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Genetics of hot-water epilepsy: A preliminary analysis

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**Table 2.** 15 papers from the 57 'best' papers of Table 1 which have RCR > 1, i.e. actually received citations in excess of XCR, ranked according to RCR

| Relative citation rate (RCR) | Cites actually received | Expected citation rate (XCR) | XCR rank from Table 1 | Name of journal       | Year |
|------------------------------|-------------------------|------------------------------|-----------------------|-----------------------|------|
| 5.56                         | 71.00                   | 12.76                        | XCR-34                | <i>Int. J. Num. M</i> | 1982 |
| 3.05                         | 51.00                   | 16.73                        | XCR-13                | <i>J. Non-Cryst.</i>  | 1986 |
| 2.80                         | 36.00                   | 12.87                        | XCR-28                | <i>Int. J. Num. M</i> | 1985 |
| 2.49                         | 26.00                   | 10.43                        | XCR-49                | <i>Int. J. Num. M</i> | 1986 |
| 2.48                         | 29.00                   | 11.70                        | XCR-40                | <i>Int. J. Num. M</i> | 1983 |
| 1.73                         | 18.00                   | 10.43                        | XCR-47                | <i>Int. J. Num. M</i> | 1986 |
| 1.66                         | 35.00                   | 21.07                        | XCR-4                 | <i>J. Non-Cryst.</i>  | 1981 |
| 1.63                         | 21.00                   | 12.87                        | XCR-29                | <i>Int. J. Num. M</i> | 1985 |
| 1.44                         | 15.00                   | 10.43                        | XCR-50                | <i>Int. J. Num. M</i> | 1986 |
| 1.34                         | 25.00                   | 18.70                        | XCR-8                 | <i>J. Non-Cryst.</i>  | 1983 |
| 1.26                         | 13.00                   | 10.30                        | XCR-53                | <i>Int. J. Num. M</i> | 1988 |
| 1.24                         | 16.00                   | 12.87                        | XCR-30                | <i>Int. J. Num. M</i> | 1985 |
| 1.15                         | 12.00                   | 10.43                        | XCR-57                | <i>Int. J. Num. M</i> | 1986 |
| 1.04                         | 22.00                   | 21.07                        | XCR-5                 | <i>J. Non-Cryst.</i>  | 1981 |
| 1.01                         | 13.00                   | 12.87                        | XCR-27                | <i>Int. J. Num. M</i> | 1985 |

Performance of a published article has been evaluated using the RCR criterion. This is computed as the ratio of the actual citations received by the item published to the expected citation rate, XCR. The criterion here is to select from the list of 57 in Table 1, only those papers which actually received citations in excess of XCR (i.e. RCR > 1). Only 15 papers are found now. Arguably, these are the best papers published from NAL during this period. Note now the reversal of fortunes: The RCR rank has little correlation to the XCR rank. One more confounding factor when XCR or IF value is used to rank quality is that these values vary across disciplines. Thus, in this instance, in a multi-disciplinary institution like NAL, science-based papers earn much higher XCR than engineering-based papers and a larger share of the former appears in Table 1. The use of RCR removes this complication, and the relative rankings have changed considerably.

If one were to relax this criterion more generously, so that journals which have XCR > 5 are all included, then we find an enlarged number of 150 papers from NAL appearing in such a list. Under this relaxation, about 37 papers from NAL (out of 587 listed in the ISI database) have received RCR > 1, i.e. citations in excess of the XCR = 5 stipulation.

skewed, with long tails, and with the mean likely to be very much to the right of the median. These papers have appeared in what can be considered to be the best journals ever used by NAL scientists during 1981–1997, implying that they have the highest IF. However, this does not mean that the paper which is fortunate to appear in such a prestigious journal will ever be used. In fact as Table 1 shows, the 57 papers which belong to this category include many which have 0 and 1 citations since they appeared! In fact more than half the

papers in this list have RCR < 0.5, confirming Tibor Braun's assessment that the RCR of Indian papers is less than one.

My further criterion is to select from this list of 57, only those papers which actually received citations in excess of XCR. This is again an extremely strict criterion, especially considering the recent debate in *Nature* which establishes that papers from the Third World are often under-cited. Only 15 papers are found now (Table 2). Arguably, these are the best papers published from NAL during this period.

The RCR criterion, more than the IF criterion, gives on a retrospective basis, an appreciation of what really are the papers that have been used over a well-defined period. Thus, this approach meets exactly Arunachalam's prescription<sup>1</sup> that 'one should count the number of times a paper is cited and see in which journals these citations occur, rather than merely look at the IF of the journal in which a paper is published'.

Discrimination here operates very unfairly at two levels. There is an accepted perception of discrimination regarding publication of papers. It is believed that a paper from 'weaker section' authors (e.g. women scientists, or those from the developing nations, as seen here) has to be much better than one from the 'stronger sections' to be accepted, i.e. the rejection criterion is more stringently applied to them. Seemingly, this would imply that their accepted publications would on an average, be of better quality. This is discrimination at one level.

One would then expect that these papers would invite better citation rates. The operation of Arun's Law of IF depreciation is an expression of the fact that discrimination probably manifests at the citation level too – that papers from the 'weaker sections', which may arguably be better than average, are fated to receive lower than average citations. Such concerns about region-based citation bias have appeared earlier<sup>2</sup>.

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Genetics of hot-water epilepsy: A preliminary analysis

Reflex or sensory epilepsy commonly refers to a group of epileptic syndromes in which convulsions are precipitated by various kinds of sensory stimuli<sup>1</sup>. Hot-water epilepsy (HWE), also known as water-immersion epilepsy<sup>2</sup> or bathing epilepsy<sup>3,4</sup>, is a particularly interesting

syndrome in which epileptic seizures are induced by the stimulus of bathing with hot water poured over the head<sup>5,9</sup>. Although sporadic cases of HWE have been reported widely from across the world<sup>10</sup>, there appears to be a surprisingly high prevalence of the disease in

southern India<sup>6,7,9,11,12</sup>; in one study, for example, HWE accounted for 3.6 to 3.9% of all reported cases of epilepsy<sup>9</sup>. A recent neuroepidemiological survey of this syndrome in the Bangalore-urban and Bangalore-rural districts of Karnataka, however, estimated that almost

6.9% of all epilepsy syndromes in these two districts may be represented by HWE (62 cases of HWE among 905 epileptics, 1,02,000 individuals surveyed); this yields a fairly high prevalence of 60 per 100,000 (P. Satishchandra, unpublished data).

Seizures in HWE are usually precipitated by a hot water bath or immersion in a hot water tub, where the temperature of the water used ranges between 40 and 50°C (at an ambient room temperature of 25 to 30°C). Children are more frequently affected although it has been reported from adults as well, particularly in the south Indian populations<sup>5,7,9,11</sup>. Moreover, a summary of the worldwide data indicates that males are about 2 to 2.5 times more likely to be afflicted than are females<sup>13</sup>. The frequency of these seizures usually depends on the frequency of head bathing, though, at a later stage, 5 to 10% of the patients had seizures even during a bath when water was not poured over the head.

The seizures typical of HWE are of complex partial type with or without secondary generalization. The symptoms at the onset of an attack include a dazed look, a sense of fear, irrelevant speech, vertigo, and visual and auditory hallucinations with complex automatisms. Nearly 10% of the subjects reported a sense of intense pleasure and continued to pour hot water over the head until they lost consciousness. These seizures have usually been observed to last 1 to 3 min and could occur either at the beginning or at the end of a bath. Finally, although about a third of the patients exhibited generalized-onset tonic-clonic seizures during HWE episodes, and 16 to 38% of the subjects developed non-reflex epilepsy a few years later, electroencephalograms (EEGs) did not suggest idiopathic generalized epilepsy<sup>6,7,9</sup>.

It is now well-accepted that there are important genetic influences in most epileptic syndromes, although most subjects are likely to be afflicted with seizure disorders that result from a combination of genetic and environmental factors<sup>14</sup>. Moreover, data from family segregation and epidemiological studies have strongly suggested that some forms of epilepsy are inherited<sup>15</sup>. A family history of HWE has been reported in 7 to 15% of Indian patients<sup>6,9</sup>, while the syndrome was found to be familial in 18% of the cases in the epidemiological survey of two districts of Karnataka mentioned earlier.

The genetic mechanism underlying the expression of HWE, however, still remains unknown. In an effort to obtain a glimpse into the underlying genetics of HWE, we report here a preliminary analysis of six pedigrees that could be followed from a group of 279 patients seen over four years in a tertiary institution (1980–1983; National Institute of Mental Health and Neurosciences, Bangalore)<sup>9,13</sup>. Each of these families had at least two or three members manifesting HWE as well as one of two syndromes often observed to be associated with it – primary generalized epilepsy and febrile convulsions (Figure 1). The disease phenotypes of those afflicted in the different pedigrees were determined either by personal interviews (of those still alive) or by medical documents and/or third-person reports (for those who had already died).

Assuming that HWE is a simply inherited disorder, a single-locus model has been invoked to explain the inheritance pattern of HWE in these families<sup>13</sup>. Autosomal dominant and sex-linked inheritance could be ruled out because only single affected generations were usually observed, and because the parental generation in all five families with afflicted siblings were completely asymptomatic (Figure 1; Families A–C, E and F).

An autosomal recessive mutation leading to HWE in the homozygous state was, however, a distinct possibility and could explain the specific appearance of the disease phenotype and its observed distribution among individuals of both sexes in all the six lineages<sup>13</sup>. This would also require, of course, that both parents of the afflicted individuals be asymptomatic carriers of the trait. We speculate that although the frequency of such a mutation in a particular population would be fairly low, the traditionally high incidence of consanguineous marriages in many south Indian families<sup>16</sup> could lead to a marked increase in the appearance of HWE in these populations. This is exemplified rather strikingly by the three lineages where marriages between first cousins have invariably yielded a number of HWE-afflicted children (Figure 1; Families C, E and F). Moreover, three of the four observed cases where more than one sibling has been affected within a generation and where the possible relatedness among the parents are known are results of first-cousin marriages

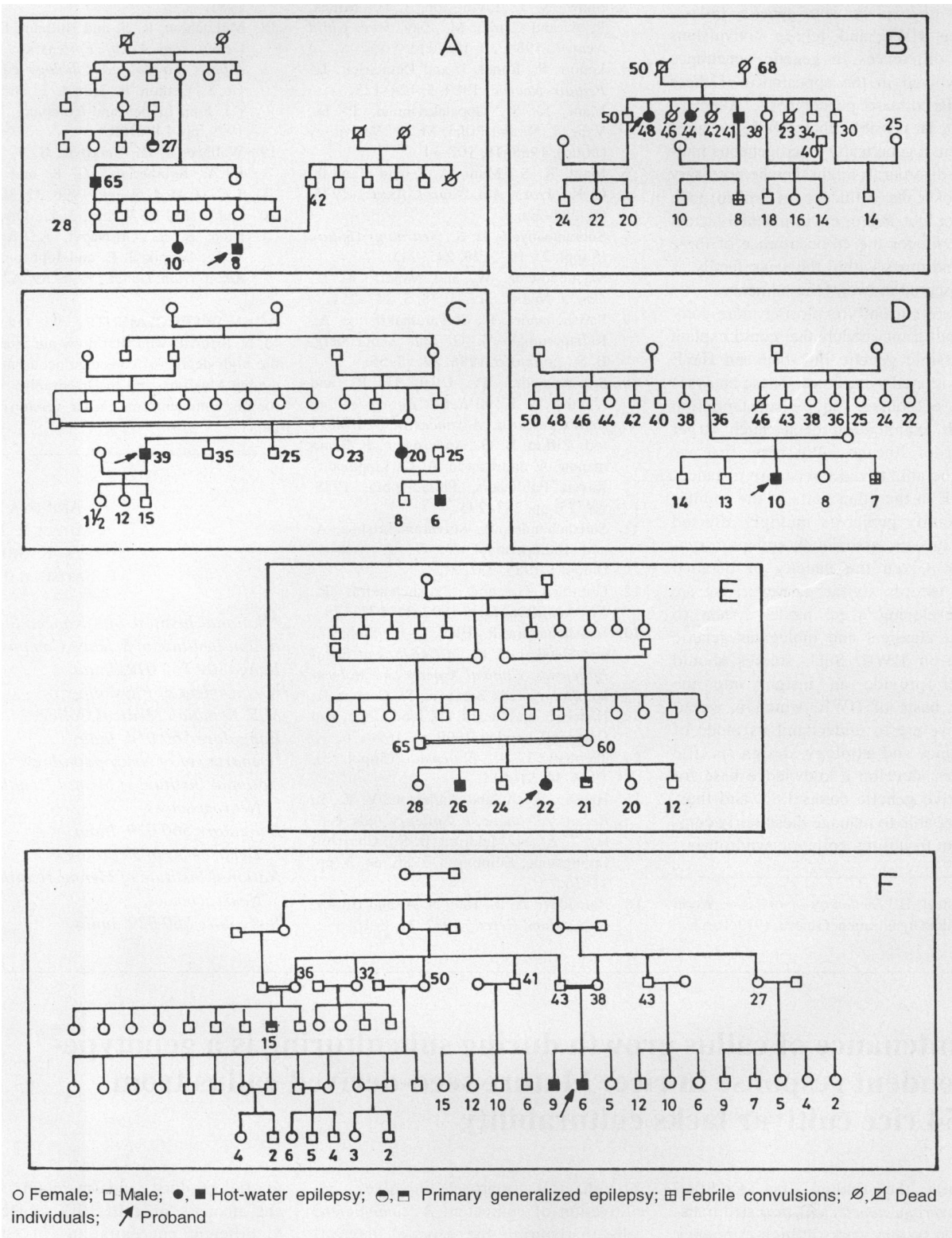
(Figure 1; Families C, E and F; A is the exception).

Another line of evidence which seems to support the view that consanguineous marriages may lead to enhanced appearance of HWE within lineages comes from an analysis of the occurrence of this syndrome among different religious groups. A significantly greater proportion of Muslims have been earlier observed to be afflicted by HWE than they were by other forms of epilepsy<sup>9</sup>. This is not surprising given that Muslims usually exhibit a positive preference for marriage where consanguinity is closest, beyond a narrowly circumscribed group of the most immediate kin, whom one may not marry<sup>17</sup>.

Three of the six lineages analysed in this study also exhibited primary generalized epilepsy among close relatives of individuals afflicted with HWE (Families A, E and F). However, in spite of this correlation and the fact that in one of these families (E) primary generalized epilepsy affected a sibling of two individuals with full-blown HWE, there did not appear to be any strong evidence of a direct genetic link between these two syndromes<sup>13</sup>.

Our analysis of the six lineages also revealed the occurrence of febrile convulsions among both siblings and offspring of HWE-afflicted individuals in two of them (Families B and D, respectively)<sup>13</sup>. Febrile convulsions, which represent another kind of hyperthermic seizures, apart from HWE, commonly occur as clonic, tonic-clonic or atonic seizures associated with fever in 2 to 5% of all children under the age of six years. This syndrome has a variety of underlying causes, but a genetic component has been recognized for a long time. Although its mode of inheritance is still not clearly understood, several genetic models have been proposed involving autosomal dominant, autosomal recessive, and polygenic or multifactorial inheritance<sup>18</sup>. Two studies using linkage analysis with chromosomal markers have also implicated single autosomal dominant mutations, and have located them at two putative foci on chromosomes 8q and 19p, respectively<sup>19,20</sup>. A very recent investigation of three large Canadian multiplex families severely afflicted by febrile convulsions has, however, failed to demonstrate the involvement of these chromosomal regions in these particular families<sup>18</sup>.





**Figure 1.** Pedigree charts of familial hot-water epilepsy. Marriages represented by double lines are consanguineous – between first cousins in all the four cases. Numbers next to particular individuals represent their age and have been given wherever known or relevant. The arrow in each lineage indicates the particular proband, or the first identified patient, in that family.

The single-locus model invoked in the present genetic analysis is, however, insufficient to explain any genetic linkage between HWE and febrile convulsions unless differences in genetic penetrance are involved in the appearance of these particular disease phenotypes<sup>13</sup>. Alternatively, it is possible that febrile seizures represent a genetically heterogeneous multigenic disorder; it might then be necessary to invoke the influence of linked loci, modifier loci, and/or environmental factors to account for the co-occurrence of these two syndromes within the same family as was observed in two of these lineages.

We are currently exploring more complex multigenic models that could explain the possible genetic link between HWE and its related syndromes. These analyses would, of course, require substantiation through examination of a much larger number of lineages. We hope that we would be able to discover more instances of HWE in the other parts of the country and identify pedigrees multiply affected by it and its associated epileptic syndromes. Given the paucity of detailed family records so far, however, we are also developing a rat model system to conduct classical and molecular genetic studies on HWE. Such studies should together provide an insight into the genetic basis of HWE, which is essential if we are to understand its mode of inheritance and aetiology, design specific therapies, develop a knowledge base for preventive genetic counseling, and thus, be better able to manage these fairly common, but troubling, epileptic syndromes.

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## Maintenance of callus growth during subculturing is a genotype-dependent response in rice: Mature seed-derived callus from IR 54 rice cultivar lacks culturability

Following the finding that modified *Agrobacterium tumefaciens*-mediated transformation system works at high-efficiency for stable genetic transformation of rice<sup>1</sup>, there is a great deal of activity as well as success in production of transgenic rice plants for varied applications<sup>2</sup>. A common protocol to achieve rice transformation

through this approach involves co-cultivation of competent *A. tumefaciens* cells (harbouring the gene of interest) with calli pieces derived from the scutellar portion of mature seeds<sup>1,3</sup>. This method warrants that mature seed-derived calli pieces must be able to survive a series of subcultures, in order

to (i) produce and maintain sufficient amounts of calli; (ii) subject calli to different concentrations of selection agent; (iii) check over-growth of *A. tumefaciens* cells on the culture plates following co-cultivation for a limited period and then washing off of the excess bacterial cells; (iv) subject calli to various