by two or more genes (locus heterogeneity). Bardet–Biedl syndrome can serve here as a well known example. Mutations in no less than 12 genes are known to cause this syndrome. There are some differences detectable in subgroups when they are sorted by genetic locus, but for most patients even the most experienced clinician is unable to reliably distinguish the phenotypes caused by mutations in the different genes. So for this syndrome it is at present not true to state "the test is negative, you do not have the disorder." Bardet–Biedl syndrome is caused by dysfunctioning cilia, the number of genes needed to have the cilia function well is exceedingly high, so one wonders even whether we will ever be able to state that "you do not have the disorder."

Still, grouping patients with clinically different syndromes together because the syndromes are caused by mutations in the same gene can be instrumental in many ways. An increasing number of families of syndromes [Pinsky, 1974] are recognized, like the ciliopathies or laminopathies or cholesterolopathies, and this enriches both research and patient care.

PATIENT CENTRAL

If patients are placed centrally in defining syndromes, then the consequences for the patient should be the main determinant in splitting and lumping of syndromes. The consequences for the patients can be divided into: (1) the phenotype; (2) natural history and complications; and (3) mode of inheritance or risk of recurrence [Cohen, 1976].

Phenotype

Strictly spoken all signs present in a patient define together the phenotype, and every sign could be considered equally important (Fig. 1A). If two patients show exactly the same phenotype with as sole difference a clinodactyly in one of them, one could argue that they have a different syndrome. However, we know from families in which a specific syndrome segregates, that patients with the same syndrome more often than not show differences in phenotype (phenotypic heterogeneity or variable expressivity). Studying variability in symptomatology of syndromes within families is very helpful anyway. Only in this way have we learned that some syndromes can show an extremely diverse phenotype, as for instance in Townes–Brocks syndrome. This has allowed us to recognize the same syndrome in individual patients in small families as well. So in part variability can account for differences between patients.

It is well accepted that signs should be of sufficient importance to allow for discriminating between syndromes (Fig. 1B+C). Such signs will often be major malformations [Spranger et al., 1982]. To make comparisons among patients it is mandatory that the phenotype in syndromes is carefully described. The passionate cry of Judith Hall [2003] to do so also in molecular literature did hopefully not fall on deaf ears.

There can be additional problems in comparing the phenotype in groups of patients. One is that the number of patients known with a syndrome can be extremely small. So variability is not well known, and uncertainty in comparing phenotypes remains. It seems safe to keep syndromes split at that time, until the complete clinical phenotype becomes better known. This way patients and families are given the information one can be sure off. It becomes difficult if one of the syndromes goes along with an increased risk for instance for cancer, while in the other no patient has been described with this. There can be no good general rules for how to deal with this, except common sense. We should not pretend we know more than we really know, so it is justified and even needed to share our uncertainty with the patient and family. Another problem is a phenotype in a closed community resembling a known, more generally occurring phenotype, and which is found to be caused by one particular mutation in the gene that also causes the more general phenotype. It will depend on how essential the difference is for the patient, and how frequent it occurs, in deciding whether this should be tagged as a separate syndrome or not. An example of this is the oculo-tricho-anal syndrome that is restricted to the Manitoba area and shows facial features characteristic of Fraser syndrome, but lacks the syndactyly and genital anomalies that define Fraser syndrome elsewhere in the world. It seems likely that oculo-tricho-anal syndrome will be allelic to Fraser syndrome and is caused by a specific mutation. The consistency of the combination of signs in Manitoba patients and the importance for the affected persons does allow discrimination of the entity. Surely, in any way it would be a waste not to use such genotype information if reliable genotype–phenotype information is available.

Natural History and Complications

A similar reasoning can be applied for the characteristics of the natural history and nature of

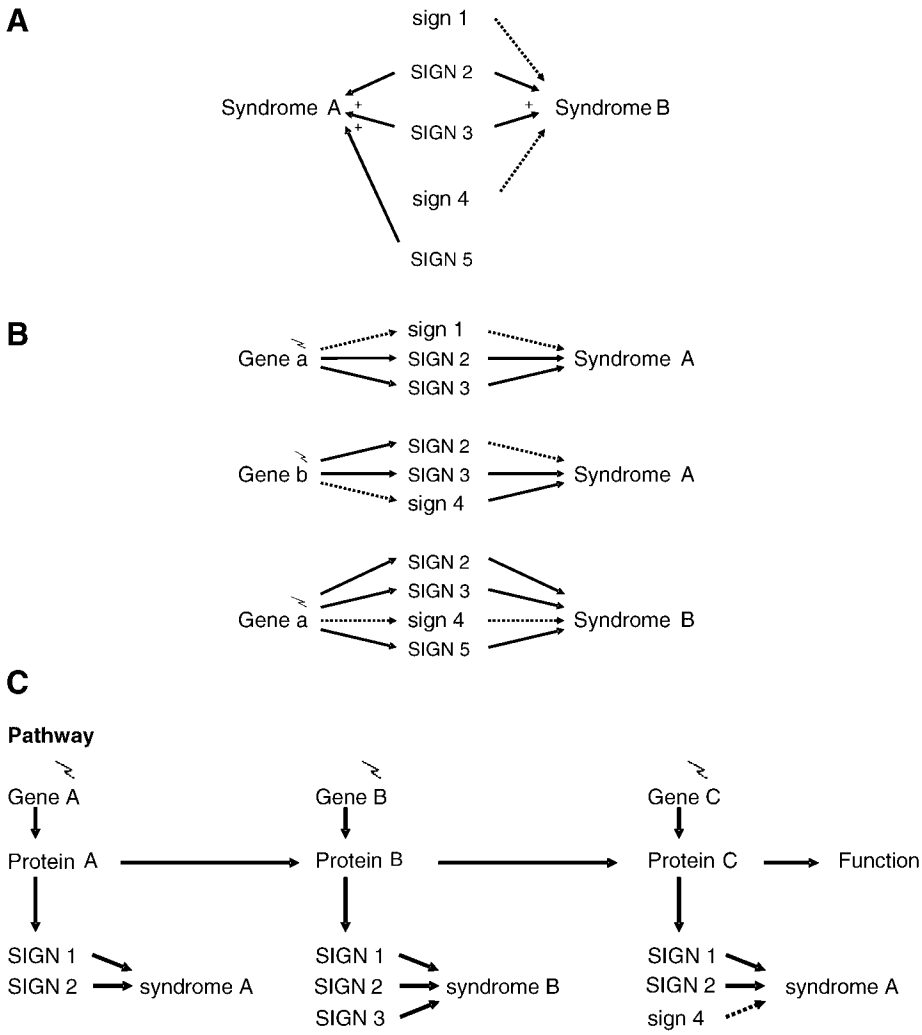

FIG. 1. SIGN: a sign that is of major importance to a patient; sign: a sign that is of minor importance to a patient and forms part of variability of a syndrome; ——▶, indicates obligatory presence; ·····▶, indicates facultative presence; ↝ event that causes a mutation. **A**: Major signs form together a syndrome and show variability based on less important signs. If another major sign is also present, this allows the combination of signs to be renamed as a separate syndrome. **B**: Mutations in different genes can cause the same syndrome although changes in signs of minor importance occur. Mutations in the same gene can cause different syndromes. **C**: In pathways signs caused by mutated genes can resemble one another, but otherwise the conclusions from (**B**) still apply.

complications. We will not use an increase in mild upper airway infections in early childhood as the decisive factor to split two syndromes, but we will often do so if one group of patients manifests cognitive impairment and another does not, or one shows a clear increase in cancer and the other not. Here also timing of a complication is important. Take Marfan syndrome and autosomal dominant ectopia lentis. In both cardiovascular problems can arise, but in Marfan syndrome already in puberty or early adulthood and in a very expressed, life-threatening way, while in ectopia lentis this can occur in the fifth decade or even later on, and often much less serious. It does make a significant difference to the patient to experience either of the two (e.g., the absence of problems during pregnancies for women affected with ectopia lentis), and, so, it remains justified to keep the two separate.

Mode of Inheritance

It makes a large difference to the patient and the family if a disorder follows a horizontal or vertical transmission and whether it is influenced by gender or not. We will commonly split syndromes that show variations in mode of inheritance. An elegant way is to use the addendum 'autosomal recessive type' or 'autosomal dominant type' if disorders are otherwise completely similar. Keeping the same name but adding the pattern of inheritance as an adjective allows for the recognition of both the phenotype being the same as the inheritance being different. One has to be careful in adding adjectives to the syndrome name however. A proposal to use a labeling system using several axes for phenotypic and etiologic factors has not found much use in practice despite its excellent design [Robin and

Biesecker, 2001]. This so-called multiaxis system has the disadvantage of using etiology as one of the factors that define an entity (see below).

PROPOSAL

I propose here to make the patient the central issue. Clinical Genetics has been defined in many ways, but all state it involves health and disease in *patients and their families*. The involvement of patients indicates the hallmark in the distinction of Clinical Genetics from Human Genetics and forms *the* basis of the existence of Clinical Genetics. Surely all direct care is patient-oriented. But also genetic research is aimed to increase our knowledge, and, so, to enable us to use this in patients related research and care [Donnai and Read, 2003]. Clinical Genetics would not exist without patients. An additional reason to put patients central is that etiology and pathogenesis may change if our understanding increases. Take Marfan syndrome again. Only 15 years ago we learned that it could be caused by mutations in fibrillin type I. Marfan is a disorder of connective tissue, and fibrillin I is a component of connective tissue. That was logical, it made sense, we thought we understood this. But we know a bit more now, and recognize that the Marfan phenotype is not so much caused by fibrillin I as a structural protein (maybe the ectopia lentis is), but by fibrillin I as an inhibitor of the function of TGFbeta-Receptor 2. This is a complete change in our understanding of the pathogenesis. Changes in etiology and pathogenesis may ask for adaptations in defining syndromes, which may have many consequences including whether a patient is diagnosed with a syndrome or not. The nature of signs and symptoms in patients, however, does not change; they will always be the same. It is best to base a diagnosis on unchanging grounds.

CONCLUSION

Our gain in knowledge through the present molecular era has been enormous, and we can expect even more to come. But it also caused difficulties in deciding what to call a separate syndrome and what not. There are arguments in favor for using etiology and pathogenesis as the core issue. There are also arguments to make the patient's phenotype as the decisive factor. It will be a matter of discussion within the total genetic community to decide what is the most appropriate. But no matter what will be decided, the most important point is that a decision will be made, and molecular and clinical geneticists agree about this and keep on using the same terminology. After all, using the same language is essential to share knowledge [Bard, 2003].

ACKNOWLEDGMENTS

It is a pleasure to thank Judith Allanson (Ottawa), Leslie Biesecker (Baltimore), John Carey (Salt Lake City), and Judith Hall (Vancouver) for critically reading the manuscript.

REFERENCES

Aimes A. 1950. Maladies et syndromes rares ou peu connus. Description clinique—Répertoire des signes et liste des noms propres. Paris: Masson, Inc. p 1–334.

Allanson J. 1989. Time and natural history: The changing face. J Craniofac Genet Dev Biol 9:21–28.

Bard J. 2003. Ontologies: Formalising biological knowledge for bioinformatics. Bioessays 25:501–506.

Biesecker LG. 2004. Phenotype matters. Nature Genet 36:323–324.

Cohen MM Jr. 1976. Syndrome designations. J Med Genet 13:266–270.

Cohen MM Jr. 1989. Syndromology: An updated conceptual overview. VI. Molecular and biochemical aspects of dysmorphology. Int J Oral Maxillofac Surg 18:339–346.

Donnai D. 1994. Dysmorphic disorders—an overview. J Inherit Metab Dis 17:442–447.

Donnai D, Read AP. 2003. How clinicians add to knowledge of development. Lancet 362:477–484.

Gorlin RJ, Pindborg JJ. 1964. Syndromes of the Head and Neck. New York: McGraw-Hill, Inc.

Hall BD. 1993. The state of the art of dysmorphology. Am J Dis Child 147:1184–1189.

Hall JG. 2003. A clinician's plea. Nature Genet 33:440–442.

Pinsky L. 1974. A community of human malformation syndromes involving the Mullerian ducts, distal extremities, urinary tract, and ears. Teratology 9:65–79.

Robin NH, Biesecker LG. 2001. Considerations for a multiaxis nomenclature system for medical genetics. Genet Med 3:290–293.

Smith DW. 1966. Dysmorphology (teratology). J Pediatr 69:1150–1169.

Spranger J, Benirschke K, Hall JG, Lenz W, Lowry RB, Opitz JM, Pinsky L, Schwarzacher HG, Smith DW. 1982. Errors of morphogenesis: Concepts and terms. Recommendations of an international working group. J Pediatr 100:160–165.

Wiedemann HR, Grosse KR, Dibbern H. 1976. Das charakteristische Syndrom. Blickdiagnose von Syndromen. Ein Atlas für Klinik und Praxis. Stuttgart: Schattauer Verlag.

Winter RM. 1996. What's in a face? Nature Genet 12:124–129.